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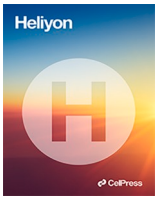

Research article

Evidence construction of Jinshuibao capsules against stable chronic obstructive pulmonary disease: A systematic review and network pharmacology

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ABSTRACT

Background: Jinshuibao capsules has been utilized in treating stable chronic obstructive pulmonary disease (COPD) for a long time. While the evidence-based evidence and network pharmacology to clarify the therapeutic efficacy and pharmacological mechanisms of Jinshuibao capsules have remained elusive.

Objectives: Integrating evidence-based medicine and network pharmacology to explain the therapeutic efficacy and pharmacological mechanisms of Jinshuibao capsules for stable COPD.

Methods: Cochrane Library, Web of Science, EMBASE, PubMed, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, VIP Information Resource Integration Service Platform (CQVIP), and China Biomedicine (SinoMed) databases were searched. Studies were selected according to the inclusion and exclusion criteria. Statistical analysis was performed using the RevMan 5.3 software (Cochrane, London, UK). In network pharmacology, components of Jinshuibao capsules were screened, stable COPD-related genes were then identified and the 'component-target-pathway' network constructed.

Results: Meta-analysis revealed that Jinshuibao capsules exerts therapeutic effects on stable COPD by increasing the levels of FEV1% pred, FEV1/FVC ratio, FEV1, FVC, and PaO2 while decreasing the level of PaCO2. In addition, Jinshuibao capsules could effectively increase the levels of $CD3^+$, $CD4^+/CD8^+$ ratio, Th17/Treg ratio, and SOD while reduce the levels of IL-8 and TNF-α. Network pharmacology identified 22 active compounds and 419 intersection gene targets. AKT1, SRC, MAPK1, STAT3, and MAPK3 were top 5 key target proteins. Besides, 20 potential pathways of Jinshuibao capsules on stable COPD were identified, like endocrine resistance, AGE-RAGE signaling pathway in diabetic complications, and chemical carcinogenesis-receptor activation.

Conclusion: Jinshuibao capsules could positively influence patients with stable COPD, while the efficacy and safety of Jinshuibao capsules in the treatment of COPD could not be reliably confirmed. These findings suggest that Jinshuibao capsules exerts effect on stable COPD through multi-target, multi-component and multi-pathway mechanism. Future studies may explore the active components of Jinshuibao capsules.

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Abbreviations

COPD	chronic obstructive pulmonary disease
CNKI	China National Knowledge Infrastructure
CQVIP	VIP Information Resource Integration Service Platform
RCTs	randomized clinical trials
FEV1% pred	FEV1 as a percentage of predicted
FEV1	forced expiratory volume in the first second
FVC	forced vital capacity
PaO_2	partial pressure of arterial oxygen
$PaCO_2$	partial pressure of arterial carbon dioxide
$CD3^+$	$CD3^+$ T cells
$CD4^+/CD8^+$	$CD4^+/CD8^+$
Th17/Treg	T helper 17 cells/regulatory T cells ratio
IL-8	interleukin-8
TNF-α:	tumor necrosis factor-α
SOD	superoxide dismutas
CI	confidence interval
MD	mean difference
GOLD	Global Initiative for Chronic Obstructive Lung Disease
TCM	traditional Chinese medicine
AEs	adverse events
SEM	standard error of the mean
SD	standard deviation
RR	risk ratio
SAMA	short-acting muscarinic antagonist
LAMA	long-acting muscarinic antagonist
SABA	short-acting beta-2 agonist
LABA	long-acting beta-2 agonist
ICS	inhaled corticosteroid

1. Introduction

Chronic obstructive pulmonary disease (COPD) is defined as an incompletely reversible airflow obstruction accompanied by persistent respiratory symptoms, including dyspnea, cough, and excessive sputum [1,2]. Worldwide, an estimated of 174 million adults with COPD were diagnosed in 2015, and the costs of COPD were $384 million in 2010 [3]. 3.2 million people died from COPD, accounting for 81.7 % of all deaths due to chronic respiratory diseases in 2017 [4]. COPD is the fourth leading cause of death worldwide and is expected to become the third leading cause by 2030 [3]. In addition, COPD is a major cause of morbidity and mortality in China [5]. The prevalence of COPD is estimated to be 8.6 % in adults aged >20 years old in China, equivalent to 99.9 million cases [6]. The burden of COPD in China is expected to continuously increase with a rapidly aging population, smoking prevalence, and increasing air pollution. In the United States, the mortality rate contributed to COPD is increasing over years [7]. The development of COPD can be attributed primarily to a chronic inflammatory response in the airways to harmful particles or gases, and it is strongly associated with a history of smoking. COPD poses a huge economic burden on the global healthcare system, and the timely diagnosis and effective treatment are essential for patient management [8].

The diagnostic criterion for COPD is based on the clinical history and spirometry. Generally, a post-bronchodilator FEV1/FVC ratio less than 70 % will result in a diagnosis of COPD [8]. Measurement of systemic inflammatory markers and oxidative stress markers has major implications for our understanding of COPD pathogenesis [9,10]. COPD patients are characterized by a progressive decline in lung function, accompanied by hypoxemia, hypercapnia, and immune dysfunction, and are prone to respiratory failure, pneumothorax, and pulmonary heart disease [5,11–14]. Long-term cigarette smoking is the significant etiological factor in the development of COPD. Smoking cessation is an important treatment for smokers with COPD. Antibiotics, systemic glucocorticoids, and bronchodilators are the primary therapeutic drugs for COPD [15]. COPD is characterized by neutrophilic airway inflammation. However, a subset of patients, ranging from 20 to 30 %, exhibit elevated levels of eosinophils in the central and small airways. Elevated blood eosinophils appear to be predictive of exacerbations and response to inhaled corticosteroid (ICS) therapy in COPD patients. Additionally, a history of ischemic heart disease is associated with a progressive increase in blood eosinophils in individuals with COPD [16]. Pulmonary rehabilitation, long-term oxygen therapy, and non-invasive ventilation can also alleviate the symptoms of COPD patients. Management of stable COPD in patients should be individualized, with the primary treatment goal of alleviating symptoms and the risk of future exacerbations according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

Moreover, COVID-19 is a highly transmissible disease that can be spread through contact, droplets, and aerosols. Clinical manifestations of COVID-19 primarily affect the respiratory system due to the targeting of the lungs by the SARS-CoV-2 virus, although

other organs may also be affected, leading to multiple organ dysfunctions [17]. Viral entry into host cells further stimulates the immune response, resulting in the secretion of inflammatory cytokines and chemokines. Consequently, SARS-CoV-2 can trigger the release of numerous cytokines in bodily fluids, resulting in acute respiratory distress and multi-organ failure. It is established that viral infections during COPD exacerbations are linked to elevated levels of activated inflammatory cells in the airways. COVID-19 infection has been correlated with significant severity and mortality rates in individuals with COPD, who also face an elevated risk of experiencing severe COVID-19 symptoms [18].

The combination of conventional pharmaceutical treatments and traditional Chinese medicine (TCM) has certain advantages of precise therapeutic activity and less adverse reactions [19–23]. *Cordycep* is a kind of TCM used in the treatment of kidney diseases, cerebrovascular diseases, respiratory diseases, diabetes and diabetes-related complications [24,25]; and Jinshuibao capsules is a pleiotropic traditional Chinese patent medicine with the main component of fermentative cordyceps fungus powder. Jinshuibao capsules have been approved by the China Food and Drug Administration (Approval No. Z10890003) for the treatment of respiratory diseases [26,27]. Clinical studies have shown that Jinshuibao capsules can improve the pulmonary function, suggesting that it may have a synergistic effect. To date, several randomized controlled trials (RCTs) have concentrated on the administration of Jinshuibao capsules in patients with stable COPD, while no evidence-based medicine has been proved. Therefore, it is highly essential to evaluate the effects of Jinshuibao capsules on patients with stable COPD. Our research will provide evidence-based medical evidence on whether the Jinshuibao capsules is effective and safe in the treatment of stable COPD. Moreover, the chemical constituents of Jinshuibao capsules and their target were analyzed using a network pharmacology method and bioinformatics analysis to explain the potential mechanism by which Jinshuibao capsules treats stable COPD.

2. Methods

2.1. Search strategy

This study has been registered on INPLASY (https://inplasy.com/inplasy-2021-10-0117/, registration number INPLASY2021100117). We conducted a systematic review and a meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. In addition, PubMed, EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, VIP Information Resource Integration Service Platform (CQVIP), and China Biomedicine (SinoMed) databases were searched from inception until September 30, 2023. Google Scholar and the China Clinical Trial Registry were also searched for retrieving missing data as appropriate. In addition, we contacted the corresponding authors of the retrieved studies if additional information was required.

The keywords search include: “Pulmonary Disease”, “Chronic Obstructive”, “Chronic Obstructive Lung Disease”, “Chronic Obstructive Pulmonary Diseases”, “COAD”, “COPD”, “Chronic Obstructive Airway Disease”, “Chronic Obstructive Pulmonary Disease”, “Airflow Obstruction, Chronic”, “Airflow Obstructions, Chronic”, “Chronic Airflow Obstructions”, “Chronic Airflow Obstruction”, “Cordyceps”, “Jinshuibao Capsules”, “Jinshuibao”, “Jinshuibao Capsule”, “Jinshuibao Tablet” and “Jinshuibao Tablets”. Different combinations of these terms were used in different databases, as shown in Supplementary File 1.

2.2. Inclusion criteria

1) Studies that were published as RCTs; 2) Patients who were diagnosed with stable COPD according to the GOLD guidelines; 3) RCTs that included the control group (i.e., patents who received conventional pharmaceutical treatments) and experimental group (i.e., patients who received Jinshuibao capsules combined with conventional pharmaceutical treatments); 4) RCTs that included one or more of the following outcomes: FEV1% pred, FEV1/FVC ratio, FEV1, FVC, PaO_2 level, $PaCO_2$ level, the number of $CD3^+$ T cells, $CD4^+/CD8^+$ ratio, Th17/Treg ratio, levels of IL-8, TNF-α, and SOD.

2.3. Exclusion criteria

1) Patients with acute exacerbation of COPD; 2) RCTs that included multiple interventions; 3) Jinshuibao capsules were not used as the primary intervention; 4) Reviews, conference abstracts, and studies that included animal experiments; 5) Duplicate publication; 6) Incomplete or incorrect data.

2.4. Data extraction

Two independent researchers read the title, abstract, and full text of the retrieved articles, and selected qualified RCTs according to the inclusion and exclusion criteria. The following data were extracted: the first authors’ full-name, year of publication, registration date, end date, random sequences, experimental and control groups, course of treatment, dose and frequency of treatment, age, gender, sample size, courses of COPD, FEV1% pred, FEV1/FVC ratio, FEV1, FVC, PaO_2 level, $PaCO_2$ level, the number of $CD3^+$ T cells, $CD4^+/CD8^+$ ratio, Th17/Treg ratio, IL-8 level, TNF-α level, SOD level, and adverse events (AEs). If no sufficient data could be extracted, we attempted to contact the corresponding authors by email to achieve further details. In case of extraction of scattering data, we multiplied the average by −1 to eliminate the scattering effect. We converted standard error of the mean (SEM) values to standard deviation (SD) values. Any disagreement was resolved through discussion with a third researcher.

2.5. Assessment of the risk of bias

The risk of bias was assessed by two reviewers using the Cochrane Collaboration's tool. The assessment included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. Each trial was evaluated at "high-", "low-", or "unclear-" risk of bias [28].

2.6. Statistical analysis

Statistical analysis was performed using the RevMan 5.3 (Cochrane, London, UK) software. The effect size was measured as a relative risk (RR) and 95 % CI (95 % CI) for dichotomous data. For continuous data, mean difference (MD) and 95 % CI were utilized to represent the effect size. We used the I^2 statistic to test the heterogeneity among the included studies [29]. $I^2 \geq 50$ % indicated a substantial heterogeneity, thus, the random-effects model was used to perform the analysis; otherwise, the fixed-effects model was utilized. The sensitivity analysis was conducted to explore whether the results are sensitive to the exclusion of low-quality studies. Subgroup analysis was used to identify the source of heterogeneity. Moreover, funnel plots were used to assess publication bias when more than ten studies were available.

2.7. Identify Jinshuibao capsules and COPD targets

Traditional Chinese Medicine Systems Pharmacology Database (https://tcmspw.com), Encyclopedia of Traditional Chinese Medicine (http://www.tcmip.cn/ETCM), TargetNet database (http://targetnet.scbdd.com), Swiss Target Prediction Database (http://www.swisstargetprediction.ch), and Batman database (http://bionet.ncpsb.org/batman-tcm) were used to find the effective active components and corresponding target proteins of Jinshuibao capsules (screening conditions: OB $\geq$ 30 %, drug-likeness $\geq$0.18). Due to an incomplete coverage of drug targets in public databases, we supplemented a number of gene targets for Jinshuibao capsules

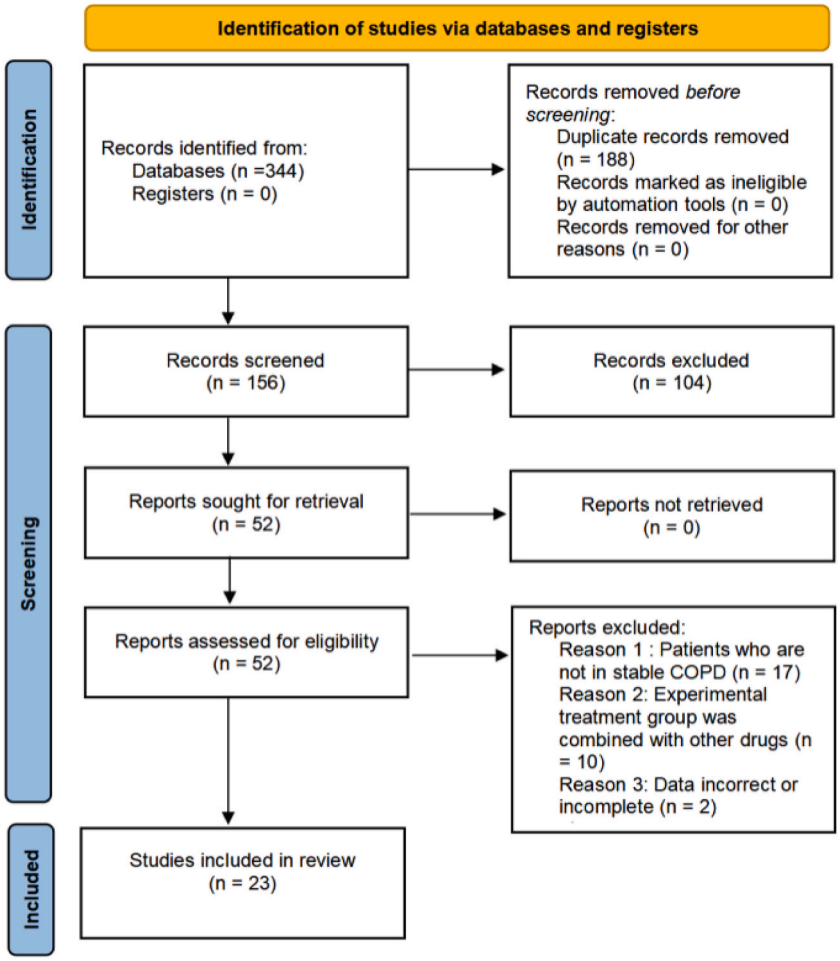

Fig. 1. Flowchart of the study selection.

Table 1
Characteristics of the included studies.

Reference	Intervention of Experimental group	Intervention of control group	Age: Mean ± SD (Experimental/ Control, years)	Sample size (Experimental/ Control)	Course of COPD (Experimental/ Control, years)	Course of treatment	Dose and frequency of Jinshuibao capsules
Guan et al., 2019 [47]	LABA + ICS + Jinshuibao capsules	LABA + ICS	50.1 ± 4.3/50.1 ± 4.2	45/45	6.6 ± 2.1/6.4 ± 2.2	1 months	0.66g, tid
Hu et al., 2019 [36]	LABA + ICS + Jinshuibao capsules	LABA + ICS	60 ± 6.2/62 ± 8.1	30/30	NA	3 months	0.66g, tid
Kang et al., 2018 [43]	LAMA + Jinshuibao capsules	LAMA	NA	39/40	4.1 ± 1.7	3 months	0.66g, tid
Liang et al., 2018 [37]	SAMA + Jinshuibao capsules	SAMA	58.6 ± 6.5/57.7 ± 6.6	48/47	8.4 ± 2.3/8.5 ± 2.4	3 months	0.66g, tid
Li et al., 2017 [50]	SAMA + Jinshuibao capsules	SAMA	63.25 ± 6.67/64.37 ± 8.87	48/48	14.21 ± 2.13/13.45 ± 3.37	6 months	0.66g, tid
Liu et al., 2021 [41]	LAMA + Jinshuibao capsules	LAMA	57.72 ± 4.69/57.63 ± 4.72	30/30	6.81 ± 1.24/6.79 ± 1.36	3 months	0.66g, tid
Lu et al., 2015 [42]	LABA + ICS + Jinshuibao capsules	LABA + ICS	62.22 ± 7.28/63.34 ± 8.36	35/35	NA	3 months	0.66g, tid
Mai et al., 2013 [52]	LABA + Jinshuibao capsules	LABA	55.2 ± 6.1/54.7 ± 4.9	38/40	17.8 ± 6.3/18.1 ± 5.6	1 months	0.66g, tid
Peng et al., 2018 [38]	LABA + ICS + Jinshuibao capsules	LABA + ICS	60.1 ± 6.7/59.8 ± 5.8	53/53	6 ± 4/5 ± 7	2 months	0.66g, tid
Shi, 2016 [51]	Doxofylline + Jinshuibao capsules	LABA + Doxofylline	70.46	43/43	NA	1 year	0.66g, tid
Wei, 2014 [46]	SABA + Jinshuibao capsules	SABA	65 ± 3/65 ± 4	50/50	NA	2 weeks	0.66g, tid
Wei et al., 2010 [39]	SABA + Jinshuibao capsules	SABA	70.1 ± 5.4/69.8 ± 6.7	41/39	NA	6 months	0.66g, tid
Wu, 2014 [45]	SABA + Jinshuibao capsules	SABA	65.3 ± 3.4	60/60	2 ± 3	2 weeks	0.66g, tid
Wu et al., 2019 [40]	LABA + ICS + Jinshuibao capsules	LABA + ICS	64.89 ± 1.99/65.08 ± 1.87	40/40	NA	1 year	0.66g, tid
Wu et al., 2020 [48]	LABA + ICS + Jinshuibao capsules	LABA + ICS	64.9 ± 4.2/65.2 ± 3.5	45/45	12 ± 2.4/11.2 ± 2.6	6 months	0.66g, tid
Xie et al., 2014 [44]	LAMA + Jinshuibao capsules	LAMA	58.3 ± 3.7/57.8 ± 3.6	35/35	3.9 ± 1.3/4 ± 1.5	3months	0.66g, tid
Xu, 2017 [49]	LABA + ICS + Jinshuibao capsules	LABA + ICS	64 ± 1.39/65 ± 1.23	37/37	NA	3 months	1.65g, bid
Xu et al., 2012 [32]	LABA + ICS + Jinshuibao capsules	LABA + ICS	72 ± 8/76 ± 10	30/30	NA	3 months	1.65g, bid
Yu et al., 2019 [34]	LABA + ICS + Jinshuibao capsules	LABA + ICS	56.32 ± 6.90/56.19 ± 6.98	47/47	5.29 ± 1.47/5.17 ± 1.52	3 months	0.66g, tid
Zheng, 2010 [31]	LABA + Jinshuibao capsules	LABA	58.3	42/42	15.5/16.1	2 months	0.66g, tid
Zhu, 2014 [33]	LABA + ICS + Jinshuibao capsules	LABA + ICS	53.2 ± 2.3/52.4 ± 3.1	36/36	NA	1 months	0.66g, tid

(*continued on next page*)

Table 1 (*continued*)

Reference	Intervention of Experimental group	Intervention of control group	Age: Mean ± SD (Experimental/ Control, years)	Sample size (Experimental/ Control)	Course of COPD (Experimental/ Control, years)	Course of treatment	Dose and frequency of Jinshuibao capsules
Zhuang et al., 2019 [35]	LABA + ICS + Jinshuibao capsules	LABA + ICS	58.9 ± 6.5/58.1 ± 6.2	60/60	7.3 ± 2/6.8 ± 2.3	3 months	0.66g, tid
Zhu et al., 2016 [30]	LABA + LAMA + ICS + Jinshuibao capsules	LABA + LAMA + ICS	63.7 ± 5.7/66.8 ± 5.3	34/34	NA	6 months	0.66g, tid

SAMA = short-acting muscarinic antagonist, LAMA = long-acting muscarinic antagonist, SABA = short-acting beta-2 agonist, LABA = long-acting beta-2 agonist, ICS = inhaled corticosteroid, SD = standard deviation, bid = twice a day, tid = three times a day, NA = Not applicable.

according to the previously published literature. The genes associated with COPD were collected from the Online Mendelian Inheritance in Man catalog (https://omim.org), the GeneCards database (https://www.genecards.org), the DisGeNET database (http://www.disgenet.org) and the Comparative Toxicogenomics Database (http://ctdbase.org/). The STRING database (https://string-db.org) and the UniProt database (https://www.uniprot.org) were used to normalize the target genes.

2.8. Construction of protein-protein interaction (PPI) network

After removal of duplicated genes, the overlap of drug genes and disease genes was represented as a Venn diagram. Using the STRING database, a protein-protein interaction (PPI) network was constructed to identify hub genes, with the species set to "Homo sapiens". The PPI information was imported in the Cytoscape 3.6.2 software (Boston, MA, USA) to visualize the network.

2.9. Gene pathway analysis

After screening out the core genes constituting the network structure, the Gene Ontology (GO) functional annotation and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted by a cluster profiler to annotate the potential function of genes.

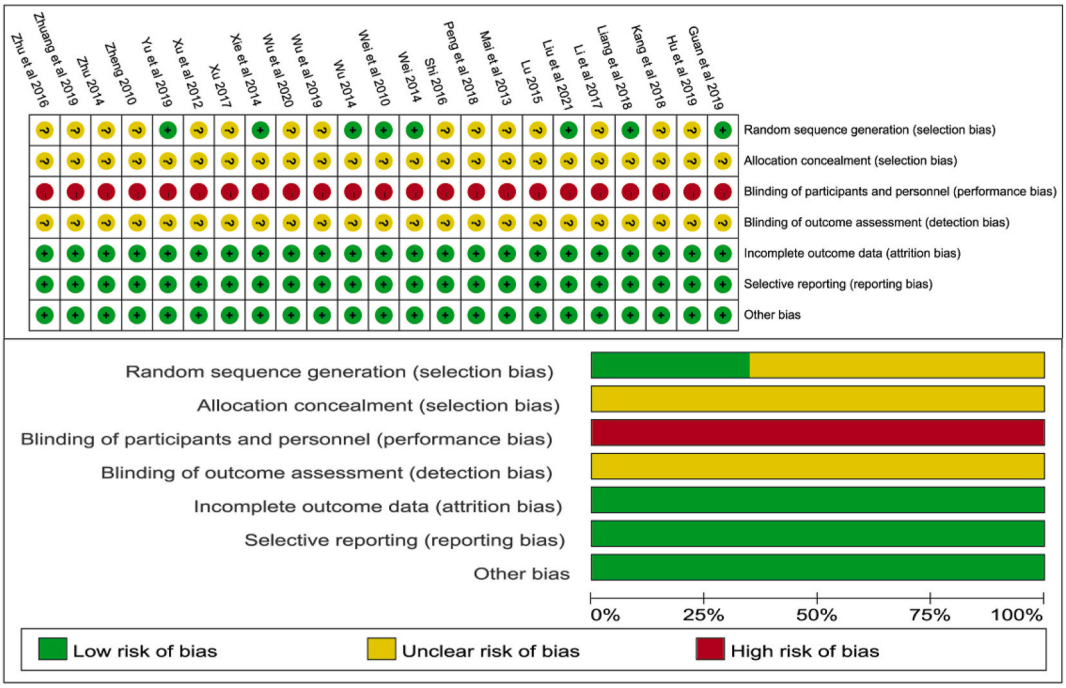

Fig. 2. The outcomes of the risk of bias assessment.

3. Results

3.1. Study selection

A total of 344 relevant RCTs were preliminarily retrieved. After removing duplicate publications, 156 RCTs were retained. After reading the title and abstract of the remaining articles, 104 articles were excluded. Among them, 29 articles were removed after reading the full text. Fig. 1 shows the flowchart of study selection.

3.2. Study characteristics

A total of 23 studies [30–52] involved 1932 patients were included in the current meta-analysis. All the 23 studies were published in China from 2010 to 2021. In the eligible studies, patients in the control group received conventional pharmaceutical treatment, such as smoking cessation, oxygen, anti-inflammatory therapy, and anti-infective. The experimental group included those who received conventional pharmaceutical treatment combined with Jinshuibao capsules. The mean age of the patients ranged from 37 to 82 years old. The treatment duration varies from 2 weeks to 1 year in our included study. All studies reported that the difference in mean ages between the experimental and control groups was not statistically significant. The characteristics of the included studies are summarized in Table 1.

3.3. Methodological quality

Among the eligible studies, 8 RCTs [34,37,39,41,44–47] were randomized using the random number table. None of the RCTs reported allocation concealment, blinding of participants and personnel, or blinding of outcome assessors. No risk of bias was found owing to incomplete outcome data, selective reporting, or other sources of bias. The risk of bias was mainly found as "unclear risk". The outcomes of the risk of bias assessment are illustrated in Fig. 2.

3.4. Primary outcomes

3.4.1. FEV1% pred

A total of 15 studies [30–32,34,35,38–40,42–46,50,51] involved 1313 patients mentioned FEV1% pred as an outcome. Due to the significant heterogeneity, a random-effects model was used ($I^2 = 97$ %, $P < 0.001$). The results of meta-analysis showed that Jinshuibao capsules significantly increased FEV1% pred in stable COPD patients (MD, 8.96; 95%CI, 5.17 to 12.75; $P < 0.001$; Fig. 3). The funnel plot was asymmetric, which suggested that there may be a publication bias (Fig. 4). Sensitivity analysis revealed the robustness of the results. Subgroup analysis showed that no significant difference was found between age ($P = 0.37$) or courses of COPD ($P = 0.24$) subgroups. The differences between subgroups of different courses of treatment were statistically significant ($P < 0.0001$), suggesting that the course of treatment may be a potential source of heterogeneity (Table 2).

3.4.2. FEV1/FVC ratio

In total, 22 RCTs [30–50,52] involved 1846 patients mentioned FEV1/FVC ratio as an outcome. We used a random-effects model because of the significant heterogeneity ($I^2 = 96$ %, $P < 0.001$). The Jinshuibao capsules combined with conventional pharmaceutical treatment significantly increased FEV1/FVC ratio compared with the conventional pharmaceutical treatment alone (MD, 7.90; 95%CI, 5.37 to 10.43; $P < 0.001$; Fig. 5). According to the funnel plot, there was no publication bias (Fig. 6). Sensitivity analysis indicated the robustness of the results. The subgroup analysis showed that there was no significant difference in the effect of intervention according

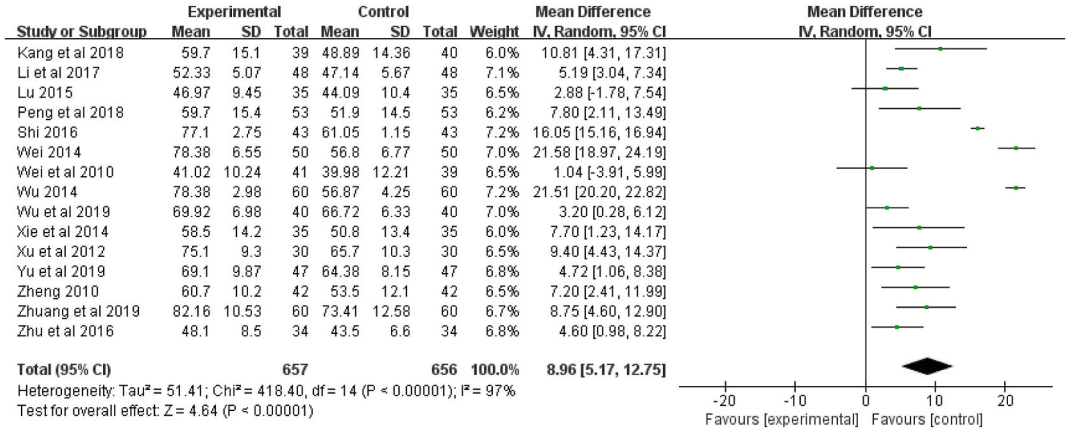

Fig. 3. Forest plot for the FEV1% pred.

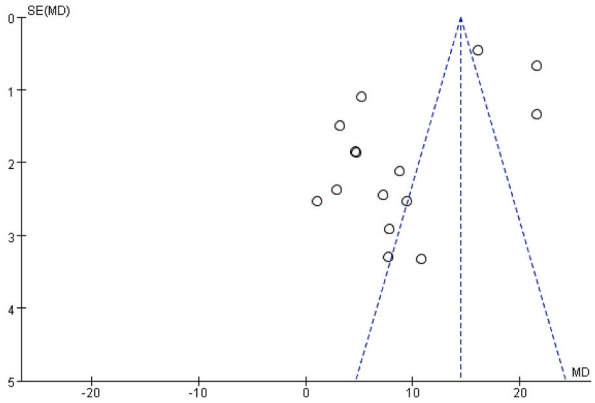

Fig. 4. Funnel plot for the FEV1% pred.

to age (P = 0.50) and course of COPD (P = 0.15). The differences between subgroups of different courses of treatment were statistically significant (P < 0.0001), suggesting that the course of treatment could be the source of heterogeneity (Table 2).

3.4.3. FEV1

A total of 19 studies [30,31,33,34,36–38,40–50,52] including 1586 patients reported FEV1. We found a significant heterogeneity among these studies (I^2 = 93 %, P < 0.001); thus, we used the random-effects model to calculate the effect size. The Jinshuibao capsules significantly increased FEV1 (MD, 0.28; 95%CI, 0.17 to 0.39; P < 0.001, Fig. 7). According to the funnel plot, there was no publication bias (Fig. 8). Sensitivity analysis revealed the robustness of the results. In terms of subgroup analysis, there was no significant difference in the effect of intervention according to age (P = 0.47) and course of COPD (P = 0.58). The differences between subgroups of different courses of treatment were statistically significant (P < 0.0001), suggesting that the course of treatment could be the source of heterogeneity (Table 2).

3.4.4. FVC

A total of 8 studies [33,36,37,40,41,48,49,52] reported FVC in 609 patients. We found a significant heterogeneity in these studies (I^2 = 78 %, P < 0.001), and used the random-effects model to calculate the effect size. The Jinshuibao capsules significantly improved FVC (MD, 0.33; 95%CI, 0.18 to 0.49; P < 0.001; Fig. 9). As fewer than 10 studies were analyzed, no evaluation of publication bias was conducted. Sensitivity analysis indicated the robustness of the results. The subgroup analysis revealed that there was no significant difference in the effect of intervention according to age (P = 0.70) and course of COPD (P = 0.54). The differences between subgroups of different courses of treatment were statistically significant (P = 0.03), suggesting that the course of treatment could be the source of heterogeneity (Table 2).

3.5. Secondary outcomes

3.5.1. PaO2 level

PaO_2 level was reported in 3 studies [36,47,49] that involved 210 patients. No significant heterogeneity was found among these studies (I^2 = 49 %, P = 0.14), and the fixed-effects model was used. Compared with the conventional pharmaceutical treatment group, the Jinshuibao capsules combined with conventional pharmaceutical treatment significantly increased the PaO_2 level (MD, 5.86; 95% CI, 3.19 to 8.53; P < 0.001; Fig. 10). As fewer than 10 studies were analyzed, no evaluation of publication bias was conducted. Sensitivity analysis showed the robustness of the results.

3.5.2. PaCO2 level

$PaCO_2$ level was reported in 3 studies [36,47,49] that included 210 patients. We found a significant heterogeneity among these studies (I^2 = 80 %, P = 0.006), and used the random-effects model to calculate the effect size. Jinshuibao capsules markedly reduced the $PaCO_2$ level (MD, −5.59; 95%CI, −10.14 to −1.04; P = 0.02; Fig. 11). As fewer than 10 studies were analyzed, no evaluation of publication bias was conducted. Sensitivity analysis revealed the robustness of the results. Subgroup analysis indicated that there were significant differences in age (P = 0.002) and course of treatment (P = 0.002), suggesting that age and course of treatment could be the source of heterogeneity (Table 2).

3.5.3. The number of $CD3^+$ T cells in peripheral blood

Two studies [41,47] reported the number of $CD3^+$ T cells in peripheral blood of 150 patients. No significant heterogeneity was found among these studies (I^2 = 0 %, P = 0.42), and we used the fixed-effects model. The Jinshuibao capsules significantly increased the number of $CD3^+$ T cells in patients with stable COPD (MD, 5.39; 95%CI, 3.99 to 6.78; P < 0.001; Fig. 12). As fewer than 10 studies were analyzed, no evaluation of publication bias was conducted. Sensitivity analysis indicated the robustness of the results.

Table 2
Subgroup analysis of the outcomes.

Outcomes	Number of studies	Results	P-value for overall effect	I^2	*P*-value for subgroup difference
FEV1% pred	15	14.44 (13.84–15.04)	<0.001	97 %	
Course of COPD					0.24
>10 years	2	5.53 (3.57–7.49)	<0.001	0 %	
<10 years	6	10.33 (2.57–18.09)	0.009	96 %	
Age					0.37
>60 years	9	9.69 (4.80–14.58)	0.001	98 %	
<60 years	6	7.28 (5.30–9.26)	<0.001	0 %	
Course of treatment					<0.0001
2 weeks	2	21.52 (20.35–22.70)	<0.001	0 %	
2 months	2	7.45 (3.78–11.11)	<0.001	0 %	
3 months	6	6.97 (4.56–9.38)	<0.001	32 %	
6 months	3	4.44 (2.51–6.38)	<0.001	12 %	
1 year	2	9.70 (−2.89 to 22.30)	0.13	99 %	
FEV1/FVC ratio	22	7.95 (7.49–8.41)	<0.001	96 %	
Course of COPD					0.15
>10 years	4	4.48 (1.10–7.86)	0.009	75 %	
<10 years	9	8.64 (4.15–13.14)	0.0002	97 %	
Age					
>60 years	10	8.90 (4.37–13.43)	0.0001	98 %	0.50
<60 years	12	7.06 (4.18–9.94)	<0.001	93 %	
Course of treatment					<0.0001
2 weeks	2	22.83 (21.26–24.49)	<0.001	0 %	
1 month	3	2.92 (−4.73 to 10.56)	0.45	78 %	
2 months	2	6.15 (2.70–9.61)	0.0005	14 %	
3 months	10	7.59 (4.79–10.38)	<0.001	70 %	
6 months	4	6.74 (4.39–9.10)	<0.001	97 %	
1 year	1	1.78 (0.22–3.34)	0.03		
FEV1	19	0.26 (0.23–0.29)	<0.001	93 %	
Course of COPD					0.58
>10 years	4	0.24 (−0.15 to 0.62)	0.23	95 %	
<10 years	8	0.35 (0.23–0.47)	<0.001	84 %	
Age					0.47
>60 years	9	0.32 (0.13–0.50)	0.0007	97 %	
<60 years	10	0.24 (0.15–0.33)	<0.001	62 %	
Course of treatment					<0.0001
2 weeks	2	0.58 (0.52–0.64)	<0.001	0 %	
1 month	3	0.11 (−0.22 to 0.43)	0.53	78 %	
2 months	2	0.30 (0.15–0.46)	0.0001	14 %	
3 months	8	0.25 (0.14–0.36)	<0.001	70 %	
6 months	3	0.31 (−0.03 to 0.66)	0.07	97 %	
1 year	1	0.13 (0.03–0.23)	0.01		
FVC	8	0.33 (0.18–0.49)	<0.001	78 %	
Course of COPD					0.54
>10 years	2	0.26 (−0.36 to 0.87)	0.42	94 %	
<10 years	2	0.48 (0.10–0.86)	0.01	82 %	
Ages					0.70
>60 years	4	0.37 (0.19–0.54)	<0.001	72 %	
<60 years	4	0.30 (0.01–0.59)	0.04	84 %	
Course of treatment					0.03
1 month	2	0.10 (−0.24 to 0.45)	0.56	73 %	
3 months	4	0.41 (0.22–0.59)	<0.001	69 %	
6 months	1	0.57 (0.37–0.77)	<0.001		
1 year	1	0.22 (0.05–0.39)	0.01		
PaCO2	3	−5.59 (−10.14 to −1.04)	0.02	80 %	
Ages					0.002
>60 years	2	−3.09 (−5.35 to −0.84)	0.007	0 %	
<60 years	1	−9.74 (−13.41 to −6.07)	<0.001		
Course of treatment					0.002
1 month	1	−9.74 (−13.41 to −6.07)	<0.001		
3 months	2	−3.09 (−5.35 to −0.84)	0.007	0 %	
TNF-α	3	−8.02 (−15.47 to −0.57)	0.03	99 %	
Course of COPD					0.74

(*continued on next page*)

Table 2 (*continued*)

Outcomes	Number of studies	Results	P-value for overall effect	I^2	*P*-value for subgroup difference
>10 years	1	−9.30 (−10.84 to −7.76)	<0.001		
<10 years	2	−7.40 (−18.70 to 3.91)	0.20	99 %	
Ages					0.74
>60 years	1	−9.30 (−10.84 to −7.76)	<0.001		
<60 years	2	−7.40 (−18.70 to 3.91)	0.20	99 %	
Course of treatment					<0.0001
1 month	1	−1.66 (−2.16 to −1.16)	<0.001		
3 months	1	−13.20 (−15.02 to −11.38)	<0.001		
6 months	1	−9.30 (−10.84 to −7.76)	<0.001		

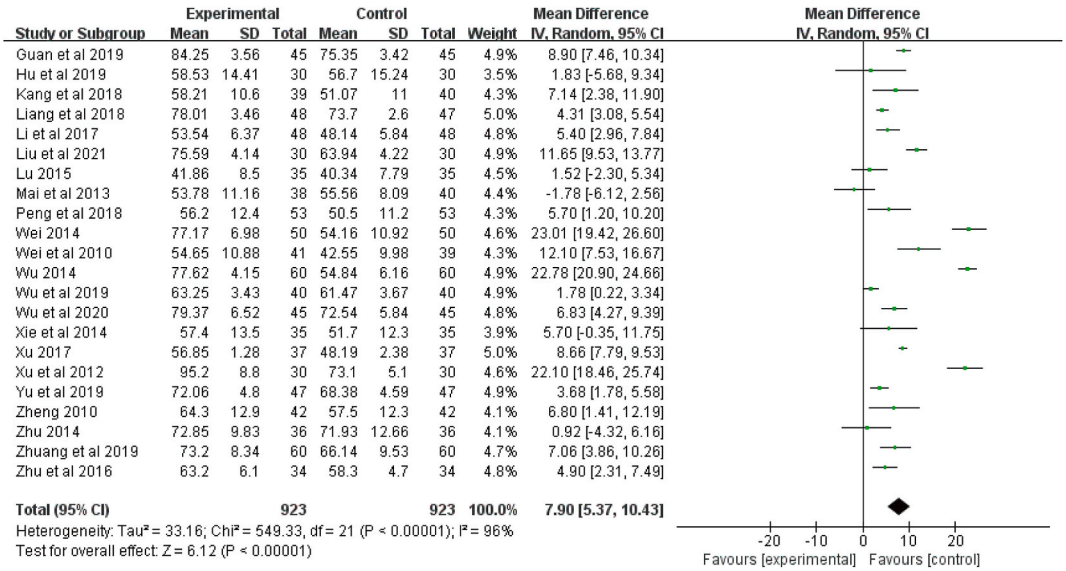

Fig. 5. Forest plot for the FEV1/FVC ratio.

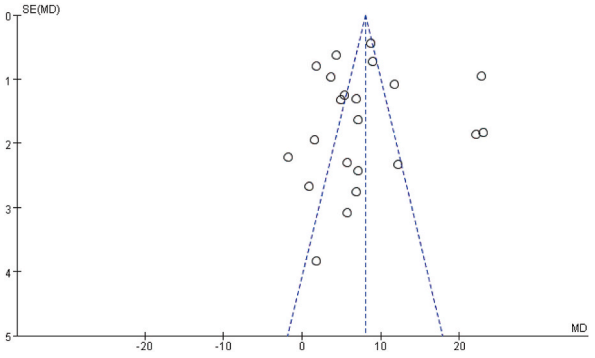

Fig. 6. Funnel plot for the FEV1/FVC ratio.

3.5.4. The ratio of CD4+/CD8+ T cells in peripheral blood

A total of 3 studies [34,38,41] reported the ratio of $CD4^+/CD8^+$ T cells in peripheral blood of 260 patients. No significant heterogeneity was found among these studies ($I^2 = 0$ %, P = 0.62), and we therefore used the fixed-effects model to calculate the effect size. As shown in Fig. 13, the Jinshuibao capsules increased the ratio of $CD4^+/CD8^+$ T cells (MD, 0.21; 95%CI, 0.14 to 0.29; P < 0.001, Fig. 13). As fewer than 10 studies were analyzed, no evaluation of publication bias was conducted. Sensitivity analysis revealed the robustness of the results.

3.5.5. The ratio of Th17/Treg cells in peripheral blood

A total of 3 studies [41,43,44] reported the ratio of Th17/Treg cells in peripheral blood of 244 patients. No significant

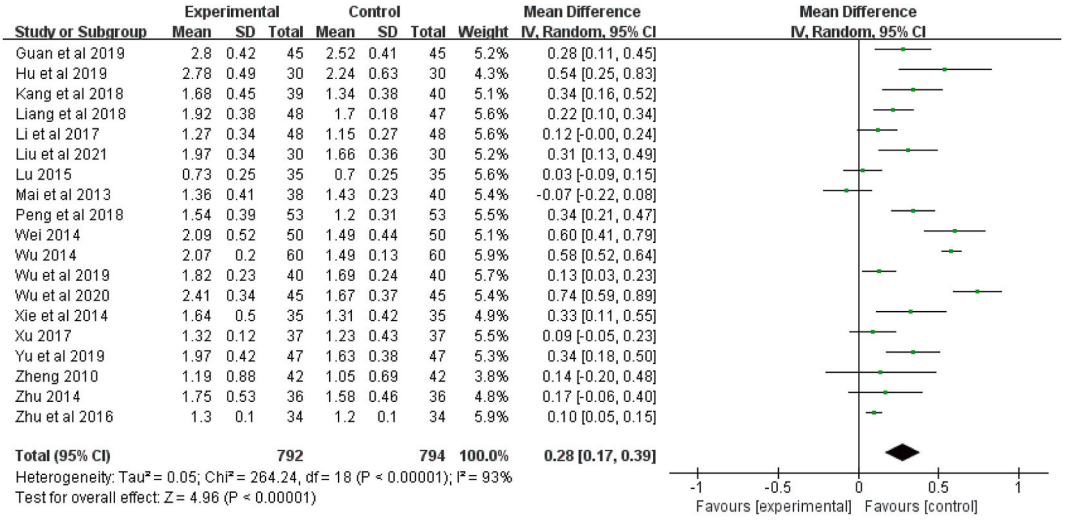

Fig. 7. Forest plot for the FEV1.

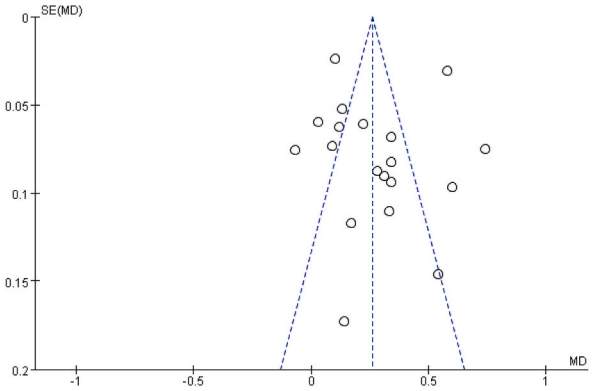

Fig. 8. Funnel plot for the FEV1.

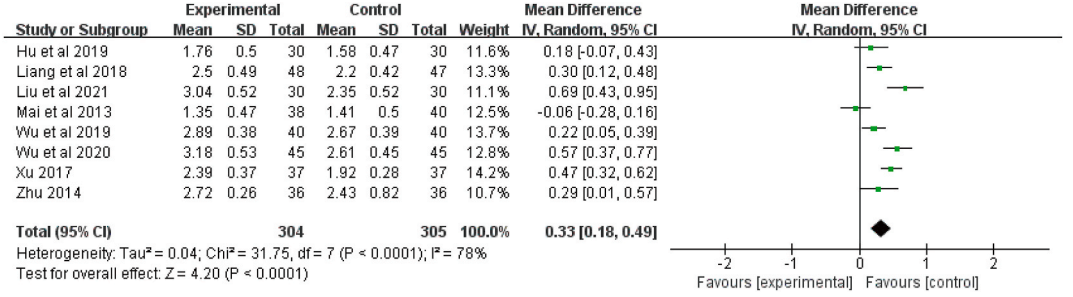

Fig. 9. Forest plot for the FVC.

heterogeneity was found among these studies ($I^2 = 0$ %, P = 0.98), and the fixed-effects model was used. As indicted in Fig. 14, the Jinshuibao capsules increased the ratio of Th17/Treg cells (MD, 0.12; 95%CI, 0.08 to 0.16; $P < 0.001$, Fig. 14). As fewer than 10 studies were analyzed, no evaluation of publication bias was conducted. Sensitivity analysis revealed the robustness of the results.

3.5.6. IL-8 level

Two studies [35,47] reported IL-8 level that included 210 patients. No significant heterogeneity was found among these studies ($I^2 = 0$ %, P = .4), and we therefore used the fixed-effects model to calculate the effect size. The Jinshuibao capsules decreased IL-8 level (MD, −3.9; 95%CI, −4.91 to −2.90; $P < 0.001$; Fig. 15). As fewer than 10 studies were analyzed, no evaluation of publication bias was

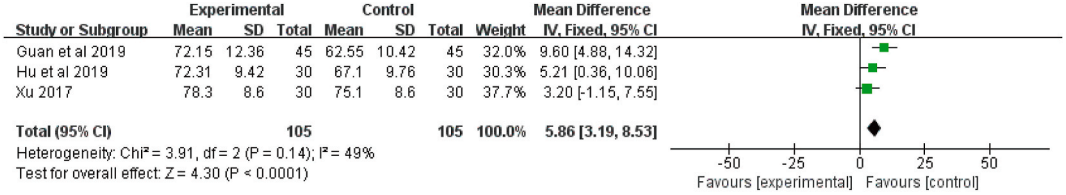

Fig. 10. Forest plot for the PaO2 level.

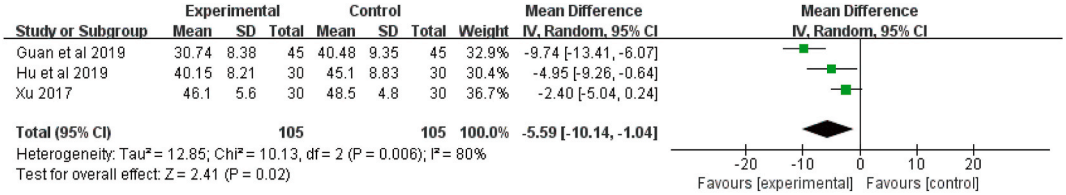

Fig. 11. Forest plot for the PaCO2 level.

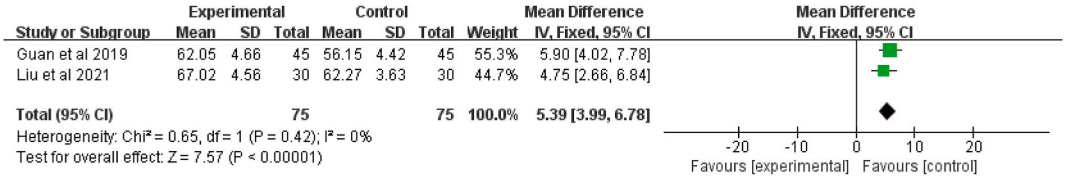

Fig. 12. Forest plot for the number of $CD3^+$ T cells in peripheral blood.

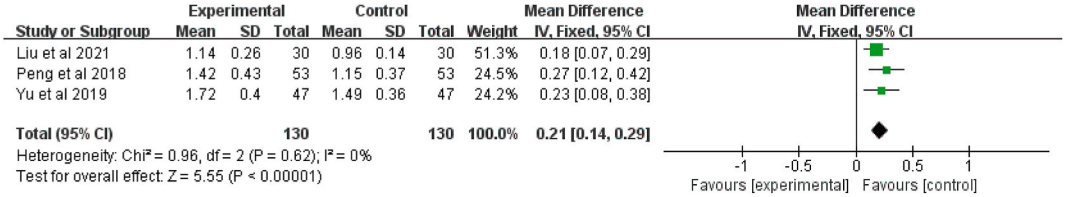

Fig. 13. Forest plot for the ratio of CD4+/CD8+ T cells in peripheral blood.

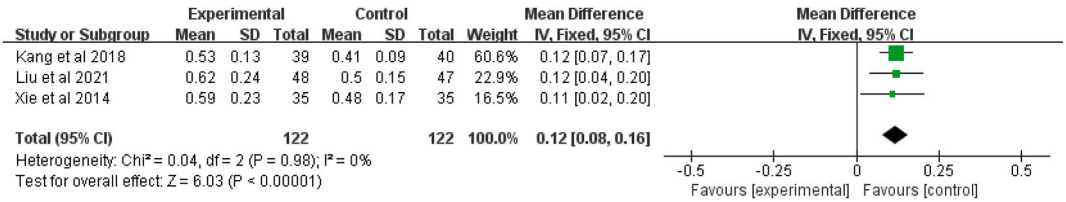

Fig. 14. Forest plot for the ratio of Th17/Treg cells in peripheral blood samples.

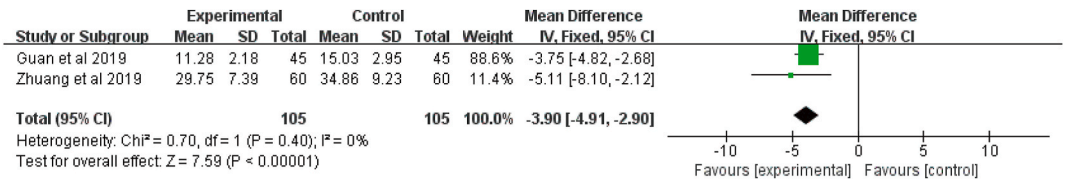

Fig. 15. Forest plot for the IL-8 level.

conducted. Sensitivity analysis indicated the robustness of the results.

3.5.7. TNF-α level

A total of 3 studies [37,47,50] reported TNF-α level in 281 patients. Based on the significant heterogeneity was noted among these studies ($I^2 = 99$ %, $P < 0.001$), we therefore used the random-effects model to calculate the effect size. The Jinshuibao capsules plus conventional pharmaceutical treatment significantly decreased TNF-α level compared with conventional pharmaceutical treatment alone (MD, −8.02; 95%CI, −15.47 to −0.57; $P = 0.03$; Fig. 16). As fewer than 10 studies were analyzed, no evaluation of publication bias was conducted. Sensitivity analysis revealed the robustness of the results. The differences between subgroups of different courses of treatment were statistically significant ($P < 0.001$), suggesting that the course of treatment could be the source of heterogeneity (Table 2).

3.5.8. SOD level

A total of 3 studies [37,48,50] reported SOD level in 259 patients. No significant heterogeneity was noted among these studies ($I^2 = 0$ %, $P = 0.73$), and the fixed-effects model was used. Jinshuibao capsules markedly increased SOD level (MD, 217.26; 95%CI, 131 to 303.53; $P < 0.001$; Fig. 17). As fewer than 10 studies were analyzed, no evaluation of publication bias was conducted. Sensitivity analysis showed the robustness of the results.

3.6. AEs

AEs were reported in 3 studies [35,37,48]. In one [37] of these studies, mild headache was found in 5 patients, vomiting in 3 patients, and insomnia in 3 patients that could be resolved spontaneously. Another study [48] reported mild headache in 4 patients, vomiting in 7 patients, and nausea in 3 patients, which were resolved spontaneously. In another study [35], 2 patients had mild headache, 2 had mild abdominal discomfort, and 1 had nausea, which could be resolved. No AEs were reported in other studies.

3.7. Analysis of Jinshuibao capsules and COPD targets

A total of 3619 candidate genes associated with COPD and 1008 candidate target genes of Jinshuibao capsules were selected based on specific screening criteria. By intersecting the disease targets with the drug targets (as depicted in Fig. 18A), a set of 419 common target genes was identified. The key targets within the were determined using the String database. Fig. 18B illustrates the top 5 targets, namely AKT1, SRC, MAPK1, STAT3, and MAPK3, based on their degree value in the core target PPI network.

3.8. Drug-targets-disease network construction

Subsequently, the protein-protein interaction network from String database were imported into the Cytoscape software for the purpose of constructing a PPI network and visualizing the findings of the analysis. In order to obtain the 121 hub genes, the screening criteria employed in the target network involved a degree centrality (DC) value greater than or equal to twice the median DC (Fig. 19A). The target genes were then ranked based on their node values (Fig. 19B), with the intensity of the color as well as the size of the node area indicating the degree value of the genes. AKT1, SRC, MAPK1, STAT3, and MAPK3 are the core target genes with high degree scores. Furthermore, a drug-targets-disease network was constructed, as depicted in Fig. 19C.

3.9. Gene enrichment analysis

The drug-disease common targets were processed by R language for GO function and KEGG pathway enrichment analysis based on the 121 hub targets. Fig. 20A displays the top 10 terms from each category and the GO pathway map. The findings revealed that the molecular function (MF) items included response to nuclear receptor binding, protein serine/threonine kinase activity, steroid hormone receptor binding, nuclear hormone receptor binding, and phosphatase binding. The main primary cellular component (CC) items consisted of ficolin-1-rich granule lumen, ficolin-1-rich granule, vesicle lumen, nuclear envelope, transcription regulator complex, and caveola. The primary biological process (BP) items observed in this study encompassed the response of cells to oxidative stress, the proliferation of muscle cells, the response to metal ions, the response to reactive oxygen species, and the response to molecules of bacterial origin. The visualization of the top 20 KEGG pathways (Fig. 20B) revealed the involvement of various pathways such as endocrine resistance, AGE-RAGE signaling pathway in diabetic complications, chemical carcinogenesis - receptor activation, lipid and

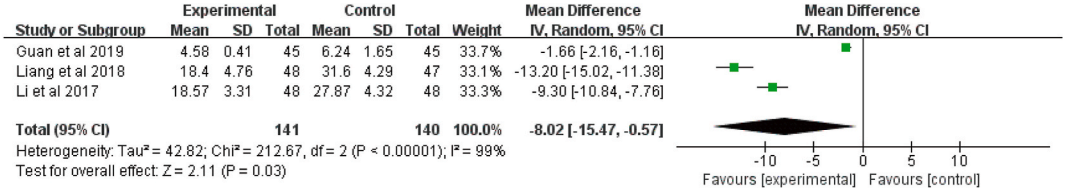

Fig. 16. Forest plot for the TNF-α level.

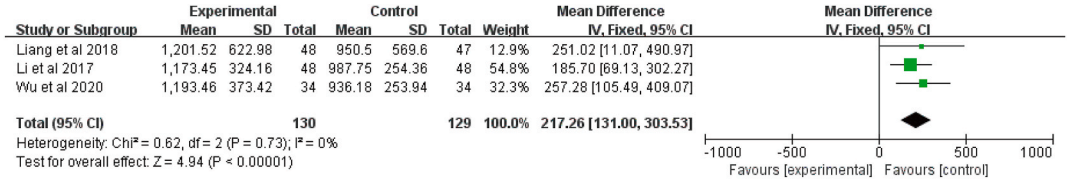

Fig. 17. Forest plot for the SOD level.

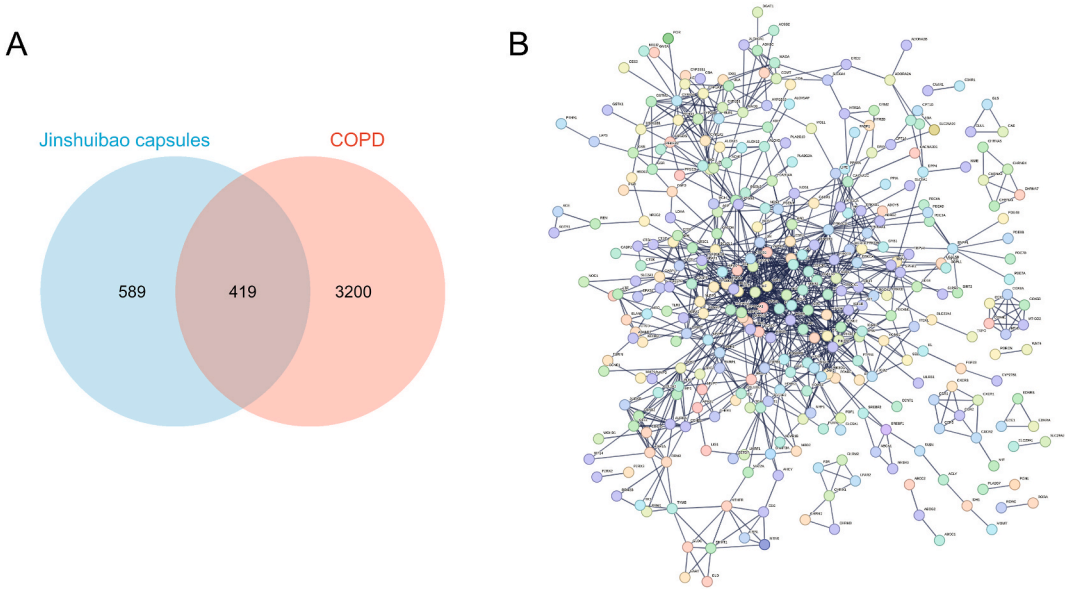

Fig. 18. Network pharmacology prediction for Jinshuibao capsules treatment in stable COPD. (A) Intersection targets between Jinshuibao capsules and COPD. (B) The intersection targets were used to construct a PPI network.

atherosclerosis, human cytomegalovirus infection, and prostate cancer.

4. Discussion

COPD is a prevalent chronic respiratory ailment that poses a significant global public health concern [53]. Traditional Chinese medicine (TCM) has been historically utilized for the clinical management of COPD, with a growing body of randomized controlled trials investigating the efficacy of proprietary TCM formulations. TCM interventions aim to alleviate symptoms such as cough, phlegm accumulation, heat retention, and asthma, while also bolstering immune function and preserving lung health in individuals with COPD [54]. The Jinshuibao capsules demonstrate notable benefits in enhancing pulmonary function, immune modulation, and anti-inflammatory effects in individuals with stable COPD; however, the existing literature frequently lacks robust evidence from rigorous clinical trials. Recent reports suggest that these capsules may hold promise in ameliorating lingering cardiopulmonary symptoms in recovering COVID-19 patients, with minimal occurrence of adverse reactions [55]. The co-administration of Jinshuibao capsule and beclomethasone propionate has demonstrated significant efficacy in alleviating clinical symptoms, enhancing pulmonary function, managing asthma symptoms, and ensuring medication safety in patients with bronchial asthma [56]. Despite widespread utilization in China, there remains a lack of systematic investigation and evaluation of Jinshuibao capsule treatments. Therefore, it is imperative to elucidate the impact of Jinshuibao capsules on the efficacy of COPD. In the current study, we examined the effectiveness and safety of Jinshuibao capsules in conjunction with CPT for individuals diagnosed with stable COPD, with the goal of advancing therapeutic options for this condition. This is the first article that integrates meta-analysis and network pharmacology to evaluate the efficacy and potential pharmacological mechanisms of Jinshuibao capsules in the treatment of COPD.

A total of 23 RCTs, which enrolled 1932 patients from 23 provinces in China, were involved in the current meta-analysis, representing different ethnic groups, genders, and age-based groups. Confounding factors, such as smoking, lung infection, and bronchial asthma have not been fully reported in the RCTs analyzed in the present study. Our study yielded findings through the integration of existing evidence. Initially, it was observed that the methodological quality of the studies included in the analysis was subpar, potentially leading to an overestimation of treatment efficacy. Furthermore, the combination of Jinshuibao capsules with CPT demonstrated effectiveness in enhancing pulmonary function, arterial blood gas analysis, anti-inflammatory therapy, and immune regulation when compared to CPT alone. Specifically, the addition of Jinshuibao capsules to CPT resulted in improvements in FEV1%

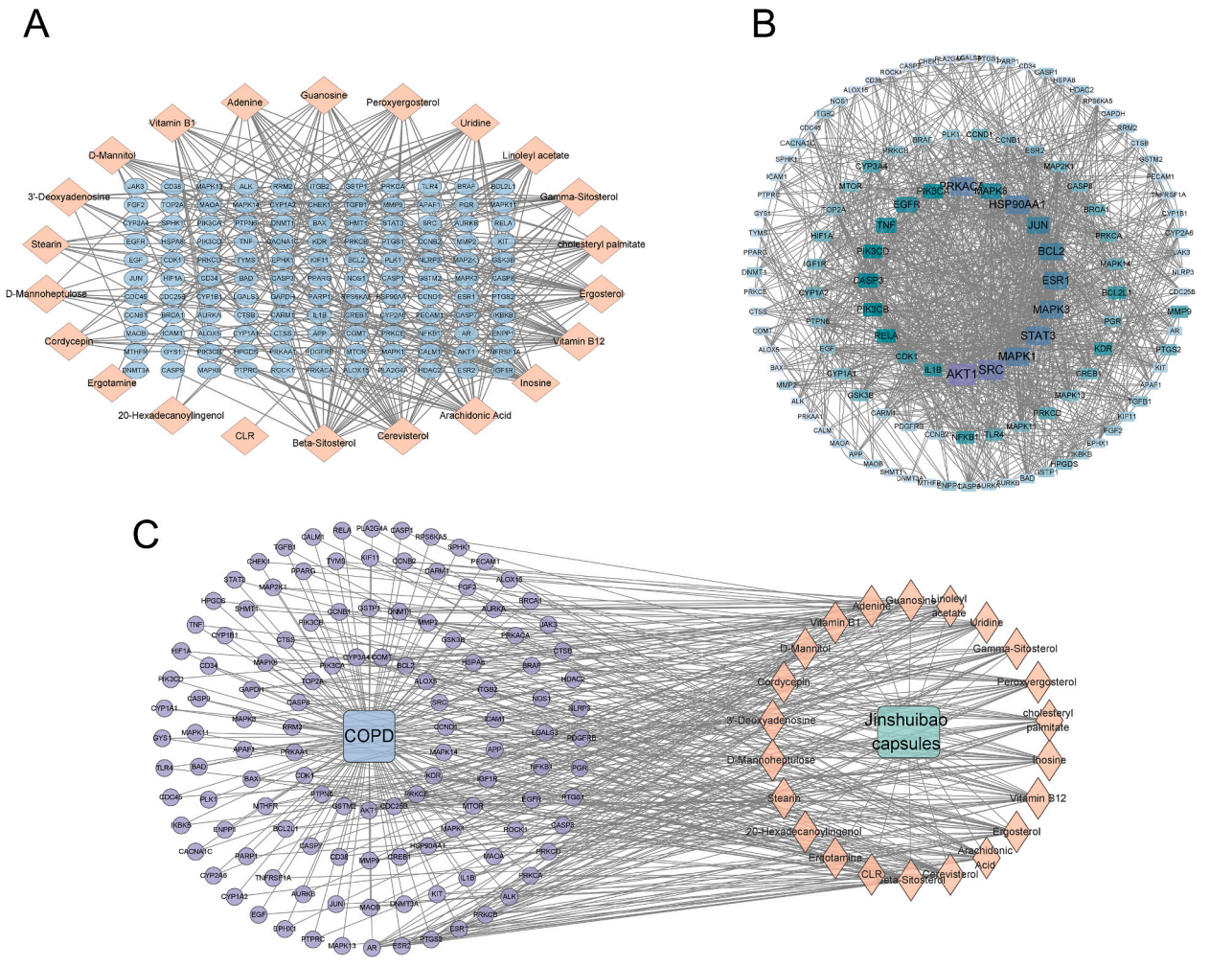

Fig. 19. Network construction. (A) compound-target intersection network. (B) hub nodes ranked by degree value. (C) drug-targets-disease network.

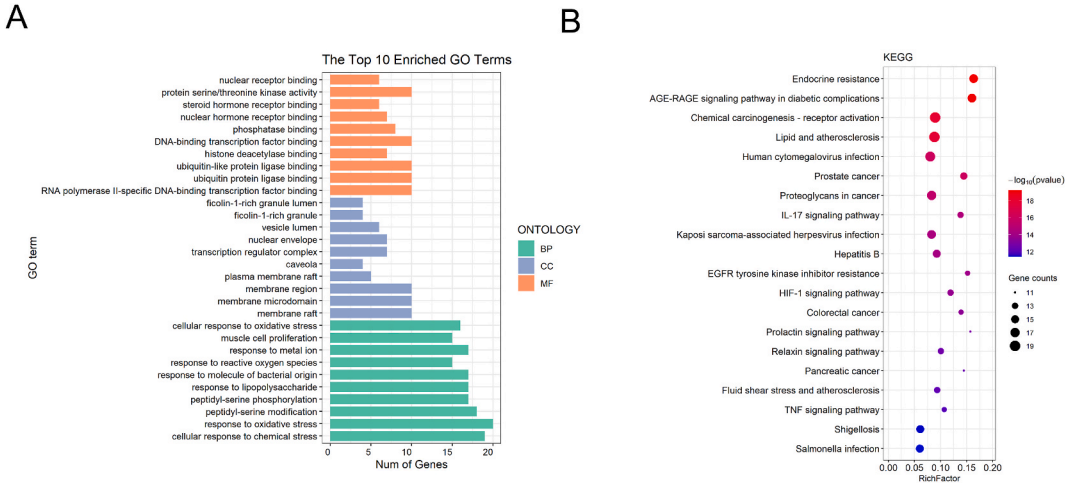

Fig. 20. GO and KEGG enrichment. (A) GO functional annotation. (B) KEGG enrichment analysis.

pred levels, FEV1/FVC ratio, as well as FEV1 and FVC levels in comparison to CPT treatment in isolation. At last, there were no serious AEs, and sensitivity analysis confirmed the robustness of the results. Larger clinical trials may provide more definite results.

All participants in the studies received daily doses of Jinshuibao capsule, consistent with standard clinical practice. The trials varied in duration, ranging from 2 weeks to 1 year. The source of heterogeneity was identified through subgroup analyses. The subgroup analyses were conducted according to different treatment courses, patients' age, and COPD courses, while no consistency was noted in the results of the subgroup analyses. Therefore, the results of the subgroup analyses need to be interpreted with caution. However, we still cannot fully determine the optimal treatment course and the advantages of combination therapy using Jinshuibao capsules.

The majority of the included studies did not report AEs in detail, and we could not draw conclusions regarding the safety and tolerability of Jinshuibao capsules. The majority of the included studies did not report AEs in detail, and we could not draw conclusions regarding the safety and tolerability of Jinshuibao capsules. In contrast to the stringent regulatory procedures governing the introduction of new pharmaceuticals, TCM herbal preparations in China are not held to the same standards of regulatory scrutiny. This study presents evidence supporting the efficacy and safety of Jinshuibao capsule in the treatment of patients with COPD. However, the study does not endorse the exclusive clinical use of Jinshuibao capsules, as none of the studies included a placebo control group. The study may provide a reliable reference for the application of Jinshuibao capsules in clinical practice.

Despite conducting subgroup analysis, the persistence of heterogeneity in the study remains evident. This heterogeneity is attributed to both clinical and methodological factors. The overall methodology quality of the included studies was found to be lacking. The clinical heterogeneity observed may be a result of varying underlying conditions and interventions. It is worth noting that the subgroup analyses were conducted post hoc, which may have impacted the reliability of the results.

The limitations of the current study are as follows: First, although we conducted a comprehensive literature search, there might still be unpublished RCTs that were not retrieved, which may have certain influences on the results. Second, all the included RCTs were conducted only in China; their methodological quality was generally low, and none of the RCTs mentioned blinding methods or assignment concealment, which might lead to selection bias, implementation bias, or measurement bias. Third, subgroup analysis based on age, course of treatment, and course of COPD might lead to certain deviations in the research. Fourth, the sample sizes of the included RCTs were small, which might negatively influence the reliability of the results. Fifth, the safety of long-term administration of Jinshuibao capsules need to be investigated. However, the majority of the included studies have not reported AEs, and those reported AEs after the drug administration had not systematically collected data related to AEs. Therefore, the safety of Jinshuibao capsules could not be analyzed. Finally, all the eligible studies were not publicly registered. Thus, the possibility of publication bias could not be ruled out, and the existence of publication bias might negatively influence the reliability and accuracy of the results.

In order to promote the applicability of the proposed therapy, it is first highly essential to carry out further multi-center, large sample-sized clinical trials. Second, further double-blind placebo-controlled randomized clinical trials on TCM should be conducted to effectively improve research quality. Last but not least, the safety of TCM needs to be investigated, and the relevant data should be collected and analyzed systematically.

Oxidative stress and chronic inflammation are widely recognized as significant pathological characteristics of COPD. This study aims to investigate the potential impact and underlying mechanism of Jinshuibao capsules on COPD through network pharmacology prediction analysis. Encouraging advancements have been made in both fundamental research and therapeutic applications of the compounds present in Jinshuibao capsules. Arachidonic acid, a 20-carbon polyunsaturated fatty acid, has been found to exhibit diverse pharmacological properties. Notably, a recent study demonstrated that arachidonic acid exacerbates inflammation expression in COPD [57]. Ergosterol, a fungal sterol with limited presence in other organisms, has demonstrated the potential to modulate macrophage polarization, enhance lung function, and suppress the infiltration of inflammatory cells in the lungs of a rat model resembling COPD [58]. Additionally, Cordyceps has been found to significantly alleviate airway wall thickening, including collagen deposition, fibrosis, smooth muscle hypertrophy, and epithelial hyperplasia in rats with COPD [59]. Collectively, the active constituents present in Jinshuibao capsules exhibit diverse pharmacological effects.

The top five targets, namely AKT1, SRC, MAPK1, STAT3, and MAPK3, play a pivotal role in the PPI network and serve as the central targets of Jinshuibao capsules for the management of stable COPD. AKT is involved in the regulation of various cellular functions, including cell survival, proliferation, metabolism, angiogenesis, and migration [60]. Consistent with the activation of AKT in human COPD, an increase in Akt phosphorylation has been observed in both rat models of COPD and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) [61]. Consequently, it has been suggested that PI3K/AKT inhibitors may represent a novel therapeutic approach for COPD treatment [62]. The SRC protein, which belongs to the family of non-receptor protein tyrosine kinases known as SRC family kinases, has been shown in vivo to activate the downstream MAPK signaling pathway. This activation of the MAPK pathway by SRC protein leads to an exacerbation of oxidative stress and cellular inflammation in rats with COPD. The MAPK signaling pathway is known to be involved in intracellular oxidative stress and plays a crucial role in the induction of cell apoptosis. Notably, the activation of p38 MAPK has been linked to COPD in humans [63]. Clinical trials have demonstrated that treatment with a p38 MAPK inhibitor for a duration of 6 weeks can improve forced expiratory volume in 1 s (FEV1) in patients with COPD [64]. The molecule STAT3 played a crucial role in the regulation of inflammatory cytokine expression in a murine model of COPD. Furthermore, research discovered an increase in the expression of the STAT3 gene in COPD patients who smoke [65]. Additionally, the literature review provided evidence supporting the possibility of combining targets and ingredients.

Several studies also demonstrated the strong binding ability of certain therapeutic components and targets, confirming their effectiveness and authenticity. Moreover, in breast carcinoma cells, arachidonic acid was found to enhance the nuclear translocation of STAT3 and the expression of phosphorylated-STAT3 (P-STAT3), contributing to tumor proliferation [66]. Cordycepin, an active constituent of Cordyceps sinensis and Cordyceps militaris, has been found to regulate cellular apoptosis in BALB/c mice through the STAT3 signaling pathway, as demonstrated in a recent study [67]. Additionally, ergosterol has been shown to inhibit the nuclear factor

kappa-light-chain enhancer of the activated B cells (NF-κB) pathway induced by lipopolysaccharide (LPS) in microglia cells, potentially through the inhibition of the NF-κB, AKT, and MAPK signaling pathways [68]. However, to further validate these findings, it is imperative to conduct more laboratory experiments and large-scale clinical trials in the future.

In order to elucidate the biological functions of hub genes, an analysis of KEGG enrichment was conducted on the 121 hub genes using R software. The primary functional pathways associated with these key targets include the AGE-RAGE signaling pathway, IL-17 signaling pathway, HIF-1 signaling pathway, and TNF pathway. Evidence suggests that the receptor for advanced glycation end products (RAGE) plays a crucial role in driving chronic inflammation [69], which is a fundamental mechanism underlying COPD pathophysiology. Additionally, HIF-1α is found to be overexpressed in hypoxic environments and regulates cellular metabolism to adapt to low oxygen conditions. It has been determined that serum levels of HIF-1α are elevated in stable patients with COPD compared to the general population [70]. This is attributed to a feedback loop in which the EGFR/PI3K/AKT pathway, induced by lung inflammation, upregulates the expression of HIF-1α, ultimately exacerbating the condition of COPD. In recent times, IL-17 and TNF-α have garnered significant attention due to their proinflammatory role in the development of COPD. Numerous studies have provided evidence of IL-17's involvement in various aspects of COPD pathogenesis, such as airway inflammation, mucus secretion, epithelial-mesenchymal transition (EMT), and airway remodeling [71,72]. In conclusion, the treatment of stable COPD using Jinshuibao capsules exhibits the attributes of containing multiple components, targeting multiple factors, and affecting multiple pathways.

5. Conclusion

In conclusion, the concurrent use of Jinshuibao capsules and CPT may have a beneficial impact on individuals with stable COPD, leading to enhancements in lung function, oxygen saturation, immune response, and exhibiting antioxidant and anti-inflammatory attributes. The potential targets of Jinshuibao capsules in treating stable COPD may involve AKT1, SRC, MAPK1, STAT3, and MAPK3. However, it is important to note that the methodological quality of the included RCTs was generally low. Thus, it is important to note that the effectiveness and safety of Jinshuibao capsules cannot be definitively ascertained due to the aforementioned limitations. Consequently, it is advisable to exercise caution when interpreting the findings of this study. To thoroughly assess the effectiveness and safety of Jinshuibao capsules in the treatment of COPD, further rigorous RCTs and laboratory experiments are necessary.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Yongjun Yin: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yilan Wang:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis. **Ying Liu:** Methodology, Investigation, Data curation. **Fei Wang:** Writing – original draft, Software, Methodology, Funding acquisition. **Zhenxing Wang:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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