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Effect of emodin on acute lung injury: a meta-analysis of preclinical trials

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Abstract

Background Emodin has protective effects on acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). This meta-analysis intended to illustrate the efficacy of emodin on ALI/ARDS animal models.

Methods Relevant preclinical studies were searched on PubMed, EMBASE, and Web of Science. Standardized mean differences (SMDs) with corresponding confidence intervals (CIs) were used to compare lung injury scores, lung wet-to-dry weight ratios (W/D), myeloperoxidase (MPO), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-18, PaO_2, and $PaCO_2$ between the treatment and control groups. The article quality was appraised using the SYRCLE tool.

Results Twenty one studies published between 2014 and 2023 were enrolled. Compared with the control group, emodin significantly reduced lung injury scores (SMD: -3.63; 95% CI: -4.36, -2.90; $p < 0.00001$), W/D ratios (SMD: -3.23; 95% CI: -4.29, -2.16; $p < 0.00001$), and MPO levels (SMD: -2.96; 95% CI: -3.92, -1.99; $p < 0.00001$). Furthermore, emodin downregulated TNF-α (SMD: -3.04; 95% CI: -3.62, -2.47; $p < 0.00001$), IL-1β (SMD: -3.76; 95% CI: -4.65, -2.87; $p < 0.00001$), IL-6 (SMD: -3.19; 95% CI: -3.95, -2.43; $p < 0.00001$), and IL-18 levels (SMD: -4.83; 95% CI: -6.10, -3.57; $p < 0.00001$). Emodin improved gas exchange dysfunction, increased PaO_2 (SMD: 3.76; 95% CI: 2.41, 5.11; $p < 0.00001$), and decreased $PaCO_2$ (SMD: -3.83; 95% CI: -4.90, -2.76; $p < 0.00001$). Sensitivity analyses and stratified analyses were conducted for outcome measures with heterogeneity.

Conclusions Emodin treatment can effectively reduce the severity of ALI in animal models. Additional animal investigations and clinical trials involving human subjects are imperative.

Keywords Emodin, Acute lung injury, Acute respiratory distress syndrome, Animal model, Meta-analysis

Introduction

ALI/ARDS is a heterogeneous disease attributed to various pulmonary and extra-pulmonary factors, such as severe sepsis caused by endotoxins, trauma, and burns [1]. Its clinical presentations encompass alveolar damage, acute diffuse inflammation, interstitial edema, enhanced pulmonary capillary permeability, and inflammatory infiltration [2]. Acute and progressive hypoxemia and ARDS are common in ALI patients [3]. According to the international epidemiological survey of "Lung Safe", the mortality rate of ARDS is 34.9%-46.1%, and its prevalence accounts for 10.4% of all ICU admissions globally [4]. Despite extensive research efforts on exploring new treatment modalities for ARDS, effective therapeutic interventions are still lacking [1]. In common mammals such

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as rats and mice, ALI/ARDS can be simulated by various methods, including cecal ligation and puncture (CLP) [5], intratracheal instillation [6], intraperitoneal injection [7] or tail vein injection [8] of lipopolysaccharide (LPS), intraperitoneal injection of taurocholate sodium [9], and pulmonary artery occlusion and reperfusion [10]. Therefore, systematic reviews of preclinical trials may enhance our understanding of the characteristics and treatment of human ALI/ARDS.

Emodin is a natural anthraquinone derivative, chemically known as 1, 3, 8 – trihydroxy – 6-methylanthraquinone, with a molecular weight of 270.23 [8]. It is extracted from various plants, such as rhubarb [11], Polygonum cuspidatum [12], Polygonum multiflorum [13], and Cassia obtusifolia [14]. Numerous prior investigations have established that emodin has a wide range of pharmacological effects against inflammation [6], oxidant stress [15], tumor [16], bacteria [17], viral infections [18], as well as immune regulation [13]. Preclinical studies have confirmed the protective effect of emodin on ALI [10, 19, 20], suggesting emodin may be a potential valuable therapeutic option for ALI. However, it is hard to assess the overall therapeutic effect because of different research methods. Currently, there is no systematic review of the role of emodin in ALI. This study was conducted to systematically evaluate the quality and comprehensive evidence of preclinical articles on the functions of emodin on different animal models of ALI.

Materials and methods

Search strategy

Systematic reviews and meta-analyses were conducted according to the PRISMA guidelines [21]. PubMed, EMBASE, and Web of Science were searched up to October 23, 2023 to filter preclinical articles related to the effect of emodin on animal models of ALI. The search terms involved "[emodin (title/abstract)] and [acute lung injury (title/abstract) or acute respiratory distress syndrome (title/abstract)]" (Appendix 1).

Eligibility criteria

The inclusion criteria were established as per the PICOS protocol: 1) animal model of ALI; 2) the emodin experimental group; 3) with a placebo control group; 4) exploring the efficacy of emodin on the animal model of ALI; 5) results including lung injury score, MPO, W/D ratio, TNF-α, IL-1β, IL-6, IL-18, PaO_2, and $PaCO_2$; 6) results expressed or converted to mean and standard deviation; 7) published in English.

Exclusion criteria covered: 1) review articles, letters, and case reports, repeatedly published articles and abstracts without full text; 2) observational studies and non-randomized controlled studies; 3) ex vivo studies, in vitro studies, human studies, and in silico studies; 4) animals treated with other drugs or surgical procedures; 5) studies testing the effects of emodin in combination with other chemicals or drugs.

Data collection

All data were independently extracted by two reviewers (Liu and Zhang). Any discrepancies were addressed through discussion with a third reviewer (Tang). The collected information encompassed: 1) author and publication year; 2) animal model: species, age, gender, and modeling method); 3) emodin treatment: intervention dose (initial and total dose), treatment time, and administration route; 4) evaluation time; 5) outcome measurement; 6) detection specimen; 7) quality score. If a study contained more than one experimental group, the experimental groups would be differentiated according to animal species, emodin doses, treatment times, evaluation time points, and detection specimen sources, and compared with the control group. For continuous variables, statistical calculations were performed using mean and standard deviation. For graphical data, Getdata Graph Digitizer was used to check the mean and standard deviation values of high magnification. Standard deviations not reported directly were calculated by multiplying the reported mean standard error (SEM) by the square root of the group size.

Quality assessment

Quality assessment was undertaken by the same two reviewers independently using the SYRCLE (adapted from the Cochrane tool) [22]. Any disputes were addressed through discussion with a third reviewer (Tang).

Statistical analysis

Review Manager (RevMan) 5.4 (Cochrane Library, London, UK) and STATA 17 (StataCorp, College Station, TX, USA) were adopted for statistical analysis. As the primary outcome was continuous variables, standard mean difference (SMD) and 95% confidence interval (95% CI) were utilized to present the effect size. I^2 was used to test the heterogeneity between studies. $I^2 < 50\%$ denoted low heterogeneity and the fixed-effect model was used, otherwise, for high heterogeneity, the random-effect model was used. Sensitivity analysis was implemented using the leave-one-out method, and stratified meta-analysis was

performed to confirm the influence of methodological differences. Egger's linear regression test was utilized to determine publication bias. $p < 0.05$ implied statistically significant.

Results

Study selection

The flowchart of literature search process is displayed in Fig. 1. 35 articles from PubMed, 69 from EMBASE, and 60 from Web of Science were searched. After eliminating duplicates, 131 articles were left. Based on the abstract and/or title, we excluded 94 irrelevant reports and selected 37 articles. Then, we read the full texts, of which 17 studies were excluded due to cell experiments, reporting different outcome indicators, and irrelevant or unclear interventions. Finally, 20 articles published from 2014 to 2023 were enrolled [5–10, 19, 20, 23–34].

Study characteristics

We included 20 articles, of which one [25] contained two studies, so there were 21 studies. Among the included animal models, there were 3 BALB/c mice, 11 SD rats, 4 Wistar rats, 1 Lewis rat, 1 C57/black mouse, and 1 C57BL/6J mouse. 14 studies reported animal age, ranging from 5 to 8 weeks. Among these studies, there were several methods of ALI modeling: 2 CLP, 4 abdominal injections of LPS, 3 intratracheal injections of LPS, 2 intravenous injections of LPS, 9 severe acute pancreatitis, and 1 pulmonary ischemia–reperfusion injury. 9 studies initiated emodin treatment before ALI and 12 studies after ALI. For the routes of emodin administration, 5 studies adopted abdominal injections and 16 used gavages. 13 studies adopted single-dose administration and 8 studies used multiple-dose administration. Detailed characteristics are exhibited in Table 1.

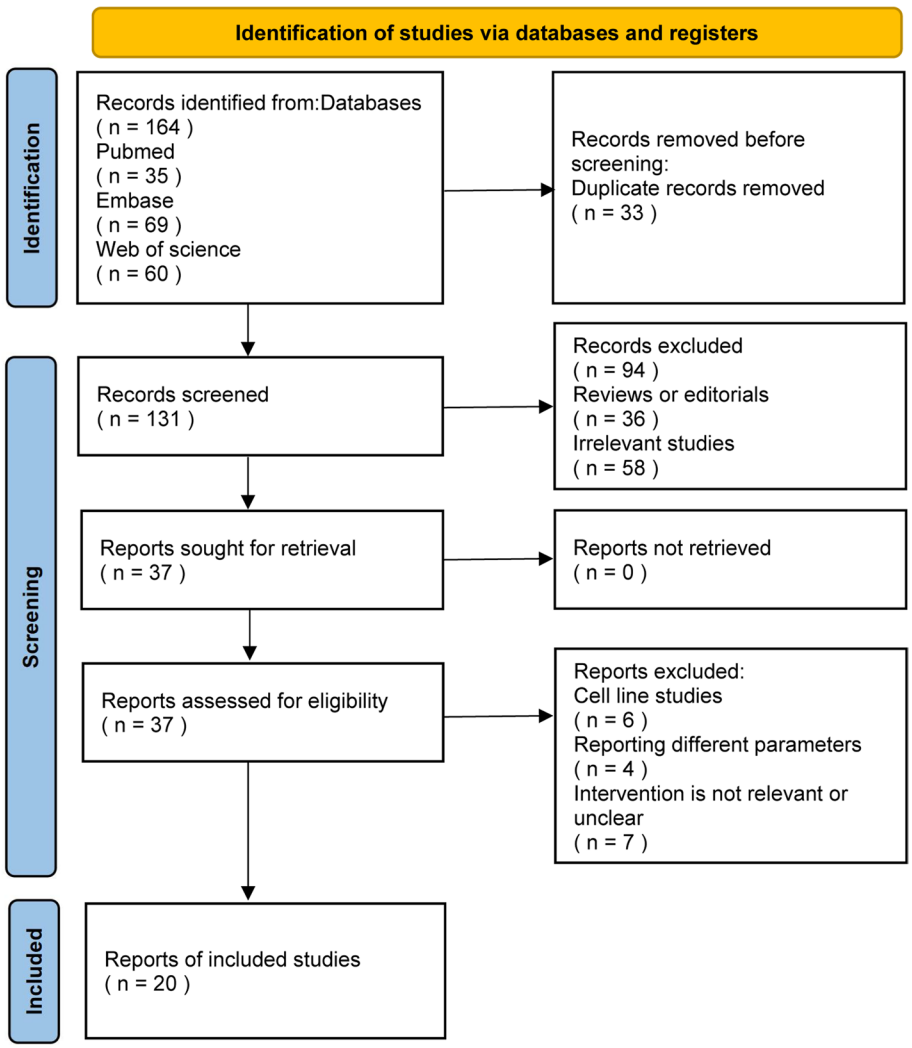


Fig. 1 PRISMA flow diagram for review and selection process of studies included in meta-analysis of Emodin in rodent models of ALI

Table 1 Characteristics of the included studies

Author, Year	Animal	Gender	Age (weeks)	ALL model	Initial dose (mg/kg)	Total dose (mg/kg)	Treatment point	Route	Assessment time(h)	Detection specimen	Outcomes
Xiao,2014 [26]	BALB/c mice	Male	6–8	LPS,i.t	100	700	after ALL	intragastric administration	72	lung tissue, balf	a, b, c, d, e, f
Xu,2016 [30]	Wistar rats	Male	6	SAP	25	25	after ALL	intragastric administration	6,12,24	lung tissue, serum	a, b, d, h, i
Cui,2017 [29]	SD rats	Male	8	SAP	10	10	after ALL	i.p	24	lung tissue	b
Yan,2019 [28]	BALB/c mice	Male	6–8	LPS,i.p	20	20	before ALI	i.p	18	lung tissue	c, d, f
Gao,2020 [9]	SD rats	Male	NR	SAP	25	25	after ALL	intragastric administration	6	lung tissue, balf	b, c, d, e, f
Guo,2020 [5]	SD rats	Male	adult	CLP	35	175	after ALL	intragastric administration	12,24	lung tissue, serum	b, d, f
Li,2020 [34]	Wistar rats	Male	8	LPS,thr-ough the caudal vein	20,50	100,250	before ALI	intragastric administration	5	lung tissue, balf	b, d, e, f
Liu,2020 [6]	C57/black mice	Male	8	LPS,i.t	5,10,20	5,10,20	before ALI	i.p	6	balf	b
Mei,2020 [8]	SD rats	Male	adult	LPS,thr-ough the tail vein	5,10,20	5,10,20	before ALI	i.p	5	lung tissue	a, d, e
Xu,2020 [31]	SD rats	Male	6–8	SAP	40,80	40,80	after ALL	intragastric administration	6,24	lung tissue, serum	a, d, h, i
Jiang,2021 [23]	Wistar rats	Male	6	SAP	40	40	after ALL	intragastric administration	24	lung tissue, serum	a, e, g
Xu,2021 [32]	SD rats	Male	8	SAP	40,80	40,80	after ALL	intragastric administration	6,24	lung tissue, serum	a, d, f, h, i
Xu,2021 [33]	SD rats	Male	NR	SAP	40	80	after ALL	intragastric administration	24	lung tissue, serum	a, e, h, i
Hu,2022 [19]	SD rats	Male	NR	SAP	10	10	after ALL	intragastric administration	24	lung tissue	a, c, d
Liu,2022 [20]	SD rats	Male	6	CLP	35	175	after ALL	intragastric administration	24	balf	c, d, e, f
Liu,2022 [24]	SD rats	Male	NR	LPS,i.p	20,40,80	20,40,80	before ALI	intragastric administration	6	lung tissue, serum	c, e, g
Wang,2022 [7]	Wistar rats	Male	NR	LPS,i.p	40,60,80	40,60,80	before ALI	intragastric administration	12	lung tissue, serum,balf	a, d, e, f, g
Wu,2022 [25]	SD rats	Male	NR	SAP	10	20	after ALL	intragastric administration	24	lung tissue, balf	a, c, d, e, g
	C57BL/6J mice	NR	NR	LPS,i.p	10	20	after ALL	intragastric administration	24	lung tissue, balf	a, c, d, e, g
Xie,2022 [27]	BALB/c mice	Male	5–6	LPS,i.t	20,40	140,280	before ALI	intragastric administration	8	lung tissue, balf	b, d, f
Jin,2023 [10]	Lewis rats	Male	11	LIRI	40	40	before ALI	i.p	2	lung tissue, serum	a, b, d, e, f

Abbreviations: *SD* Sprague–Dawley, *NR* not report, *LPS* Lipopolysaccharide, *i.t*. Intratracheal injection, *i. p* Intraperitoneal injection, *SAP* severe acute pancreatitis, *CLP* cecal ligation and puncture, *LIRI* Limb ischemia–reperfusion injury, *ALI* acute lung injure, *balf* bronchoalveolar lavage fluid, *h* hour, *d* day, *W/D* Lung wet–dry weight ratio, *MPO* Myeloperoxidase, *TNF–α* Tumor necrosis factor–α, *IL–1β* Interleukin–1β, *IL–6* Interleukin–6, *IL–18* Interleukin–18, a, Lung injury score, b W/D, c MPO, d, TNF-α, e, IL-1β, f, IL-6, g, IL-18, h, PaO_2, i, $PaCO_2$

Quality assessment

The quality assessment results are detailed in Table 2. A high score indicates high methodological quality. In our study, the research scores ranged from 4 to 6. The reported baseline characteristics between the two groups were similar in all studies, without incomplete outcome data, nor biases in the selection of outcome recording or other sources. All studies used randomization methods for animal grouping but no specific method was mentioned. No study described allocation concealment or blinding for outcome evaluators, animal breeders, and researchers.

Meta-analysis

Emodin significantly reduced lung injury scores (SMD: -3.63; 95% CI: -4.36, -2.90; $p<0.00001$, 11 articles, 18 comparisons, Fig. 2A), with high heterogeneity ($I^2=62\%$; $p=0.0002$). Emodin diminished the W/D ratio (SMD: -3.23; 95% CI: -4.29, -2.16; $p<0.00001$, 8 articles, 13 comparisons, Fig. 2B), with notable heterogeneity ($I^2=86\%$; $p<0.00001$). Emodin downregulated MPO (SMD: -2.96; 95% CI: -3.92, -1.99; $p<0.00001$, 9 articles, 13 comparisons, Fig. 2C), with marked heterogeneity ($I^2=79\%$; $p<0.00001$). Emodin downregulated TNF-α (SMD: -3.04; 95% CI: -3.62, -2.47; $p<0.00001$, 16 articles, 32 comparisons, Fig. 2D), with significant heterogeneity ($I^2=73\%$; $p<0.00001$). Emodin downregulated IL-1β (SMD: -3.76; 95% CI: -4.65, -2.87; $p<0.00001$, 12 articles, 26 comparisons, Fig. 2E) with significant heterogeneity ($I^2=83\%$; $p<0.00001$). Emodin downregulated IL-6 (SMD = -3.19; 95% CI: -3.95, -2.43; $p<0.00001$, 10 studies, 21 comparisons, Fig. 2F) with notable heterogeneity ($I^2=76\%$; $p<0.00001$). Emodin downregulated IL-18 (SMD: -4.83; 95% CI: -6.10, -3.57; $p<0.00001$, 4 articles, 8 comparisons, Fig. 2G) with marked heterogeneity ($I^2=64\%$; $p=0.007$). Emodin increased PaO_2 (SMD = 3.76; 95% CI: 2.41, 5.11; $p<0.00001$, 4 articles, 8 comparisons, Fig. 2H) with notable heterogeneity ($I^2=75\%$, $p=0.0002$). Emodin reduced $PaCO_2$ (SMD = -3.83; 95% CI: -4.90, -2.76; $p<0.00001$, 4 articles, 8 comparisons, F ig. 2I) with notable heterogeneity ($I^2=58\%$, $p=0.02$).

Stratified analyses

Stratified analyses were performed based on animal species, ALI modeling methods, emodin treatment time points, administration routes, dosing frequency, total emodin dose, and detection specimen sources. For lung injury scores, there were significant differences

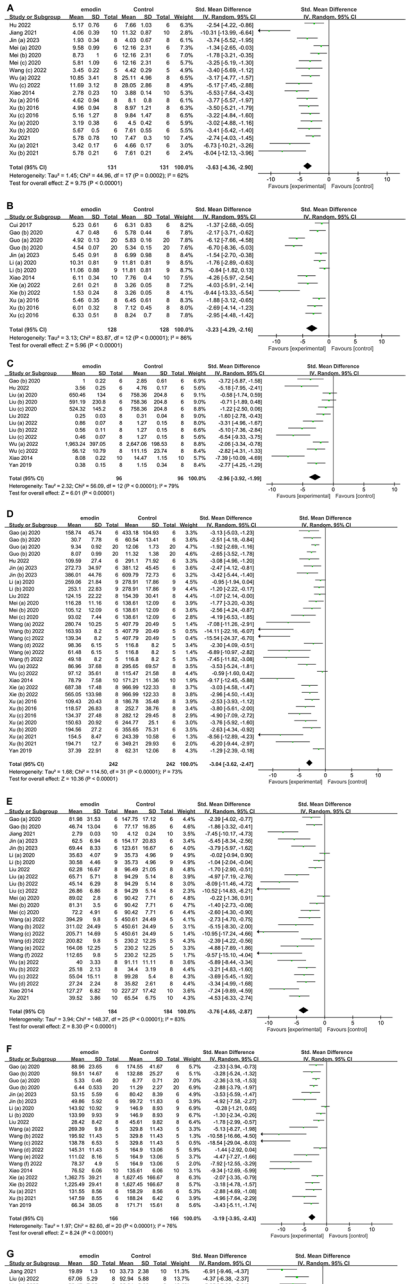
Table 2 Methodological quality of studies

Author, Year	1	2	3	4	5	6	7	8	9	10	Score
Xiao,2014 [26]	※	+	※	※	※	+	※	+	+	+	5
Xu,2016 [30]	※	+	※	※	※	+	※	+	+	+	5
Cui,2017 [29]	※	+	※	+	※	※	※	+	+	+	4
Yan,2019 [28]	※	+	※	※	※	※	※	+	+	+	4
Gao,2020 [9]	※	+	※	+	※	+	※	+	+	+	6
Guo,2020 [5]	※	+	※	※	※	+	※	+	+	+	5
Li,2020 [34]	※	+	※	+	※	+	※	+	+	+	6
Liu,2020 [6]	※	+	※	※	※	+	※	+	+	+	5
Mei,2020 [8]	※	+	※	※	※	+	※	+	+	+	5
Xu,2020 [31]	※	+	※	+	※	+	※	+	+	+	6
Jiang,2021 [23]	※	+	※	+	※	+	※	+	+	+	6
Xu,2021	※	+	※	+	※	※	※	+	+	+	5
Xu,2021	※	+	※	+	※	+	※	+	+	+	6
Hu,2022 [19]	※	+	※	※	※	+	※	+	+	+	5
Liu,2022	※	+	※	※	※	※	※	+	+	+	4
Liu,2022	※	+	※	+	※	+	※	+	+	+	6
Wang,2022 [7]	※	+	※	※	※	+	※	+	+	+	5
Wu,2022 [25]	※	+	※	+	※	+	※	+	+	+	6
	※	+	※	+	※	+	※	+	+	+	6
Xie,2022 [27]	※	+	※	+	※	+	※	+	+	+	6
Jin,2023 [10]	※	+	※	+	※	※	※	+	+	+	5

1-stochastic distribution sequence; 2-analogous baseline traits; 3-distribution concealment; 4-stochastic housing; 5-blinded intervening; 6-random collection for outcome measurement; 7-blinded evaluation of result; 8-unfinished outcome data; 9-selecting outcome recording; 10-else sources of bias

+: yes

no: ※: unclear



◀ **Fig. 2** **A** Forest plot analyzing the effect of emodin treatment of lung injury score. **B** Forest plot analyzing the effect of emodin treatment of W/D ratio. **C** Forest plot analyzing the effect of emodin treatment of MPO. **D** Forest plot analyzing the effect of emodin treatment of TNF − α. **E** Forest plot analyzing the effect of emodin treatment of IL − 1β. **F** Forest plot analyzing the effect of emodin treatment of IL − 6. **G** Forest plot analyzing the effect of emodin treatment of IL − 18. **H** Forest plot analyzing the effect of emodin treatment of PaO_2. **I** Forest plot analyzing the effect of emodin treatment of $PaCO_2$

in estimated effects on animal species, ALI modeling methods, emodin treatment time points, administration routes, dosing frequency, and total dose ($p < 0.05$) (Table S1). For the W/D ratio, there were significant differences in estimated effects on animal species, ALI modeling methods, emodin treatment time points, administration routes, dosing frequency, and total dose ($p < 0.05$) (Table S2). For MPO, there were significant differences in estimated effects on animal species, ALI modeling methods, emodin treatment time points, administration routes, dosing frequency, and detection specimen ($p < 0.05$); there was significant estimated effect only in the 10–50 mg/kg and > 200 mg/kg groups of total emodin dose ($p < 0.05$) (Table S3). For TNF-α, there were significant differences in estimated effects on ALI modeling methods, emodin treatment time points, administration routes, dosing frequency, total emodin dose, and detection specimen ($p < 0.05$); there was marked estimated effect except for the C57BL/6J mice group within animal species group ($p < 0.05$) (Table S4). For IL-1β, there were significant differences in estimated effects on animal species, ALI modeling methods, emodin treatment time points, administration routes, dosing frequency, and detection specimen ($p < 0.05$); there were notable estimated effects only in the 10–50 mg/kg and 50–200 mg/kg groups of total emodin dose ($p < 0.05$) (Table S5). For IL-6, there were significant differences in estimated effects on animal species, emodin treatment time points, administration routes, dosing frequency, total emodin dose, and detection specimen ($p < 0.05$); there was visible estimated effect except for the tail vein LPS injection group within ALI modeling methods group ($p < 0.05$) (Table S6). For IL-18, there were significant differences in estimated effects on animal species, ALI modeling methods, emodin treatment time points, dosing frequency, and detection specimen ($p < 0.05$) (Table S7). There were significant differences in estimated effects on animal species, dosing frequency, and total emodin dose for PaO_2 ($p < 0.05$) (Table S8) and $PaCO_2$ ($p < 0.05$) (Table S9).

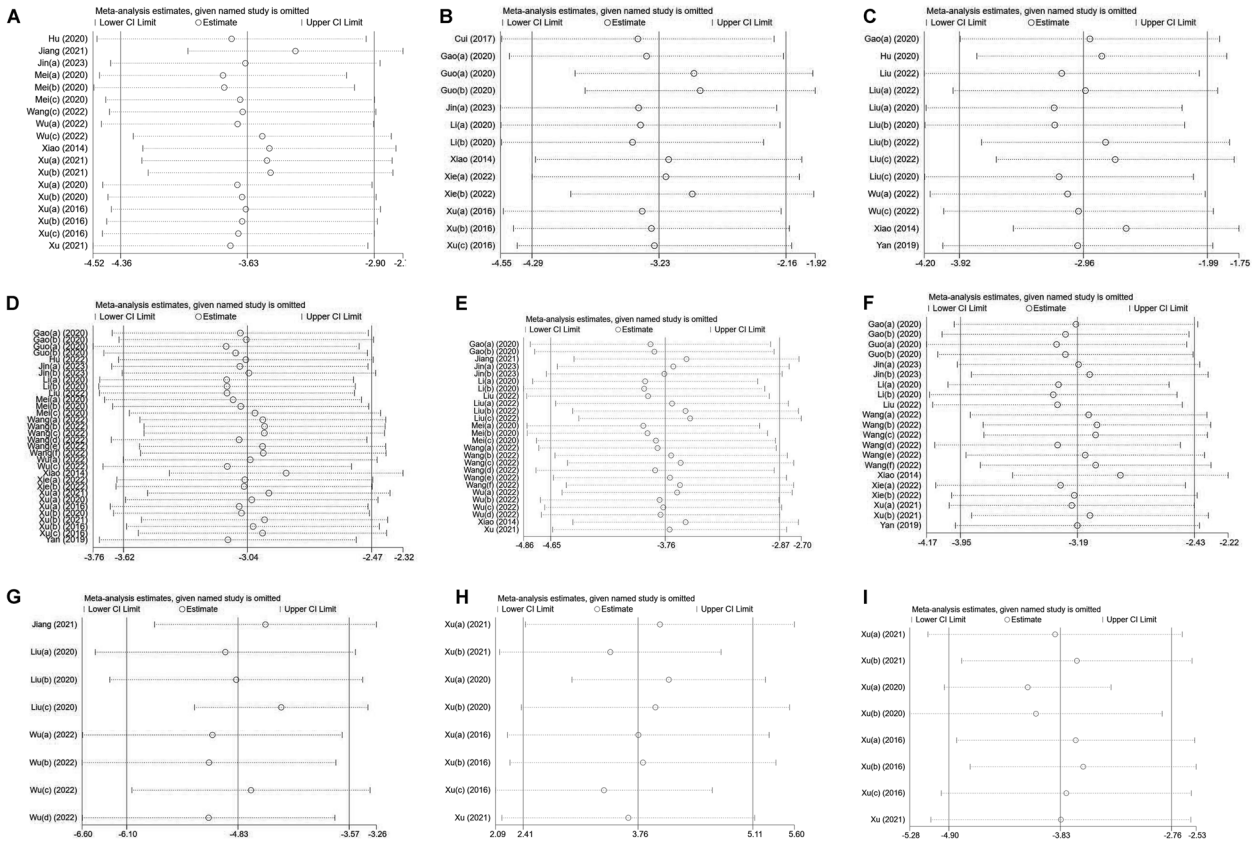


Fig. 3 **A** Sensitivity analysis of emodin treatment of lung injury score. **B** Sensitivity analysis of emodin treatment of W/D ratio. **C** Sensitivity analysis of emodin treatment of MPO. **D** Sensitivity analysis of emodin treatment of TNF – α. **E** Sensitivity analysis of emodin treatment of IL – 1β. **F** Sensitivity analysis of emodin treatment of IL – 6. **G** Sensitivity analysis of emodin treatment of IL – 18. **H** Sensitivity analysis of emodin treatment of PaO_2. **I** Sensitivity analysis of emodin treatment of $PaCO_2$

Sensitivity analysis

Sensitivity analyses were implemented to judge the result stability. Lung injury score (Fig. 3A), W/D ratio (Fig. 3B), MPO (Fig. 3C), TNF-α (Fig. 3D), IL-1β (Fig. 3E), IL-6 (Fig. 3F), IL-18 (Fig. 3G), PaO_2 (Fig. 3H), and $PaCO_2$ (Fig. 3I) were not significantly affected by any combined SMD studies.

Publication *bias*

According to the Egger test, there was a publication bias in the lung injury score ($p < 0.001$), W/D ratio ($p = 0.002$), MPO ($p < 0.001$), TNF-α ($p < 0.001$), IL-1β ($p < 0.001$), and IL-6 ($p < 0.001$). In this case, to estimate the missing studies and recalculate the effect estimates, we conducted a trim-and-fill analysis on the lung injury score, W/D, MPO, TNF-α, IL-1β, and IL-6, which showed no small sample effect (Figure S1A-F and Table S10).

Time-dose interval analysis

Lung injury score is a microscopic pathological scoring scale extensively adopted in preclinical trials to assess the severity of lung injury [35]. The time-dose effect diagram showed that the minimum dose of emodin to improve the lung injury score was 5 mg/kg ($p < 0.05$), and the maximum dose was 700 mg/kg ($p < 0.05$). The shortest expected duration of emodin administration to improve the lung injury score ($p < 0.01$) was 2 h, and the longest expected duration was 72 h ($p < 0.05$). The overall results disclosed that emodin at doses of 5–700 mg/kg and expected durations of 2–72 h showed relatively superior efficacy (Fig. 4).

Discussion

Summary of evidence

Emodin can alleviate tissue damage in various diseases. Studies have shown that emodin can effectively repress the inflammatory response and tissue damage in animal models of keratitis, nephritis, and hepatitis [36–38]. In terms of lung injury, emodin is also a promising protective agent in animal models of ALI [7, 24, 25]. To date, there has been no meta-analysis on the efficacy of emodin in animal models of ALI. Our research in animal

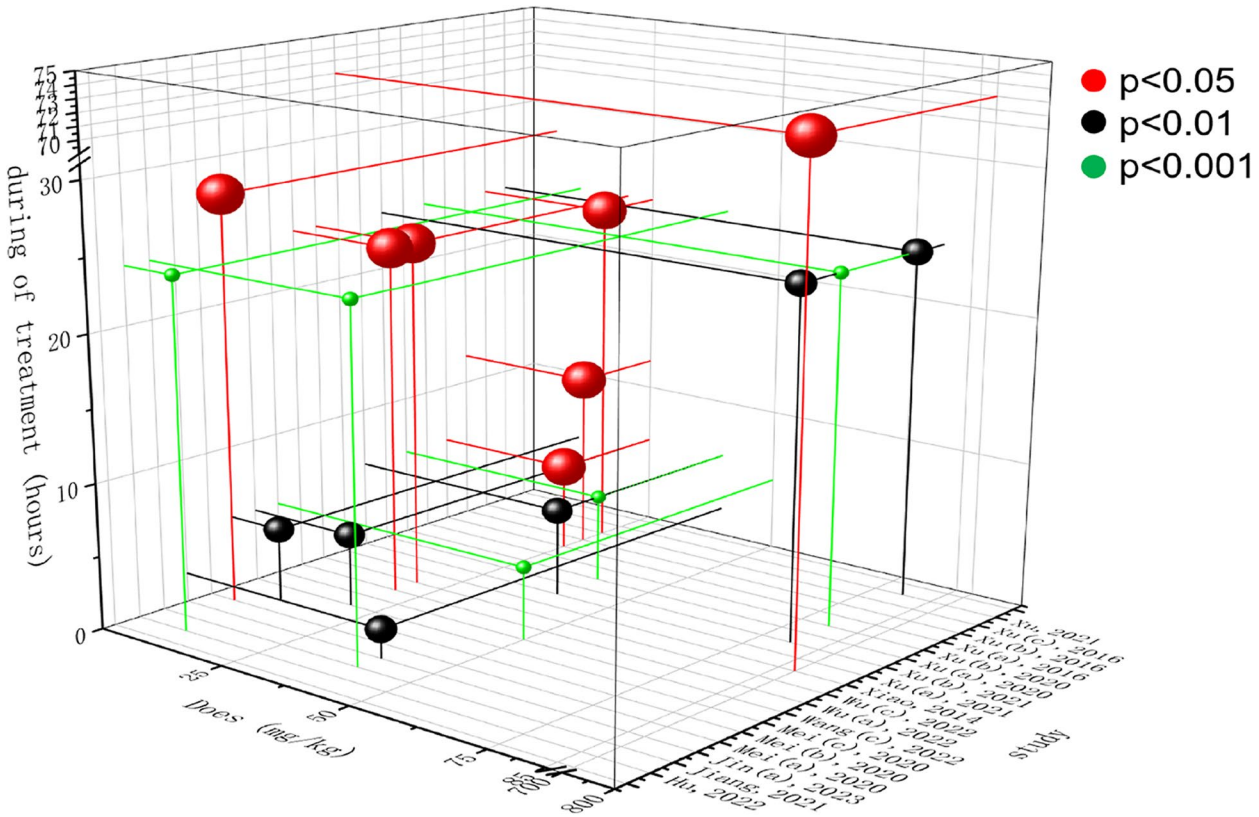


Fig. 4 Time-dose interval analysis scatter plot for lung injury score

models of ALI confirmed the therapeutic effect of emodin. The pooled results indicated that emodin could markedly reduce the lung injury score, directly proving the alleviation of emodin on lung injury [39]. The lung W/D ratio is widely used in animal experiments to evaluate pulmonary vascular permeability. Our analysis of the studies suggested a decrease in pulmonary vascular permeability, indicating that emodin could improve lung water clearance [35]. TNF-α, IL-1β, and IL-6 are major initiators of lung injury. These prominent cytokines actively recruit leukocytes to the lungs and accelerate lung injury by inducing the production of monocytes and macrophages [40, 41]. Additionally, an excessive release of IL-1β enhances the permeability of alveolar epithelium and vascular endothelial cells, leading to pulmonary edema [42]. Our study results indicated that emodin downregulated TNF-α, IL-1β, and IL-6 levels. Neutrophils-released MPO acts as a marker for neutrophil accumulation [43]. During inflammation, it is released into the extracellular fluid and participates in lipid oxidation. Increased MPO activity is recognized as a sign of neutrophil activation and accumulation, potentially resulting in tissue damage [44, 45]. Our study confirmed the downregulating effect of emodin on MPO. As a product of apoptosis, IL-18 triggers a cascade of inflammatory reactions to exacerbate the inflammatory response in ALI [46]. IL-18 expression is conversely correlated with long-term survival in patients with ARDS [47]. Our results unraveled that emodin downregulated IL-18 levels. Gas exchange dysfunction is an important pathological feature of ARDS, which manifests as hypoxemia and hypercapnia [48, 49]. Our analysis of the studies found that emodin increased PaO_2 level, decreased $PaCO_2$ level, and improved gas exchange. The meta-analysis of preclinical articles suggests that emodin could potentially be utilized to protect patients with ALI.

Possible mechanisms

Over the past several years, extensive research has been conducted to examine the effectiveness and mechanism of emodin in ALI. Emodin has shown great potential as a therapeutic drug for lung injury. Emodin treatment has demonstrated its potential to ameliorate the detrimental effects of LPS-induced ALI. It effectively alleviates pulmonary pathological damage, pulmonary edema, oxidative stress, the hypercoagulable state of alveoli, and fibrinolysis [6]. For ischemia–reperfusion-induced ALI,

emodin can mitigate alveolar damage and pulmonary edema and increase arterial oxygenation and dynamic compliance [10]. For CLP-induced ALI, emodin can reduce pulmonary cell apoptosis [5]. Emodin treatment also alleviates pulmonary edema and tissue damage and inhibits inflammation in SAP-ALL [23]. The therapeutic effects of emodin treatment may achieved by inhibiting the activation of NLRP3 inflammasome [9], the activation of NF-κB [6], the MAPK inflammatory pathway [27], the aggregation of inflammatory cells, the release of inflammatory cytokines [6], PMN infiltration, and promoting PMN apoptosis [29], tight junction proteins and aquaporin [5], and autophagy pathways [28]. These mechanisms will guide future exploration of the therapeutic targets of ALI. Therefore, we believe that emodin is a promising drug for ALI and deserves more research.

Interpretation of stratified analysis

Emodin significantly improved lung injury scores, W/D ratio, MPO, TNF-α, IL-1β, IL-6, IL-18, PaO_2, and $PaCO_2$. However, there was significant heterogeneity. Therefore, we conducted stratified analyses based on animal species, ALI modeling methods, emodin treatment time points, administration routes, dosing frequency, total doses, and detection specimens.

Animal species

The stratified analysis of animal species demonstrated that emodin treatment effectively improved lung injury scores, W/D ratio, MPO, IL-1β, IL-6, IL-18, PaO_2, and $PaCO_2$ in all animal species. Except for C57/black mice, the other animal species showed significantly improved TNF-α. Among all animal species, BALB/c mice exhibited the largest effect size. Due to fewer studies on BALB/c mice, the efficacy of emodin may be overestimated. Most studies selected SD rats and Wistar rats as research subjects. We cannot confirm which animal species is more suitable for ALI models. Therefore, the choice of animal species ought to be standardized in future investigations.

ALI modeling methods

The stratified analysis of the methods of inducing ALI modeling methods displayed that emodin treatment effectively improved lung injury scores, W/D ratio, MPO, TNF-α, IL-1β, and IL-18 in all induction method groups. Except for the LPS tail vein injection, the other groups showed significantly improved IL-6. We further found differences in the total dose of emodin within the LPS tail vein injection group [34], which were 20mg/kg and 50mg/kg. Emodin of 20mg/kg did not significantly improve IL-6, while 50mg/kg emodin significantly improved IL-6. Therefore, the difference in the total dose of emodin may explain the insignificant combined results. Among all ALI induction methods, most studies selected the construction of SAP-induced ALI, followed by LPS-induced ALI. The induction methods included LPS intratracheal perfusion, LPS intraperitoneal injection, and LPS tail vein injection. The LPS doses varied across studies; few studies selected CLP for modeling. However, CLP had the largest effect size. Previous studies have considered LPS as one of the most compatible methods for inducing animal models of ALI [50]. Furthermore, compared with CLP-induced ALI models, ALI models induced by LPS intratracheal perfusion are more similar to human ARDS in the acute stage [51]. However, regardless of the induction method, it can only simulate a part of the basic diseases of human ALI. Therefore, more studies are needed in the future to determine which method is more suitable for ALI research.

Time, frequency, route, and dose of emodin treatment

Firstly, the stratified analysis of the time points denoted that emodin treatment effectively improved lung injury scores, W/D ratio, MPO, TNF-α, IL-1β, IL-6, and IL-18 whether administered before or after ALL modeling. Therefore, emodin treatment had both preventive and therapeutic effects on ALI.

Secondly, the stratified analysis of emodin dosing frequency found that both single-dose and multiple-dose administration displayed effective improvement in all outcomes. Besides, multiple doses of emodin administration were superior to single-dose administration in improving lung injury scores, W/D ratio, MPO, PaO_2, and $PaCO_2$; single-dose administration was superior to multiple-dose administration in improving TNF-α, IL-1β, IL-6, and IL-18. More studies are needed to explore the optimal dosing frequency.

Thirdly, the stratified analysis of administration routes found that both intragastric and intraperitoneal injections of emodin showed effective improvement. Most studies used intragastric administration and had a larger effect size. Therefore, intragastric administration may be more suitable than intraperitoneal injection, and more studies are required to determine more appropriate administration routes.

Finally, our stratified analysis of the total dose of emodin found that emodin at all four doses effectively improved the lung injury score and TNF-α. At doses of 10–50 mg/kg, 50–200 mg/kg, and > 200 mg/kg, emodin effectively improved the W/D ratio and IL-6. At doses of 10–50 mg/kg and > 200 mg/kg, emodin effectively improved MPO. However, there was no significant improvement in MPO at the dose of 50–200 mg/kg. Additionally, MPO was markedly improved in two studies within the group of 50–200 mg/kg [20, 24], but the detection specimens were

lavage fluid and lung tissue, with large heterogeneity, which may lead to insignificant combined results. Emodin at > 200 mg/kg had no significant improvement in IL-1β. However, two studies within the group [26, 34] showed significant improvement effects on IL-1β. Moreover, there were differences in animal species, ALI modeling method, emodin treatment time point, and total emodin dose. High heterogeneity may lead to insignificant combined results. This conclusion should be interpreted with caution. At doses of 10–50 mg/kg and 50–200 mg/kg, emodin effectively improved PaO_2 and $PaCO_2$. In addition, emodin at < 10 mg/kg had no significant improvement in IL-1β and MPO. The above studies suggest a certain correlation between the effect size of emodin treatment and the total dose of emodin. Previous studies have shown that within a certain dose range, emodin dose-dependently inhibits lung inflammation in LPS-stimulated ARDS mice to improve lung injury [6]. The total dose of emodin was 5–700 mg/kg in the included studies. The groups with 50–200 mg/kg and > 200 mg/kg of emodin showed significant results. However, fewer studies chose these doses, and most studies chose 10–50 mg/kg. Therefore, we currently cannot determine the more appropriate emodin dose. To date, there is a lack of clinical trials on the effect of emodin on ALI/ARDS. Adequate time and research are essential for the clinical application of emodin in ALI/ARDS. Consequently, additional studies are warranted to ascertain the time, frequency, administration route, and dose of emodin.

Animal detection specimens

Stratified analysis based on lung tissue, serum, and lavage fluid specimens all confirmed the efficacy of emodin in acute lung injury. The degree of improvement in MPO activity in lung tissue specimens was superior to that in lavage fluid; the serum specimens showed a greater improvement in TNF-α levels compared to lavage fluid and lung tissue; in terms of the detection of IL-1β, IL-6, IL-18, serum specimens outperformed lung tissue, which in turn was better than lavage fluid. Lung tissue and serum may more sensitively reflect changes in these biomarkers, suggesting the need for further research to explore which type of specimen exhibits higher sensitivity for the detection of specific indicators.

Advantages and limitations

First, we endeavored to gather an extensive range of research in this field to obtain complete data; second, data extraction and evaluation were undertaken by two reviewers independently. Any disputes were addressed through consultation with a third reviewer. The meta-analysis of the differences in relevant articles confirmed the therapeutic effect of emodin in animal models of ALI. Sensitivity analysis confirmed stable results on lung injury score, W/D ratio, TNF-α, MPO, IL-1β, IL-6, IL-18, PaO_2 and $PaCO_2$. These findings signal that emodin has a certain positive effect on the treatment of ALI and is expected to provide a new treatment strategy for clinical ALI patients.

However, we only included studies published in English and already published studies, which omitted studies published in other languages and unpublished studies with negative results, which may exaggerate the effect. In addition, the published studies included were limited and presented with high heterogeneity, possibly due to insufficient sample size. Thereby, sufficient evidence is needed in future studies with large sample sizes.

Conclusion

Our meta-analysis confirmed that emodin treatment could improve the pathological conditions, pulmonary edema, and inflammation in animal models of ALI. These results offer valuable insights for future preclinical and clinical research to a certain extent and hold significant implications for human health.

Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
SMDs	Standardized mean differences
Cis	Confidence intervals
MPO	Myeloperoxidase

Supplementary Information

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Supplementary Material 1: Table S1 Stratified meta-analysis of lung injury score. Table S2 Stratified meta-analysis of lung wet-dry weight ratio. Table S3 Stratified meta-analysis of MPO. Table S4 Stratified meta-analysis of TNF-α. Table S5 Stratified meta-analysis of IL−1β. Table S6 Stratified meta-analysis of IL−6. Table S7 Stratified meta-analysis of IL−18. Table S8 Stratified meta-analysis of PaO_2. Table S9 Stratified meta-analysis of $PaCO_2$. Table S10 Publication bias evaluated used by Egger's.

Supplementary Material 2: Figure S1 (A) Trim-and-fill analysis of emodin treatment of lung injury score. (B)Trim-and-fill analysis of emodin treatment of W/D ratio. (C) Trim-and-fill analysis of emodin treatment of MPO. (D) Trim-and-fill analysis of emodin treatment of TNF−α. (E) Trim-and-fill analysis of emodin treatment of IL−1β. (F) Trim-and-fill analysis of emodin treatment of IL−6.

Supplementary Material 3.

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Authors' contributions

Writing—original draft preparation: [Yu Zhang]; Writing—review and editing: [Lei Liu]; Conceptualization: [Shan Zhou]; Methodology: [Xiao-Ren Tang]; Formal analysis and investigation: [Guo-Bing Jia and Guo-Long Yue]; Funding acquisition: [Cheng-Shi He and Lei Liu]; Resources: [Lei Liu]; Supervision: [Cheng-Shi He],and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

Declarations

Ethics approval and consent to participate
All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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