Trop J Nat Prod Res, September 2025; 9(9):4111 - 4116 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

Effects of Quercetin Administration on TNF-*α*, IL-6, Hydroxyproline, and Ashcroft Scores in Preclinical Study of Pulmonary Fibrosis: A Systematic Review and Meta-Analysis

Lukman N. Rahman[1], Gondo Mastutik[2], Anny S. Rahaju[2]

[1]*Master Program of Basic Medical Sciences, Faculty of Medicine, Universitas Airlangga, 60132 Surabaya, Indonesia.*
[2]*Department of Anatomical Pathology, Faculty of Medicine, Universitas Airlangga, 60132 Surabaya, Indonesia.*

ARTICLE INFO

Article history:
Received 16 March 2025
Revised 11 September 2025
Accepted 17 September 2025
Published online 01 October 2025

ABSTRACT

Lung fibrosis, a chronic respiratory diseases which is marked by alveolar fibrosis wall thickening with limited treatment options and progression to respiratory failure. There are molecular pathways of signaling associated with pulmonary fibrosis, namely the transforming growth factor beta (TGF-*β*)/Smad pathway, WNT/*β*-catenin pathway, and PI3K/Akt/mTOR pathway. Quercetin is a flavonoid which has demonstrated potential antifibrotic and anti-inflammatory actions. This compound suppressing reactive oxygen species dependent on Smad/*β*-catenin. These studies were designed to evaluate the potency of quercetin in treating pulmonary fibrosis. The studies were conducted via systematic review and meta-analysis following the PRISMA 2020 protocol. Quercetin was administered at a dose of 5–100 mg/kg for 21–42 days. Meta-analysis resulted in a significant reduction in TNF-*α* (SMD = −3.63; 95% CI: −6.07 to −1.18; p = 0.0037), IL-6 (SMD = −1.29; 95% CI: −1.90 to −0.68; p < 0.0001), hydroxyproline (SMD = −2.95; 95% CI: −4.16 to −1.74; p < 0.0001), and Ashcroft score (SMD = −5.90; 95% CI: −9.44 to −2.36; p = 0.0011). These findings indicate that quercetin effectively reduces inflammation and severity of fibrosis in a preclinical model of pulmonary fibrosis, highlighting its potential as a therapeutic candidate.

Keywords: Quercetin, Inflammatory Biomarkers, Pulmonary Fibrosis, Chronic Respiratory Diseases

Introduction

Lung fibrosis, a chronic respiratory disease which is marked by alveolar fibrosis wall thickening, due to impaired ventilation and insufficient air exchange, and breathing failure that occurs in the end. This heterogeneous condition exhibits diverse parenchymal damage patterns, Interstitial lung disease (ILD) in addition to idiopathic pulmonary fibrosis (IPF) representing which is worst and cannot be changed forms marked by escalating parenchymal fibrosis.[1] IPF prevalence ranges globally from 0.9-13.0/100,000, predominantly affecting males (7:3 ratio) and individuals >60 years.[2,3] Recent evidence indicates approximately 30% of fibrotic ILD patients develop progressive pulmonary fibrosis (PPF), a recently defined entity demonstrating IPF-like progression. PPF carries a grave prognosis (3-5 year median survival), significant socioeconomic burden, and irreversible clinical decline.[4] Current pathophysiological models attribute pulmonary fibrosis to dysregulated wound repair mechanisms, where heterogeneous etiological factors including thermal injury, infections, autoimmune processes, traumatic insults (surgical/non-surgical), foreign bodies, and malignancies elicit aberrant inflammatory and fibrogenic responses.[4]

*Corresponding author. Email: gondomastutik@fk.unair.ac.id
Tel: +62-82293924734

Citation: Rahman LN, Mastutik G, Rahaju AS. Effects of Quercetin Administration on TNF-α, IL-6, Hydroxyproline, and Ashcroft Scores in Preclinical Study of Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Trop J Nat Prod Res. 2025; 9(9) 4111 – 4116 https://doi.org/10.26538/tjnpr/v9i9.5

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

The pathways of molecular signalling at play in PF encompasses the TGF-*β*/Smad, WNT/*β*-catenin, and PI3K/Akt/mTOR signalling pathways. This process involves chemokine, cytokine, and growth factor-mediated damage to both parenchymal and inflammatory cells, driving disease pathogenesis.[5] During fibrotic progression, macrophages secrete essential mediators including Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumour Necrosis Factor-alpha (TNF-*α*), Transforming Growth Factor-beta (TGF-*β*), Matrix Metalloproteinases (MMPs), and Insulin-like Growth Factor-1 (IGF-1). That orchestrate fibroblast activation, endothelial proliferation, angiogenic signalling, and pathological extracellular matrix (ECM) deposition. Crucially, macrophages exert dual roles by simultaneously secreting tissue inhibitors of metalloproteinases (TIMPs) to counter-regulate fibrotic expansion.[4,6] Both the drugs nintedanib and pirfenidone received FDA approval for IPF management, with conditional recommendations in guidelines reflecting moderate confidence in their benefits despite therapeutic limitations.[7] As a result, clinical trials have recently reported significant adverse effects associated with pirfenidone, with gastrointestinal disorders (36%) and skin-related issues (28–32%) being the most common.[8] Similarly, nintedanib is known to cause diarrhoea as a common side effect (up to 63.2%).[9] This side effect has limited the extensive use of pirfenidone and nintedanib. Novel medications and treatment strategies are now needed to enhance IPF individual's quality of life and prognosis.[8,9]

Quercetin a naturally occurring flavonoid in plant-based foods demonstrates antiinflammatories, antioxidant, and immunomodulatory attributes. It inhibits bleomycin-induced epithelial-mesenchymal transition via Smad/*β*-catenin-dependent ROS suppression and exhibits antifibrotic effects through Nrf2-mediated redox balance modulation.[10,11] Quercetin's pleiotropic actions position it as a promising adjunctive candidate for fibrotic lung diseases, warranting further clinical investigation. A thorough assessment of the clinical feasibility of quercetin in idiopathic pulmonary fibrosis requires comprehensive evaluation of its therapeutic efficacy. Given this current lack of clinical evidence, exploring its mechanistic basis and potential efficacy through animal models remains an urgent priority.[11] To our

knowledge, only two prior meta-analyses have examined flavonoid efficacy in pulmonary fibrosis, with just one providing detailed focus on quercetin though notably omitting clinical fibrosis grading outcomes. While existing research has explored quercetin's anti-inflammatory properties broadly, no comprehensive synthesis has quantified its impact on specific inflammatory biomarkers (TNF-α, IL-6, hydroxyproline) or histopathological fibrosis severity via Ashcroft scoring in pulmonary disease contexts.[12,13] This systematic review aims to advance quercetin understanding and generate robust preclinical evidence to inform future clinical trials.

Materials and Methods

Following the recommendations established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), a systematic review was conducted.[14,15] The prospective registration for this systematic review was made on PROSPERO (CRD420250627865). Population, intervention, control group, and outcome (PICO) framework was used, where the population consisted of mice or rats induced with pulmonary fibrosis. The primary intervention analysed was all treatments involving quercetin, compared to a control group receiving standard care, placebo, or no treatment. Quantitative inflammatory biomarkers, such as TNF-α and IL-6, have been detected by the Enzyme-Linked Immunosorbent Assay (ELISA) from Bronchoalveolar Lavage Fluid (BALF), collagen content was biochemically assessment based on ELISA measurement of hydroxyproline in lung samples, and Ashcroft system of scoring was applied to semi-quantitatively assess degree of severity of lung fibrosis.[16]

Search Strategy and Selection Criteria

A methodical search for research was performed in the scientific databases PubMed, ProQuest, ScienceDirect, and Google Scholar, covering publications from January 1, 2010, to December 1, 2024. The search was performed using keywords and terms for "Quercetin" AND "lung fibrosis" OR "pulmonary fibrosis" AND "preclinical."

This meta-analysis included only experimental study designs comparing quercetin with a control in pulmonary fibrosis. Randomized controlled trials, in vitro, ex vivo, case-control, cross-sectional, cohort studies, and non-randomized controlled trials were excluded.

Data Extraction

This methodology outlines systematic data extraction from included studies, encompassing nine core parameters: (1) authorship, (2) publication year, (3) study design, (4) sample size, (5) pulmonary fibrosis induction method, (6) experimental intervention, (7) dosage regimen, (8) treatment duration, and (9) key outcomes. All authors independently verified data against full-text sources. Discrepancies underwent tiered resolution: primary discussion between involved parties, secondary multi-author consultation for persistent disagreements, and final majority adjudication when consensus proved unattainable.

Risk of Bias

Risk of bias assessment employed SYRCLE's validated framework, examining selection, performance, detection, attrition, reporting, and other systematic error domains in animal intervention studies. This review did not use any other tools as all included studies were preclinical or animal studies.[17]

Data Analysis

All included studies were tabulated to document: authorship, publication year, design, sample size, animal model, interventions, dosing, treatment duration, and quantitative outcomes (TNF-α/IL-6 ELISA biomarkers, hydroxyproline content, Ashcroft scores) presented as mean±SD. For meta-analytical consistency, data originally reported as median/IQR or median/range were converted to mean/SD using established Luo-Wan algorithms.[18,19] Standard Error of the Mean (SEM) values underwent SD conversion via SEM×√n computation Graphical data extraction employed WebPlotDigitizer and Meta-Analysis Accelerator, though direct author correspondence remains recommended for optimal numerical accuracy.[20-22]

The studies were conducted using R Studio 2024.04.2+764 and the current version of R 4.4.1, both developed by the R Core Team in Vienna, Austria.[23] The Standardized Mean Difference (SMD) with the relevant 95% confidence interval was used in the meta-analysis. The I^2 statistic was used to measure the heterogeneity among the included studies. When no substantial heterogeneity was found ($p \geq 0.05$ and $I^2 \leq 50\%$), a model with fixed effects was used. However, when sufficient heterogeneity was found ($p < 0.05$ or $I^2 > 50\%$), the model with random effects was employed. For all test data, a p-value of less than 0.05 was deemed statistically significant.[24]

Results and Discussion

Study selection process and quality assessment

The PRISMA 2020 flowchart (Figure 1) documents systematic literature screening. Initial retrieval identified 543 publications across four repositories: PubMed (n=26), ProQuest (n-10), ScienceDirect (n=486), and Google Scholar (n=21), with six studies qualifying for meta-analysis.

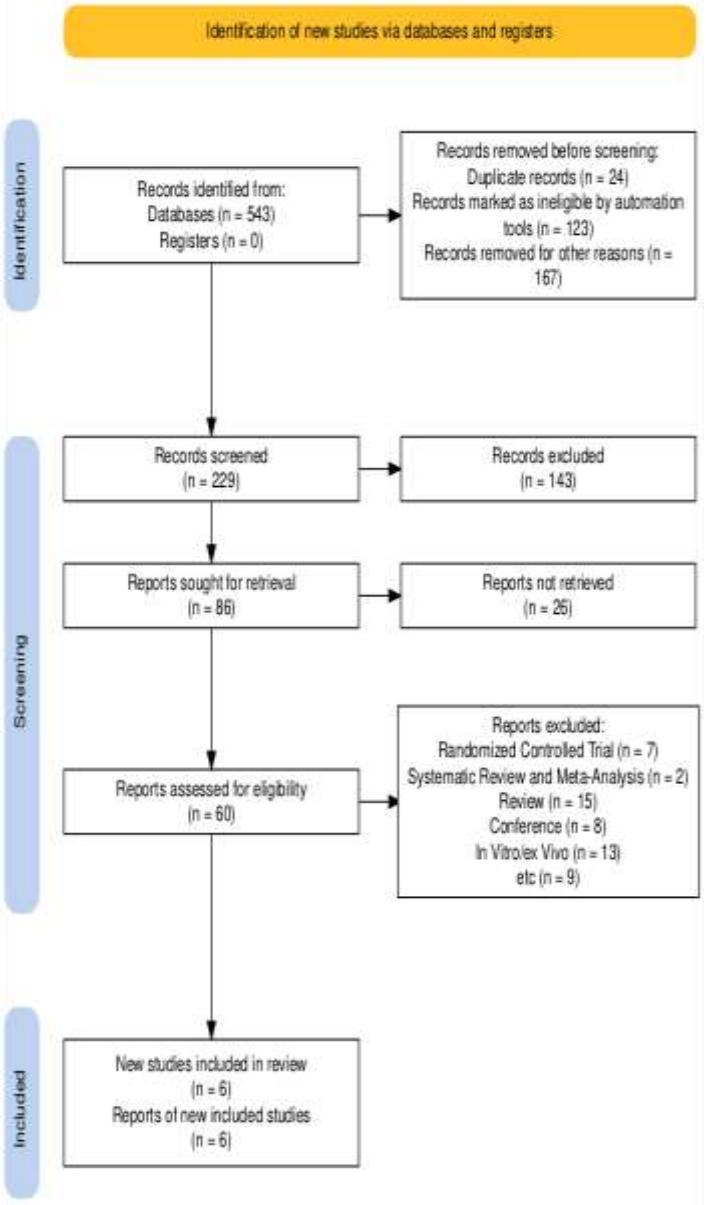

Figure 1: PRISMA flow diagram of the selection process[14,15]

Study Characteristics

Six studies involving 216 animals, including Sprague-Dawley and Wistar rats, as well as C57Bl/6 mice induced with pulmonary fibrosis through intratracheal bleomycin administration at doses of 5 U/kg, 6.5 U/kg, or 7.5 IU/kg, were included.[25-30] Experimental protocols employed intratracheal bleomycin administration (3 mg/mL concentration; 2.5 µL/g volume) or thoracic gamma irradiation (12 Gy dose). Quercetin interventions utilized variable dosing regimens (5, 10, 25, 50, 75, or 100 mg/kg) across treatment durations of 21, 28, or 42 days.[25-30] Comprehensive experimental parameters are detailed in Table 1.

Risk of Bias Assessment

SYRCLE's RoB tool evaluated six bias domains in animal intervention studies. Ten criteria were appraised: (1) random sequence generation, (2) baseline homogeneity, (3) allocation concealment, (4) randomized housing, (5) caregiver/investigator blinding, (6) randomized outcome assessment, (7) incomplete outcome management, (8) selective reporting, (9) other biases, and (10) conflicts of interest. Based on this evaluation, each research was classified as exhibiting low risk of bias, high risk of bias, or "some concerns.".[17] The SYRCLE risk assessment categorized included studies as: two with high bias risk, three raising methodological concerns, and one demonstrating low bias susceptibility. Figure 2 illustrates the complete bias profile distribution.

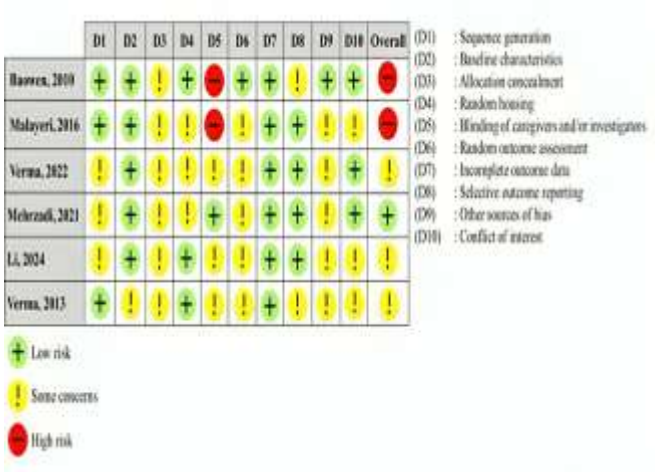

Figure 2: Risk of Bias (RoB) chart using the SYRCLE's tool for animal intervention studies

Outcome Results

Our preclinical meta-analysis showed the significant potential of quercetin in reducing key inflammatory biomarkers in pulmonary fibrosis. For TNF-*α*, a random-effects meta-analysis of five studies (112 animals) convincingly showed a significant decrease in levels in the quercetin intervention group compared to the control group (SMD = -3.63; 95% CI: -6.07 to -1.18; p = 0.0037; Figure 3), although substantial heterogeneity was observed (I^2=91.4%). Similarly, for Interleukin-6 (IL-6), two studies (52 animals) reported a significant quercetin-mediated decrease (SMD = -1.29; 95% CI: -1.90 to -0.68; p < 0.0001; Figure 4), with minimal heterogeneity (I^2=0.0%).[25-27] This finding is very important considering the pathophysiology of fibrosis of the lung is a progressive condition that results from an inflammatory cascade within the bronchial and alveolar epithelium. Cytokine and growth factor dysregulation are key mechanisms driving the development of this disease, which ultimately manifests itself through fibroblast hyperproliferation, pathological extracellular matrix (ECM) deposition, and abnormal collagen accumulation.[4,6] Excessive expression of pro-inflammatory cytokines, particularly TNF-*α* and IL-1*β*, has been demonstrated to exacerbate pulmonary fibrosis in animal models. Additionally, IL-6 derived from alveolar macrophages possess a well-established pathophysiological involvement in both experimental and clinical pulmonary fibrosis.[25,26]

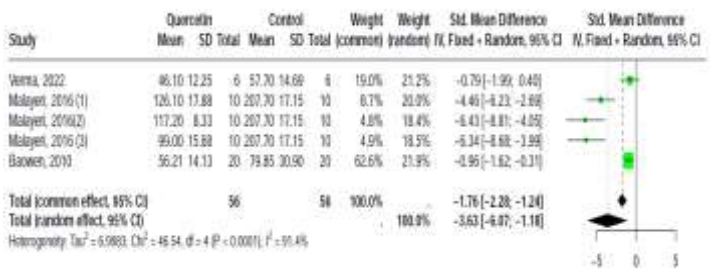

Figure 3: Forest plot TNF-*α*[25-27]

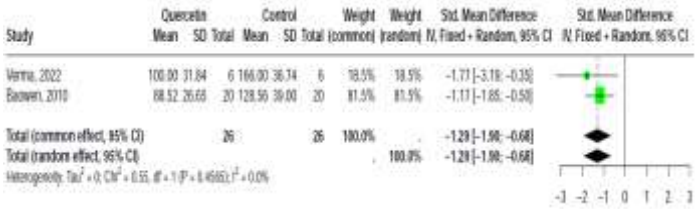

Figure 4: Forest plot IL-6[25,27]

Meta-analytical findings confirm quercetin's significant attenuation pertaining to inflammation biomarkers TNF-*α* and IL-6. Current evidence indicates localized overproduction of pro-inflammatory cytokines (notably TNF-*α*, IL-1*β*) exacerbates bleomycin-induced pulmonary fibrosis across animal models.[26] Furthermore, alveolar macrophage-derived IL-6 demonstrates established pathophysiological involvement in both experimental and clinical pulmonary fibrosis.[27,28] Contemporary research underscores the pivotal involvement of innate and adaptive immunity in fibrotic progression, including IPF. T lymphocytes localize within active disease foci and tertiary lymphoid structures in pulmonary parenchyma and bronchoalveolar lavage, confirming their mechanistic role. IPF pathogenesis through polarized cytokine secretion Th1-type cytokines (IFN-*γ*, IL-12) drive inflammation, while Th2-associated mediators (IL-4, IL-5, IL-9, IL-13) promote fibrogenesis.[29-31] Quercetin exhibits anti-inflammatory properties via regulating secretions of basic inflammation-related substances including cytokines, histamines, and chemokines.[33]

Quercetin, a naturally abundant polyhydroxylated flavonoid in plant-based foods, suppresses pulmonary fibrosis progression through pleiotropic molecular pathways. Verma et al.[27] identified TNF-*α* as a critical fibrosis mediator, with bleomycin models showing marked TNF-*α* elevation via ROS-induced NF-κB activation. Oral quercetin (20-day regimen) normalized TNF-*α* expression and attenuated lung injury, confirming anti-inflammatory or fibrotic efficacy.[25-27] Radiation-induced fibrosis similarly activates NF-κB, upregulating IL-6, IL-18, TNF-*α*, and IL-1*β*. Quercetin-3-rhamnoside (Q-3-R) inhibits this pathway and downstream cytokines (IL-1*β* and TNF-*α*), demonstrating therapeutic potential.[31] Quercetin additionally downregulates TNF-*α*, IL-6, IL-1*β* mRNA and pro-inflammatory miR-155 while elevating anti-inflammatory miR-122 and miR-125b. Upregulation of miR-26b/miR-27b correlates with reduced inflammation, suggesting miRNA-mediated actions. Furthermore, it suppresses senescence-associated secretory phenotype (SASP) transcripts (MCP1, MMP12, IL6), indicating multimodal anti-fibrotic activity.[30-32]

Additional to anti-inflammatory effects, our meta-analysis findings clearly demonstrate quercetin's capacity to reduce fibrosis markers. Hydroxyproline analysis from three studies (80 animals) showed a highly significant reduction in collagen deposition with Quercetin intervention compared to controls (SMD = -2.95; 95% CI: -4.16 to -1.74; p < 0.0001; Figure 5), with moderate heterogeneity (I^2=69.4%).[25,28,30] This reduction is highly relevant because hydroxyproline, as a proline-derived collagen constituent, serves as a validated IPF biomarker reflecting pathological collagen accumulation in lung tissue.[16,30]

Table 1: Characteristics of quercetin intervention studies

No	Authors, Year	Study Design	Sample Size (n)	Animal Model	Pulmonary Fibrosis Induction	Intervention	Dose	Treatment Duration	Inflammatory Biomarkers (pg/ml)		Hydroxyproline (mg/g) mean±SD	Ashcroft Score mean±SD
									TNF-α (mean±SD)	IL-6 (mean±SD)		
1.	Baowen, 2010[25]	*In Vivo*	20	Rats *Sprague-Dawley*	Intratracheal bleomycin 5 U/kg	Liposomal quercetin	5 mg/kg	28 day	56.21± 14.13	88.52± 26.65	34.78±2.84	-
2.	Malayeri, 2016[26]	*In Vivo*	60	Rats *Sprague-Dawley*	Intratracheal bleomycin 7.5 IU/kg	Quercetin hydrate	25 mg/kg 50 mg/kg 75 mg/kg	21 day	126.1± 17.88 117.2± 8.33 99±15.68	- - -	-	-
3.	Verma, 2022[27]	*In Vivo*	24	Mice C57Bl/6	Gamma radiation (12 Gy)	Quercetin-3-rutinoside (Q-3-R)	10 mg/kg	42 day	46.1±12.25	100±31.84	-	4.98±0.76
4.	Mehrzadi, 2021[28]	*In Vivo*	50	Rats Wistar	Intratracheal bleomycin 7.5 IU/kg	Quercetin	75 mg/kg	28 day	-	-	6.25± 0.6	2.16± 0.22
5.	Li, 2024[29]	*In Vivo*	32	Mice	Intratracheal bleomycin (3 mg/mL, 2.5 µl/g)	Quercetin	50 mg/kg	21 day	-	-	-	3.33±0.63
6.	Verma, 2013[30]	*In Vivo*	30	Rats Wistar	Intratracheal bleomycin 6.5 U/kg	Quercetin	100 mg/kg	21 day	-	-	1.88± 0.11	-

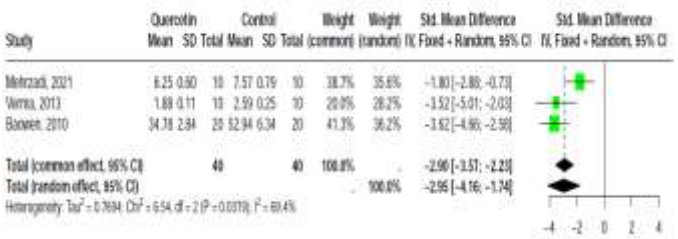

Figure 5: Forest plot hydroxyproline[25,28,30]

Moreover, histopathological evaluation via Ashcroft scores from three trials (48 animals) revealed a significant attenuation of pulmonary fibrosis severity mediated by quercetin, showing marked histopathological improvement in comparison to the control group (SMD = -5.90; 95% CI: -9.44 to -2.36; p = 0.0011; Figure 6), with high heterogeneity (I^2=82.5%).[27-29] The effectiveness of quercetin in reducing hydroxyproline levels and alleviating the severity of pulmonary fibrosis per Ashcroft score strongly supports its potential as an antifibrotic agent. Quercetin administration significantly reduces hydroxyproline levels and attenuates pulmonary fibrosis severity per Ashcroft scoring.[28]

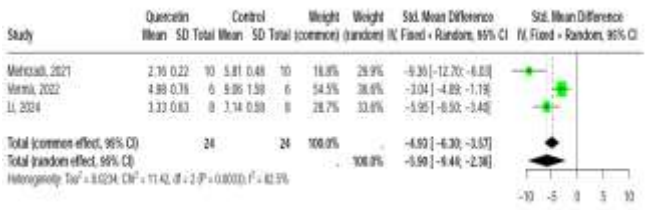

Figure 6: Forest plot Ashcroft score[27-29]

Crucially, gallic acid-quercetin coadministration demonstrates synergistic hydroxyproline reduction exceeding monotherapy efficacy versus bleomycin-exposed controls.[28] Histopathological analyses confirm superior architectural preservation exclusively with combination therapy, effectively reversing bleomycin-induced parenchymal remodelling. Hydroxyproline a proline-derived collagen constituent serves as a validated IPF biomarker, reflecting pathological collagen accumulation in pulmonary tissue. Previous investigations establish both polyphenols' capacity to mitigate bleomycin-induced fibrotic histopathology, including alveolar septal thickening and edema. Notably, quercetin monotherapy requires elevated dosing (100 mg/kg) for comparable efficacy, while clinical translation remains constrained by limited safety data.[28,34]

Conclusion

Quercetin demonstrates significant therapeutic potential in reducing inflammatory biomarkers and pulmonary fibrosis. Administration of quercetin effectively lowers TNF-*α*, IL-6, hydroxyproline, and the Ashcroft score, all of which contribute to the reduction in the severity of pulmonary fibrosis. Quercetin's ability to reduce inflammation and fibrosis indicates its potential in preventing or slowing the progression of pulmonary fibrosis. While this study provides compelling evidence for the benefits of quercetin, further research involving larger sample sizes, varied doses, and further trials on humans are recommended to confirm the potential benefits of quercetin in treating pulmonary fibrosis.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Savin IA, Zenkova MA, Sen'kova A V. Pulmonary fibrosis as a result of acute lung inflammation: molecular mechanisms, relevant *in vivo* models, prognostic and therapeutic approaches. Int J Mol Sci. 2022; 23(23):14959. Doi :10.3390/ijms232314959
2. Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. N Engl J Med. 2020; 383(10):958–968. Doi: 10.1056/NEJMra2005230
3. Lee JH, Park HJ, Kim S, Kim YJ, Kim HC. Epidemiology and comorbidities in idiopathic pulmonary fibrosis: a nationwide cohort study. BMC Pulm Med. 2023; 23(1):54. Doi: 10.1186/s12890-023-02340-8
4. Koudstaal T, Funke-Chambour M, Kreuter M, Molyneaux PL, Wijsenbeek MS. Pulmonary fibrosis: from pathogenesis to clinical decision-making. Trends Mol Med. 2023; 29(12):1076–1087. Doi: 10.1016/j.molmed.2023.08.010
5. Zhou Y, Ling T, Shi W. Current state of signaling pathways associated with the pathogenesis of idiopathic pulmonary fibrosis. Respir Res. 2024; 25(1):245. Doi:10.1186/s12931-024-02878-z
6. Moss BJ, Ryter SW, Rosas IO. Pathogenic mechanisms underlying idiopathic pulmonary fibrosis. Annu Rev Pathol Mech Dis. 2021; 17:515-546. Doi: 10.1146/annurev-pathol-042320-030240
7. Liu H, Shen J, He C. Advances in idiopathic pulmonary fibrosis diagnosis and treatment. Chin Med J Pulm Crit Care Med. 2025; 3(1):12-21. Doi: 10.1016/j.pccm.2025.02.001.
8. Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, Wijsenbeek MS, Stauffer JL, Kirchgaessler KU, Costabel U. Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. Eur Respir Rev. 2017; 26(146):170057. Doi: 10.1183/16000617.0057-2017.
9. Wang T, Cui Z, Ou Y, Lou S, Chen H, Zhu C, Zhou L, Zou F. Post-marketing safety concerns with pirfenidone and nintedanib: an analysis of individual case safety reports from the FDA adverse event reporting system database and the Japanese adverse drug event report databases. Front Pharmacol. 2025; 16:1530697. Doi: 10.3389/fphar.2025.1530697.
10. Cho S, Park S, Lee JA, Jung HJ, Kim KI, Lee BJ. The efficacy and safety of herbal medicine with pirfenidone in the treatment of idiopathic pulmonary fibrosis: a systematic review. Processes. 2022; 10(12):2477. Doi: 10.3390/pr10122477
11. Geng F, Xu M, Zhao L, Zhang H, Li J, Jin F, Li Y, Li T, Yang X, Li S, Gao X, Cai W, Mao N, Sun Y, Liu H, Xu H, Wei Z, Yang F. Quercetin alleviates pulmonary fibrosis in mice exposed to silica by inhibiting macrophage senescence. Front Pharmacol. 2022; 13:912029. Doi: 10.3389/fphar.2022.912029.
12. Geng Q, Yan L, Shi C, Zhang L, Li L, Lu P, Cao Z, Li L, He X, Tan Y, Zhao N, Liu B, Lu C. Therapeutic effects of flavonoids on pulmonary fibrosis: a preclinical meta-analysis. Phytomedicine. 2024; 132:155807. Doi: https:// doi. org/ 10. 1016/j. phymed. 2024. 155807
13. Wu X, Xiao X, Su Y, Zhang Y, Li G, Wang F, Du Q, Yang H. Use quercetin for pulmonary fibrosis: a preclinical systematic review and meta-analysis. Inflammopharmacology. 2025; 33(4):1879–1897. Doi: https://doi.org/10.1007/s10787-025-01678-1
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Brit. Med. J. 2021; 372:n71. Doi: 10.1136/bmj.n71.
15. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. Brit. Med. J. 2021; 372: n160. Doi: 10.1136/bmj.n160.
16. Jenkins RG, Moore BB, Chambers RC, Eickelberg O, Königshoff M, Kolb M, Laurent GJ, Nanthakumar CB, Olman MA, Pardo A, Selman M, Sheppard D, Sime PJ, Tager AM, Tatler AL, Thannickal VJ, White ES; ATS Assembly on Respiratory Cell and Molecular Biology. An Official American Thoracic Society workshop report: use of animal models for the preclinical assessment of potential therapies for pulmonary fibrosis. Am J Respir Cell Mol Biol. 2017; 56(5):667–679. Doi: 10.1165/rcmb.2017-0096ST.
17. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies BMC Med Res Methodol. 2014; 14:43. Doi: 10.1186/1471-2288-14-43.
18. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018; 27(6): 1785-1805. Doi: 10.1177/0962280216669183.
19. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range

and/or interquartile range. BMC Med Res Methodol. 2014; 14:135. Doi: 10.1186/1471-2288-14-135.
20. Abbas A, Hefnawy MT, Negida A. Meta-analysis accelerator: a comprehensive tool for statistical data conversion in systematic reviews with meta-analysis. BMC Med Res Methodol. 2024; 24(1):243. Doi: 10.1186/s12874-024-02356-6.
21. Drevon D, Fursa SR, Malcolm AL. Intercoder reliability and validity of WebPlotDigitizer in extracting graphed data. Behav Modif. 2017; 41(2):323-339. Doi: 10.1177/0145445516673998.
22. Rohatgi A. WebPlotDigitizer [Online]. 2020 [cited 2025 March 18]. Available from: https://automeris.io/WebPlotDigitizer.
23. RStudio Team. RStudio: Integrated development environment for R [Online]. 2019 [cited 2025 March 18]. Available from: http://www.rstudio.com/
24. Clephas PRD, Heesen M. Interpretation of meta-analyses. Interv Pain Med. 2022; 1(Suppl 2):100120. Doi: https://doi.org/10.1016/j.inpm.2022.100120.
25. Baowen Q, Yulin Z, Xin W, Wenjing X, Hao Z, Zhizhi C, Xingmei D, Xia Z, Yuquan W, Lijuan C. A further investigation concerning correlation between anti-fibrotic effect of liposomal quercetin and inflammatory cytokines in pulmonary fibrosis. Eur J Pharmacol. 2010; 642(1–3):134–139. Doi: 10.1016/j.ejphar.2010.05.019.
26. Malayeri AR, Hemmati AA, Arzi A, Rezaie A, Ghafurian-Boroojerdnia M, Khalili HR. A Comparison of the effects of quercetin hydrate with those of vitamin E on the levels of IL-13, PDGF, TNF-α, and INF-γ in bleomycin-induced pulmonary fibrosis in rats. Jundishapur J Nat Pharm Prod. 2016; 11(2):e277705. Doi: 10.17795/jjnpp-27705.
27. Verma S, Dutta A, Dahiya A, Kalra N. Quercetin-3-rutinoside alleviates radiation-induced lung inflammation and fibrosis via regulation of NF-κB/TGF-β1 signaling. Phytomedicine. 2022; 99:54004. Doi: 10.1016/j.phymed.2022.154004.
28. Mehrzadi S, Hosseini P, Mehrabani M, Siahpoosh A, Goudarzi M, Khalili H, Malayeri A. Attenuation of bleomycin-induced pulmonary fibrosis in Wistar Rats by combination treatment of two natural phenolic compounds: quercetin and gallic acid. Nutr Cancer. 2021; 73(10):2039–2049. Doi: 10.1080/01635581.2020.1820053.
29. Li Z, Jiao Y, Wu Z, Liu H, Li Y, Cai Y, Wei W, Cao F. The role of quercetin in ameliorating bleomycin-induced pulmonary fibrosis: insights into autophagy and the SIRT1/AMPK signaling pathway. Mol Biol Rep. 2024; 51(1):795-802. Doi: 10.1007/s11033-024-09752-7
30. Verma R, Kushwah L, Gohel D, Patel M, Marvania T, Balakrishnan S. Evaluating the ameliorative potential of quercetin against the bleomycin-induced pulmonary fibrosis in Wistar Rats. Pulm Med. 2013; 2013(1): 921724. Doi: 10.1155/2013/921724.
31. Toker Ç, Kuyucu Y, Şaker D, Kara S, Güzelel B, Mete UÖ. Investigation of miR-26b and miR-27b expressions and the effect of quercetin on fibrosis in experimental pulmonary fibrosis. J Mol Histol. 2024; 55(1):25–35. Doi: 10.1007/s10735-023-10168-z.
32. Hohmann MS, Habiel DM, Coelho AL, Verri WA, Hogaboam CM. Quercetin enhances ligand-induced apoptosis in senescent idiopathic pulmonary fibrosis fibroblasts and reduces lung fibrosis *in vivo*. Am J Respir Cell Mol Biol. 2019; 60(1):28–40. Doi: 10.1165/rcmb.2017-0289OC.
33. Kristianingsih A, Soetrisno, Reviono R, Wasita B. Molecular docking study of quercetin from ethanol extract of *Mimosa pudica Linn* on asthma biomarkers. Trop J Nat Prod Res. 2024; 8(10):8640–8645. Available from: https://www.tjnpr.org/index.php/home/article/view/5039
34. Al-Mamoori FF, Wahab HA, Ahmad W. Formulation and Characterisation of pH-sensitive eudragit L-100 nanoparticles for quercetin delivery in lung carcinoma. Trop J Nat Prod Res. 2024; 8(8):8081–8086. Available from: https://tjnpr.org/index.php/home/article/view/4603