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Review Article

Hepatorenal complications in bleomycin-induced pulmonary fibrosis: a comprehensive review on its biochemical mechanisms and prophylactic considerations

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ABSTRACT

Bleomycin induced pulmonary fibrosis (PF) has been one of the most habituated experimental models in idiopathic PF (IPF) exploration since the 1970s. The bleomycin model is a classic model of lung toxin. Though utmost of the studies established lung part, its dangerous goods on the liver and kidneys are still under explored. The applicable studies were searched on PubMed, Web of Science, and Google Scholar using the keywords “bleomycin”, “pulmonary fibrosis”, “hepatorenal toxin”, “oxidative stress”, “nephroprotection”, “liver injury”, “order injury”, “Nrf2 activators”, and “factory-deduced antioxidants” published in 2017-2024." Substantiation from these studies showed that bleomycin treatment significantly raises the situations of serum biochemical labels, like alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (peak), creatinine, and blood urea nitrogen (BUN). Increase in all biochemical labels suggest serious damage to the liver and kidneys. Studies have shown that the main mechanisms involved in this toxin are oxidative stress (ROS), mitochondrial dysfunction, activation of seditious cytokines and TGF-β1/Smad signalling. Curcumin, quercetin, silymarin and resveratrol are among factory- deduced bioactive composites which displayed promising defensive parcels These effects are suggestively through their antioxidant, anti-inflammatory, and antifibrotic conduct. These findings punctuate the need to consider and pierce multiple organs in bleomycin studies to make experimental fibrosis exploration more applicable systemically. Herbal antioxidants and Nrf2 activators can offer effective forestalment against liver and renal damage caused by bleomycin.

Keywords: Bleomycin, Pulmonary fibrosis, Hepatotoxicity, Nephrotoxicity, Oxidative stress, Medicinal plants

INTRODUCTION

Pulmonary fibrosis (PF), especially idiopathic PF (IPF), is a serious, progressive lung complaint that causes unrecoverable scarring of lung tissue by collagen deposit. This scarring gradationally affects normal breathing and gas exchange in alveoli. Worldwide, IPF affects nearly 3 million people and has a median survival of about 3 times if remain unaddressed.[1] Indeed, though pulmonary exploration has seen significant progress over the once 50 times, the lung fibrosis is still hard to diagnose and treat. This is incompletely because numerous cases do not show any radiological signs in the early stages of the complaint.[2]

Bleomycin-convinced PF is the most generally using experimental model to study the causes of IPF and other fibrotic interstitial lung conditions (ILDs). Numerous studies can set up in this model and has greatly helped to bettered our understanding of the molecular and cellular processes involved in fibrosis and to develop new treatments.[3] Bleomycin (BLM), a glycopeptide antibiotic set up in 1962, was introduced into cancer remedy in the

1970s. It's known for its dangerous goods on the lungs, importantly its capability to beget PF. In rodents, giving bleomycin through the intratracheal route set up to be the stylish experimental system. A single dose of Bleomycin can reliably spark inflammation within 3 to 7 days, followed by peak fibrosis being between days 14 and 28.[4] Although pulmonary toxin is the most honoured adverse effect of bleomycin exposure, growing substantiation suggests that the medicine can also produce considerable liver and kidney damage.[5] The systemic effects do due to oxidative stress and inflammation leads to fibrosis, still, these complications outside the lungs are frequently undervalued or not well established in exploration. Recent studies show significant oxidative stress- related liver and order injury after treating with bleomycin.[6] This review will epitomize the mechanisms behind bleomycin-induced liver and kidney damage, important biomarkers, and to assess the implicit benefits of factory-grounded treatments and antioxidant approaches.

PATHOPHYSIOLOGY OF THE BLEOMYCIN MODEL

Pulmonary mechanism

One crucial reason for bleomycin toxin is the low quantum of bleomycin hydrolase set up in lung parenchyma. This enzyme plays a pivotal part in detoxifying and breaking down the medicine. Because of this insufficiency, bleomycin tends to make up in the lungs, leading to the conformation of an active bleomycin-Fe2-oxygen complex. This metallo- glycopeptide complex generates reactive oxygen species (ROS), leading to DNA breaks, oxidative damage, and apoptosis.[7]

Structurally, bleomycin contains a bithiazole element that intercalates into DNA strands and pyrimidine and imidazole groups that bind iron and oxygen to forms activated oxidants. These oxidants induce DNA chain scission, release of free bases, and will results in structural DNA differences. In addition to this direct DNA damage, bleomycin also causes lipid peroxidation and seditious responses, leading to interstitial oedema, vulnerable cell infiltration, fibroblast activation and extracellular matrix deposit.[8] An inordinate product of ROS similar as superoxide and hydroxyl radicals causes a severe oxidative stress, as substantiated by high situations of malondialdehyde and membrane lipid peroxidation.[9] Contemporaneously, bleomycin induces cytokines similar as TNF-α, IL-6 and IL-1β, which contribute to habitual inflammation and tissue remodelling.[10] Activation of the TGF-β1/Smad signalling pathway also results in fibroblast proliferation, isolation into myofibroblasts, and collagen deposit, leading to destruction of alveolar armature and disabled gas exchange.

Hepatic involvement

Although bleomycin is majorly associated with pulmonary toxin, substantial substantiation indicates that it also produces significant hepatic injury .Walters et al reported an increase of nearly 2.5-folds in serum ALT and AST situations by day 14 after bleomycin administration, with centrilobular necrosis and seditious infiltration.[11] Bleomycin induced liver injury appears as a result of a combination of oxidative stress, mitochondrial damage, inflammation, and progressive fibrotic changes. Bleomycin forms complexes with ferrous iron and generates ROS through Fenton- type reactions. Thus, causing lipid peroxidation and membrane damage in hepatocytes. Since hepatic towel exhibits fairly low bleomycin hydrolase exertion, the liver becomes susceptible to oxidative injury.[12]

Mitochondrial dysfunction also plays a cruciate part in hepatic injury. Bleomycin impairs mitochondrial electron transport chain, decreases ATP synthesis. This will induces cytochrome c release, thereby cranking apoptotic pathways.[13] The injury occurs through ROS-intermediated activation of Kupffer cells and NF-κB signalling, and increases the product of TNF-α, IL-β, and IL-6, results in neutrophil infiltration and centrilobular necrosis.[14]

Habitual exposure latterly activates the TGF-β1/Smad signalling pathway, converting hepatic stellate cell activation and collagen deposit, which causes progressive hepatic fibrosis.[15]

Table 1: Histopathological and biochemical changes in liver.

Parameters	Observed change	Time point	Experimental model
ALT, AST	Increased 2-3-fold	Day 7-14	Mice, intratracheal 2.5 mg/kg
ALP, GGT	Increased 1.8-fold	Day 14	Rat, intravenous 15 mg/kg
MDA	Increased 2.5-fold	Day 14	Mice
GSH, SOD	Decreased 40-60%	Day 14	Mice
Histology	Centrilobular necrosis, portal inflammation, sinusoidal dilatation	Day 14-21	Rat

Clinically, roughly 20-30 of cases on bleomycin- grounded chemotherapy, although severe hepatotoxicity is fairly uncommon because of cure limitation assessed by pulmonary toxin.[16]

Biomarkers and evaluation

Routine monitoring of hepatic biomarkers in bleomycin beast studies should include serum ALT, AST, ALP, bilirubin and albumin. Labels of oxidative stress are liver

MDA, glutathione (GSH), superoxide dismutase (SOD) and catalase conditioning. Fibrotic progression can be estimated using hydroxyproline estimation and α-SMA immunohistochemistry, while apoptosis can be assessed through caspase-3 expression and TUNEL assays. Histopathology can be estimated by using Masson's trichome stain and picrosirius red.

Table 2: Remedial interventions for hepatoprotection.

Agents	Mechanism	Therapeutic outcome
Curcumin (200 mg/kg)	Nrf2/HO-1 activation	Reduced ALT, reduced MDA, increased GSH
Silymarin (100 mg/kg)	Membrane stabilization and antioxidant activity	Reduced necrosis and liver enzyme elevation
Quercetin (50 mg/kg)	TGF-β1 inhibition and ROS scavenging	Reduced fibrosis score
N-acetylcysteine	GSH precursor	Reduced apoptosis and hepatocellular injury

Kidney involvement

While PF remains the top poisonous effect of bleomycin, the kidneys are also largely susceptible because renal excretion is the primary route through which the medicine is cleared from the body.

Bleomycin gets accumulated in proximal tubular epithelial cells, where low renal bleomycin hydrolase exertion promotes ROS generation, lipid peroxidation, and tubular necrosis.[17] Bleomycin-convinced mitochondrial dysfunction further damages renal mitochondrial membrane, which inhibits electron transport chain complexes I and IV, therefore decreases ATP conflation, and induces cytochrome c-intermediated apoptosis of tubular epithelial cells.[18]

Oxidative stress also activates seditious pathways, particularly NF-κB activation in mesangial cells, and increases the expression of TNF-α, IL-1β and MCP-1. Habitual inflammation facilitates the infiltration of macrophages, interstitial nephritis and progressive fibrosis.[19]

Cardio vascular changes also contribute to renal injury. Bleomycin-convinced endothelin-1 upregulation causes renal vasoconstriction, reducing glomerular filtration rate (GFR) and contributing to ischemic tubular injury.[17] Activation of TGF-β1/Smad signalling pathway stimulates renal fibroblast activation, extracellular matrix deposit, and interstitial fibrosis analogous to pulmonary tissues.[15]

Histopathological and biochemical changes in kidneys

Flash serum creatinine elevations are seen in about 15- 25 of cases in clinical practice on bleomycin chemotherapy, but acute order injury is rare because of cure limitations grounded on pulmonary toxin.[20]

Table 3: Histopathological and biochemical changes in kidneys.

Parameters	Observed change	Time point	Experimental model
Serum creatinine	Increased 1.8-2.5-fold	Day 7-14	Mice
BUN	Increased 2.2-fold	Day 14	Mice
Proteinuria	Increased 3-fold	Day 21	Rat
Renal MDA	Increased 2.3-fold	Day 14	Mice
GSH, catalase	Decreased 50-65%	Day 14	Mice
Histology	Tubular necrosis, interstitial fibrosis, glomerular atrophy	Day 14-28	Rat/mice

Biomarkers and evaluation

Routine renal assessment in studies with bleomycin should include serum creatinine, BUN, cystatin C, KIM-1, and NGAL. Urinary biomarkers include protein/ creatinine rate, and β2- macroglobulin. Renal MDA, GSH, SOD, and 8- OHdG situations can be used as labels for oxidative stress. Collagen I/ III staining, α-SMA and TGF-β1 immunohistochemistry can be used to assess fibrosis.[21]

Table 4: Therapeutic strategies for nephroprotection

Agents	Dose and route	Mechanism	Outcome
N-acetylcysteine	150 mg/kg IP	GSH precursor and ROS scavenger	Reduced creatinine, BUN, and tubular necrosis
Quercetin	50 mg/kg oral	Nrf2 activation and TGF-β1 inhibition	Reduced proteinuria and fibrosis
Curcumin	200 mg/kg oral	Reduced NF-κB activation and mitochondrial ROS	Reduced creatinine and renal inflammation
Resveratrol	20 mg/kg oral	SIRT1 activation and anti-apoptotic activity	Reduced BUN and caspase-3
Amifostine	200 mg/kg IP	Free radical scavenging and DNA protection	Reduced tubular injury

CLINICAL APPLICABILITY

Since about 70% of the medicine is excreted unchanged in the urine, renal function is a major factor affecting bleomycin pharmacokinetics. Thus, renal impairment may affect in accumulation of medicines and increased systemic toxin, especially pulmonary toxicity. However, toxin can be minimized by cure adaptation or dose adjustment.[22] When creatinine concurrence is lower than 50 mL/ min.

The findings reviewed in this composition emphasize the necessity of a further comprehensive multi-organ approach in assessing bleomycin toxin in experimental and clinical studies. remedial agents conferring protection to pulmonary tissue are frequently observed to have analogous defensive goods in hepatic and renal aspects because of participated pathogenic pathways involving oxidative stress, Nrf2 signaling and TGF- β- intermediated fibrosis.

Synthetic medicines

Pirfenidone and Nintedanib are the only approved antifibrotic medicines by the FDA for IPF at present. The medicines may also have hepatotoxic effects, although they decelerate the progression of complaint. Nrf2 activators, similar as dimethyl fumarate, have presented encouraging anti- fibrotic and antioxidant effects in pulmonary and hepatic tissues.[23]

Table 5: Plant-based therapeutic approaches.

Plant compound	Dose	Reported effects
Curcumin	200 mg/kg	Reduced lung collagen deposition and ALT levels
Quercetin	50 mg/kg	Reduced TGF-β and MDA levels
Silymarin	100 mg/kg	Hepatoprotective and antioxidant effects
Polyherbal formulations	400 mg/kg	Reduced fibrosis score

Curcumin has demonstrated significant antifibrotic exertion through activation of the Nrf2/HO-1 pathway.[24] Unpublished experimental substantiation in our lab also suggests that medicinal plants similar as Emilia sonchifolia may ameliorate liver and renal biomarkers by reducing oxidative stress- intermediated tissue injury.

LIMITATIONS AND UNBORN DIRECTIONS

While the bleomycin model is a go-to for studying PF, it does come with some significant downsides. For one, the fibrosis it causes can frequently be reversed to some extent, and it does not relatively capture the habitual, progressive nature of mortal IPF. Plus, using a single cure might not reflect how the complaint actually progresses over time.

Recent findings indicate that administering bleomycin in multiple boluses and using aged beast models could more mimic the pathological features of mortal IPF. To enhance the applicability of experimental fibrosis exploration, future studies should routinely assess liver and kidney function as standard endpoints.

CONCLUSION

The bleomycin-induced PF model doesn't just affect the lungs; it also leads to significant liver and kidney damage due to oxidative stress, inflammation, and profibrotic signalling pathways. Increased levels of ALT, AST, creatinine, and oxidative stress markers highlight the hepatorenal toxicity that accompanies PF.

Therefore, it's crucial to include routine assessments of multiple organs in bleomycin studies. Exploring plant-based antioxidants and Nrf2 activators could offer promising and budget-friendly treatment options, especially in settings with limited resources. By taking a more comprehensive view that includes multiple organs, we can enhance the relevance of antifibrotic research and pave the way for safer therapeutic strategies.

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REFERENCES.

1. Koudstaal T, Wijsenbeek MS. Idiopathic pulmonary fibrosis. Presse Med. 2023;52(3):104166.
2. Salisbury ML, Xia M, Murray S, Bartholmai BJ, Kazerooni EA, Meldrum CA, et al. Predictors of Idiopathic Pulmonary Fibrosis in Absence of Radiologic Honeycombing: A Cross Sectional Analysis in ILD Patients Undergoing Lung Tissue Sampling. Respir Med. 2016;118:88-95.
3. Liu T, De Los Santos FG, Phan SH. The Bleomycin Model of Pulmonary Fibrosis. Methods Mol Biol. 2017;1627:27-42.
4. Kolb P, Upagupta C, Vierhout M, Ayaub E, Bellaye PS, Gauldie J, et al. The importance of interventional timing in the bleomycin model of pulmonary fibrosis. Eur Respir J. 2020;55(6):1901105.
5. Hay J, Shahzeidi S, Laurent G. Mechanisms of bleomycin-induced lung damage. Arch Toxicol. 1991;65(2):81-94.
6. Pérez-Figueroa DC, Reyes-Jiménez E, Velázquez-Enríquez JM, Reyes-Avendaño I, González-García K, Villa-Treviño S, et al. Evaluation of renal damage in a bleomycin-induced murine model of systemic sclerosis. Iran J Basic Med Sci. 2023;26(7):760-7.
7. Hay J, Shahzeidi S, Laurent G. Mechanisms of bleomycin-induced lung damage. Arch Toxicol. 1991;65(2):81-94.

8. Li X, Zhang W, Cao Q, Wang Z, Zhao M, Xu L, et al. Mitochondrial dysfunction in fibrotic diseases. Cell Death Discov. 2020;6(1):80.
9. Li S, Hong M, Tan HY, Wang N, Feng Y. Insights into the Role and Interdependence of Oxidative Stress and Inflammation in Liver Diseases. Oxid Med Cell Longev. 2016;2016:4234061.
10. Xu F, Liu C, Zhou D, Zhang L. TGF-β/SMAD Pathway and Its Regulation in Hepatic Fibrosis. J Histochem Cytochem. 2016;64(3):157-67.
11. Walters DM, Kleeberger SR. Mouse Models of Bleomycin-Induced Pulmonary Fibrosis. Curr Protoc Pharmacol. 2008;40(1):5.46.1-5.46.17.
12. A G, Cb O. Hepatotoxicity Secondary to Chemotherapy. J Clin Transl Hepatol. 2014;2(2):1.
13. Bhatia D, Capili A, Choi ME. Mitochondrial dysfunction in kidney injury, inflammation, and disease: Potential therapeutic approaches. Kidney Res Clin Pract. 2020;39(3):244-58.
14. Kandel R, Roy P, Singh KP. Molecular Basis of Oxidative Stress-Induced Acute Kidney Injury, Kidney Fibrosis, Chronic Kidney Disease, and Clinical Significance of Targeting Reactive Oxygen Species-Regulated Pathways to Treat Kidney Disease. Front Biosci Sch Ed. 2025;17(3):38963.
15. Xu F, Liu C, Zhou D, Zhang L. TGF-β/SMAD Pathway and Its Regulation in Hepatic Fibrosis. J Histochem Cytochem Off J Histochem Soc. 2016;64(3):157-67.
16. Brandt JP, Gerriets V. Bleomycin. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2026.
17. Wilhelm SM, Simonson MS, Robinson AV, Stowe NT, Schulak JA. Endothelin up-regulation and localization following renal ischemia and reperfusion. Kidney Int. 1999;55(3):1011-8.
18. Bhatia D, Capili A, Choi ME. Mitochondrial dysfunction in kidney injury, inflammation, and disease: potential therapeutic approaches. Kidney Res Clin Pract. 2020;39(3):244-58.
19. Hao X min, Liu Y, Hailaiti D, Gong Y, Zhang X dong, Yue B nan, et al. Mechanisms of inflammation modulation by different immune cells in hypertensive nephropathy. Front Immunol. 2024;15:1333170.
20. Kawai K, Hinotsu S, Tomobe M, Akaza H. Serum creatinine level during chemotherapy for testicular cancer as a possible predictor of bleomycin-induced pulmonary toxicity. Jpn J Clin Oncol. 1998;28(9):546-50.
21. Bartani Z, Nemati H, Heshmati S, Tarlan M, Sadeghi M. The protective effect of curcumin nanoparticles on renal damage caused by a combination of bleomycin, etoposide, and cisplatin. BMC Nephrol. 2025;26(1):354.
22. Renal impairment dosage adjustment for cytotoxics. Available at: https://www.stonybrookmedicine.edu/sites/default/files/renal-impairment-dosage-adjustment-for-cytotoxics.pdf. Accessed on 02 May 2026.
23. Chianese M, Screm G, Salton F, Confalonieri P, Trotta L, Barbieri M, et al. Pirfenidone and Nintedanib in Pulmonary Fibrosis: Lights and Shadows. Pharmaceuticals. 2024;17(6):709.
24. Kim JS, Oh JM, Choi H, Kim SW, Kim SW, Kim BG, et al. Activation of the Nrf2/HO-1 pathway by curcumin inhibits oxidative stress in human nasal fibroblasts exposed to urban particulate matter. BMC Complement Med Ther. 2020;20:101.

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