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An Evaluation of The Effects of Glabridin, Dexamethasone, and Iberiotoxin on Liver Injury in A Rat Model of Bleomycin-Induced Pulmonary Fibrosis

Elfide Gizem Bakırhan[1*]

[1]Department of Histology and Embryology, Faculty of Medicine, Adıyaman University, Adıyaman, Türkiye

***Corresponding Author:**
Elfide Gizem Bakırhan
Department of Histology and Embryology, Faculty of Medicine, Adıyaman University, Adıyaman, Türkiye.
E-mail: ekivrak@adiyaman.edu.tr
Orcid ID: 0000-0002-7401-2317

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ABSTRACT

This study investigated the potential protective effects of glabridin (Gla), dexamethasone (DEX), and iberiotoxin (Ibx), a BKCa channel inhibitor, against liver damage in a bleomycin (BLM)-induced pulmonary fibrosis model. Thirty-six female Wistar Albino rats were randomly divided into six equal groups. Rats in the Sham group received 0.1 ml physiological saline intratracheally. Rats in the BLM group were administered 0.1 ml of BLM (5 mg/kg) intratracheally to induce pulmonary fibrosis. In the treatment groups with induced pulmonary fibrosis, the BLM+Gla group received 30 mg/kg Gla dissolved in 20% dimethyl sulfoxide (DMSO) intraperitoneally (i.p.), the BLM+Dex group 1 mg/kg Dex i.p. following the same dosing schedule, and the BLM+Ibx+Gla group rats 6 µg/kg Ibx i.p. 30 minutes before 30 mg/kg Gla. At the end of the experiment, liver tissues were evaluated histopathologically using hematoxylin-eosin (H&E) staining. Significant histopathological alterations were observed in the liver tissues from the BLM, BLM+Dex, and BLM+Vehicle groups, including disorganized hepatocyte architecture, loss of cellular boundaries, increased numbers of degenerative cells, and marked infiltration of inflammatory cells. In contrast, liver tissues from the BLM+Gla and BLM+Ibx+Gla groups largely maintained a normal histological architecture. These groups exhibited a reduced number of degenerative cells, preservation of acidophilic cytoplasmic characteristics, and a connective tissue density comparable to that of the sham group. The findings of this study suggest that BLM-induced pulmonary fibrosis may lead to secondary liver injury characterized by histopathological alterations and fibrotic changes. Gla demonstrated notable hepatoprotective effects by preserving liver architecture and reducing tissue damage, while Dex exhibited only partial efficacy. Furthermore, Gla combined with Ibx enhanced protective outcomes, highlighting its potential therapeutic value. These results provide new insights into the systemic consequences of pulmonary fibrosis and support the exploration of Gla-based strategies for managing hepatic fibrosis.

Keywords: Bleomycin, Dexamethasone, Glabridin, Iberiotoxin, Liver fibrosis

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INTRODUCTION

The extent to which fibrotic responses in one organ can trigger similar manifestations in distant organs via shared pathophysiological pathways is still not completely understood. Pulmonary fibrosis is a progressive, life-threatening disease characterised by high morbidity and mortality, frequently exceeding those of several malignancies [1]. While pulmonary fibrosis primarily affects the lungs, emerging evidence suggests that fibrotic alterations may also occur in extrapulmonary organs, including the liver.

Bleomycin (BLM) is a chemotherapeutic agent commonly used to establish experimental models of pulmonary fibrosis due to its strong fibrogenic potential [2]. Despite its benefits in the treatment of human cancers, the use of BLM is limited due to its pulmonary toxicity leading to fibrogenesis [3]. Since BLM models are the most widely recognized models for studying pulmonary fibrosis, due to their high level of similarity to human anatomy, patients with the disease are likely also to experience liver dysfunction. However, studies have shown that a significant proportion of patients with pulmonary fibrosis also have hepatic fibrosis [4]. The BLM-induced pulmonary fibrosis model has been reported to cause histopathological changes in the liver and to trigger systemic sclerosis [5]. BLM-induced pulmonary fibrosis may cause dysfunction and tissue damage in liver tissue due to inflammation and the oxidative stress it causes.

Oxidative stress refers to a biochemical disequilibrium that arises when intracellular antioxidant mechanisms are insufficient to neutralise pro-oxidant species. Cellular integrity is safeguarded by a complex antioxidant defence system comprising enzymatic components such as catalase, superoxide dismutase, and glutathione peroxidase, as well as non-enzymatic molecules including glutathione [6]. This system plays a critical role in maintaining the balance between oxidants and antioxidants; however, disruption of this equilibrium is implicated in the pathogenesis of numerous human diseases [7]. Oxidative stress leads to structural and functional damage to biomolecules, including DNA, lipids, and proteins. It also interferes with intracellular signaling cascades and can alter gene expression [8, 9]. Furthermore, oxidative modifications play a role in abnormal cell proliferation, inflammation, and other pathological mechanisms [10]. BLM, an antineoplastic agent, promotes the generation of reactive oxygen species (ROS) and intercalates into DNA, thereby facilitating close interaction with genetic material. The formation of ROS is a well-established contributor to the development of fibrosis. [10]. From that perspective, oxidative stress plays a pivotal role in promoting cellular proliferation associated with chronic diseases such as fibrosis. Numerous pharmacological agents have been used in both experimental and clinical settings for the treatment of pulmonary fibrosis in recent years. However, their limited therapeutic efficacy and associated side effects have prompted growing interest in natural compounds with high biological activity as potential alternative treatment strategies.

Glabridin (Gla) is a natural plant-derived polyphenolic flavonoid obtained from liquorice root (*Glycyrrhiza glabra*) with pharmacological effects such as anti-inflammatory and antimicrobial activities [11]. Studies evaluating the hepatoprotective effects of Gla have shown that it exhibits liver hepatoprotective activity, such as improving liver damage, ameliorating hepatocyte destruction, and preventing liver steatosis and liver cancer [12].

Dexamethasone (Dex) is a synthetic corticosteroid with potent glucocorticoid activity, exhibiting both anti-inflammatory and antifibrotic properties. Widely employed in the treatment of both acute and chronic inflammatory conditions, Dex attenuates inflammatory cell infiltration by downregulating the expression of proinflammatory cytokines such as tumour necrosis factor-α, interleukin (IL)-1β, and IL-6. It has also been reported to modulate fibrogenic responses by inhibiting the tumour growth factor-β/Smad signaling pathway [13]. In light of these properties, Dex is considered a potential therapeutic agent not only for suppressing inflammation but also for limiting fibrotic tissue development. However, long-term use can lead to severe complications, such as immunosuppression and metabolic side effects [14].

Iberiotoxin (Ibx) is a peptide toxin and selective inhibitor of large-conductance calcium-activated potassium (BKCa) channels. Recent studies show that BKCa channels play critical regulatory roles in cellular processes such as inflammation, apoptosis, proliferation, and fibrosis [15]. Inhibition of these channels may contribute to reducing cellular stress and preserving tissue integrity in various pathophysiological processes [16]. However, the literature evaluating the specific effects of Ibx on liver fibrosis is still quite limited, and further research is needed in this area.

In this study, we hypothesised that BLM-induced lung fibrosis may lead to hepatic fibrosis by causing oxidative stress, leading to tissue damage and dysfunction in the liver. We anticipated that Gla and Dex may attenuate the fibrotic process induced by BLM and regulate profibrotic activity. No previous study has investigated the potential effects of Gla and Dex on hepatic fibrosis. We also intended to contribute to the gap in current knowledge in this area by examining the potential impact of the BKCa channel inhibitor Ibx on hepatic

fibrosis.

MATERIAL AND METHODS

Thirty-six healthy, 12-week-old female Wistar Albino rats weighing 250-300 g were used in the study. Approval was received from the Adıyaman University rat experiments local ethics committee, Türkiye (number 2023/027 dated 27.12.2023). The rats were obtained from the Adıyaman University Experimental Animal Research Centre, where they were housed during the 28-day experimental period, with a maximum of six rats per cage. Throughout the study, the rats were maintained at 22±2 ^{0}C room temperature, in 50±10% relative humidity, and in a 12/12-h day/night photoperiod. Ad libitum access was permitted to standard rat chow, and their water (~50 mL/day/rat) was refreshed daily.

Formation of The Groups and Surgical Procedures

Thirty-six rats were divided into six groups of six rats each. In order to induce pulmonary fibrosis, all rats except those in the saline group received intratracheal administration of 5 mg/kg BLM (Onko Koçsel İlaç San. Tic. A.Ş., Türkiye) dissolved in 0.1 ml saline once a vertical midline incision had been made to the neck [17].

Saline (Sham): Rats in this group were given 0.1 ml of physiological saline intratracheally on day 0 of the experiment.

Bleomycin (BLM): Rats in this group received 0.1 ml of BLM (5 mg/kg) dissolved in saline intratracheally on day 0 of the experiment [17].

Bleomycin+Glabridin (BLM+Gla): Rats in this group received 0.1 ml of BLM (5 mg/kg) in saline intratracheally on day 0 of the experiment. Starting from day 0, all rats in this group received 30 mg/kg of Gla dissolved in 20% dimethyl sulfoxide (DMSO) intraperitoneally for seven days and on days 14, 21, 24, and 27 [18].

Bleomycin+Iberiotoxin+Glabridin (BLM+Ibx+Gla): The rats in this group were administered 0.1 ml of BLM (5 mg/kg) dissolved in saline intratracheally on day 0 of the experiment. The rats in this group were administered 30 mg/kg Gla i.p. starting from day 0 and on days 14, 21, 24, and 27 of the experiment. Ibx was administered i.p. at a dose of 6 µg/kg 30 minutes before Gla, starting from day 0 and on days 14, 21, 24, and 27 [19].

Bleomycin+Dexamethasone (BLM+Dex): This group received 0.1 ml of BLM (5 mg/kg) dissolved in saline and administered intratracheally on day 0 of the experiment. These rats also received 1 mg/kg of Dex i.p. for 7 days, starting from day 0 of the experiment and on days 14, 21, 24, and 27 [18].

Bleomycin+DMSO (BLM+Vehicle): On day 0 of the experiment, 0.1 ml of BLM (5 mg/kg) dissolved in saline was administered intratracheally to the rats in this group. In order to investigate the effect of the solvent (DMSO), 20% DMSO was administered intraperitoneally to these rats for seven days, starting from day 0 of the experiment and on days 14, 21, 24, and 27.

At the end of the 28-day experiment, all rats were anaesthetised with ketamine (50 mg/kg)/xylazine (10 mg/kg) and sacrificed.

Histological Tissue Procedure

At the end of the experiment, liver tissues were dissected and placed in 10% formaldehyde for histopathological analysis. After 10 days of fixation, the lung tissues were subjected to routine processing and embedded in paraffin. Seven micrometre-thick sections were obtained by means of a Thermo Shandon Finesse ME microtome (Thermo Fisher Scientific, Cheshire, UK) using systematic random sampling of 1/15 of the prepared paraffin blocks. An average of 15–20 sections was obtained from this sampling. These sections were then stained with hematoxylin and eosin (H&E) for histological analysis. Evaluations were performed using images obtained using a Carl Zeiss Axiocam ERc5 model microscope (Carl Zeiss Microscopy GmbH, 07745 Jena, Germany) equipped with a digital camera.

RESULTS

Light Microscopic Findings

Liver tissue sections stained with H&E from the sham group exhibited a healthy architecture. Hepatocyte cords and sinusoids were normal, and polygonal liver cells were well-defined and prominent. Cell nuclei were centrally located, large, round, and euchromatic, and some hepatocytes were binucleated with a normal structure (Figure 1). Loose connective tissue was observed around the central vein, located in the centre of the liver lobules, and in the periportal area (Figure 1). The central vein and portal triads were normal in appearance.

Examination of H&E-stained sections of rat liver tissues from the BLM and BLM+Vehicle groups revealed that the arrangement of hepatocyte cords was disrupted, and the lobule structure and boundaries were not clearly distinguishable. The polygonal shapes of the hepatocytes constituting the parenchyma were lost, cell boundaries were indistinct, and cytoplasmic boundaries were not clearly identifiable.

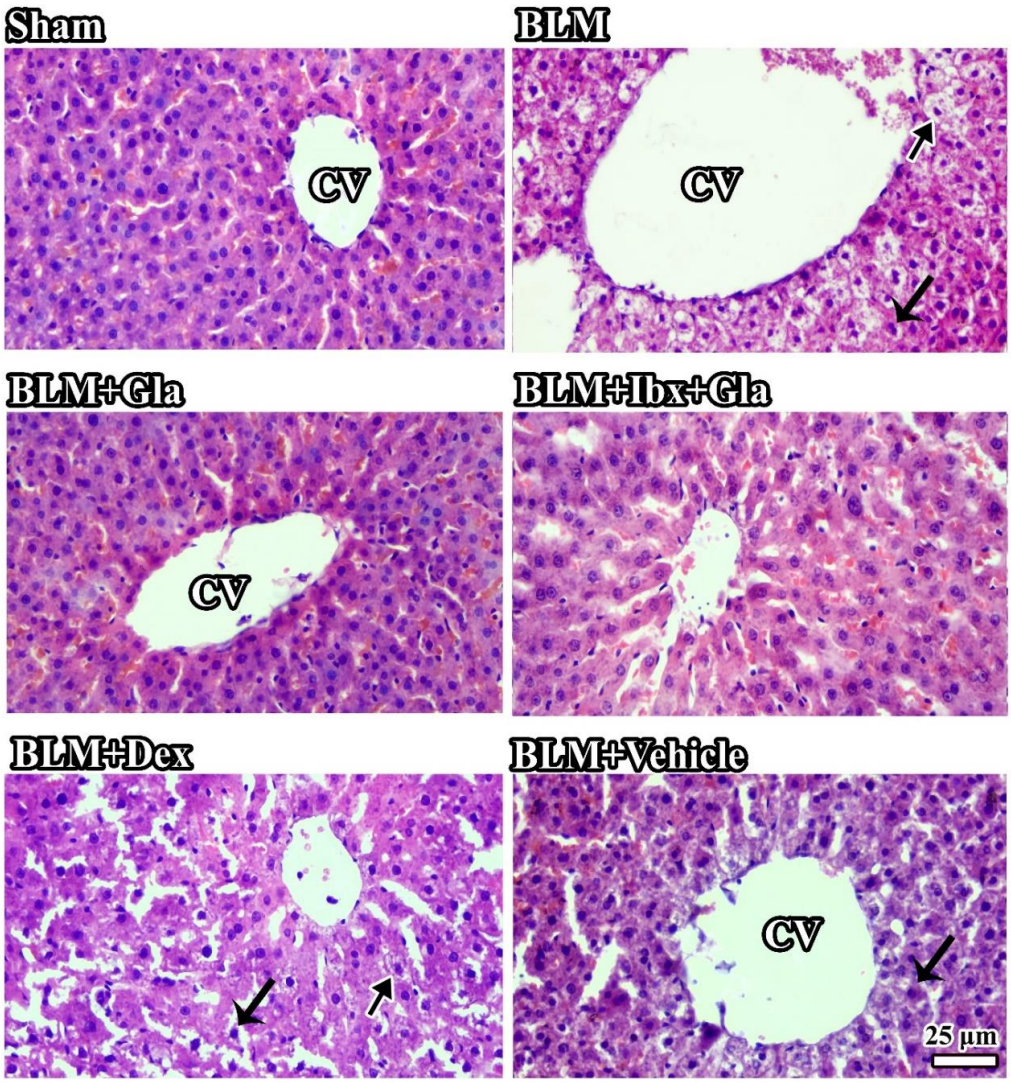

Figure 1. Light microscopic images of liver tissues from all groups (H&E staining). CV: Central vein, ***Thick arrow:*** *Hpertropic hepocytes,* ***Black thin arrow:*** *Acidophilic cytoplasm and degenerative cells with pyknotic stained nuclei of hepatocytes.*

However, the density of degenerative cells was high. The presence of hepatocytes with dark pyknotic nuclei was noted in some places. Widespread severe steatosis, hydropic degeneration, sinusoidal dilatation, and dense mononuclear cell infiltration were also observed (Figure 1). In the BLM group, an increase in connective tissue volume was observed around the central vein (CV) and in the periportal area compared to the other groups (Figure 1).

Examination of H&E-stained sections from the BLM+Gla and BLM+Ibx+Gla groups revealed that the normal tissue architecture was preserved, similarly to the sham and Gla groups. The number of degenerated hepatocytes decreased in the BLM+Gla and BLM+Ibx+Gla groups, and these retained their acidophilic structure. The connective tissue density around the central vein and periportal area was similar to that in the sham and Gla groups. The central vein and portal triads maintained their normal appearance. No inflammation or hemorrhagic findings were observed in the liver tissues from these groups. In the BLM+Dex group, the protective effect was less pronounced than in the Gla-treated groups. Localised hepatocellular degeneration and sinusoidal dilatation were still observed.

DISCUSSION

This study examined the systemic effects of BLM-induced pulmonary fibrosis, specifically focusing on histopathological changes in liver tissue. The findings demonstrated that BLM administration caused significant histological damage not only in lung tissue, but also in liver tissue. In the BLM and BLM+Dex groups, hepatocyte alignment was disrupted, cell

boundaries were blurred, and an increase in the number of degenerative cells, pronounced steatosis, hydropic degeneration, and intense inflammatory cell infiltration were observed. These findings are consistent with previous studies suggesting systemic fibrotic effects of BLM [20].

BLM-induced toxicity is closely linked to oxidative stress generation and subsequent DNA damage within affected tissues [21]. Karamalakova et al. (2019) demonstrated that BLM administration reduces hepatic antioxidant capacity, elevates ROS levels and oxidative stress markers, and induces inflammation as well as alterations in liver function enzymes [22]. In the present study, it may be suggested that elevated ROS levels contribute to liver damage by inducing oxidative stress in the presence of inadequate antioxidant defence mechanisms.

However, ROS production is clearly involved in the development of fibrosis. Oxidative stress induces cell proliferation in a number of chronic diseases, such as fibrosis. One notable finding of this study is that pulmonary fibrosis is not limited to the lungs, but can also trigger fibrotic responses in distant organs such as the liver [23]. This finding supports the concept of systemic fibrosis and suggests that fibrotic processes progress through common pathological mechanisms affecting multiple organs [24].

This study also investigated the potential protective effects of Gla and Dex against BLM-induced fibrotic processes. Gla is a natural flavonoid known for its antioxidant, anti-inflammatory, and hepatoprotective properties. Dogra et al. (2021) revealed the protective effects of Gla against hepatotoxicity [25]. Those authors showed that it led to improvements in terms of serum enzyme levels, oxidative stress markers, and histopathological deteriorations in methotrexate-induced liver injuries, and reduced collagen accumulation in fibrosis models [25, 26]. Histological evaluations showed that liver tissue architecture in this study was largely preserved in the BLM+Gla and BLM+Ibx+Gla groups, with reduced numbers of degenerative cells and limited connective tissue accumulation. This suggests that Gla may reduce fibrosis by inhibiting ROS generation and oxidative stress, thereby suppressing oxidative stress-induced tissue damage.

Partial histological protection was observed in the Dex-treated group; however, the extent of that improvement was more limited than in the Gla-treated groups. Although corticosteroids exert well-established short-term anti-inflammatory effects, their efficacy in preventing long-term tissue damage remains limited [20].

Some experimental studies have reported that Ibx, a selective inhibitor of BKCa channels, exhibits protective effects at the tissue level by reducing cellular damage associated with oxidative stress [27]. In the present study, Ibx administered in combination with Gla appeared to reduce cellular stress during the BLM-induced fibrotic process, thereby contributing to the preservation of tissue integrity and more effectively attenuating fibrosis. However, the current literature on the specific effects of Ibx in hepatic fibrosis remains limited, highlighting the need for further investigation. Additionally, DMSO alone produced no significant alterations in liver histology in the BLM+Vehicle group, indicating that the observed effects of Gla are independent of the carrier solvent.

There are a number of limitations to this study. In particular, the molecular characteristics of mast cells and the biochemical markers associated with inflammatory and fibrotic responses were not assessed. Additionally, the absence of quantitative stereological analysis of fibrotic regions limits the generalizability of the findings. Future research addressing these limitations will contribute to a better understanding of inter-organ interactions in the pathogenesis of fibrosis.

CONCLUSION

The findings of this study show that the systemic effects of BLM-induced pulmonary fibrosis are not limited to the lungs but can also lead to significant histopathological changes in liver tissue. Gla administration exhibited substantial protective effects against these fibrotic and inflammatory processes, while Dex registered only limited efficacy. As a natural antioxidant, Gla is thought to represent a potential therapeutic agent in combating fibrosis. Furthermore, the use of Gla in combination with Ibx appears promising as an alternative therapeutic approach in hepatic fibrosis. In this context, future comprehensive studies involving molecular and quantitative analyses may contribute to clinical applications by further elucidating the mechanisms of action of Gla.

Acknowledgements

The Animal Ethics Committee of Adıyaman University approved the study protocol, and appropriate measures were taken by our study group to minimise pain or discomfort in the rats. The experimental part of this study and the stereological and histopathological examinations were performed at the Adıyaman University Department of Histology and Embryology.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Conflicts of Interest

There is no conflict of interest for the publication of this article.

Disclosure

The authors have reported no conflicts of interest in preparing and publishing this article.

Ethics committee approval

The experimental animals were provided and cared for by the Adıyaman University Experimental Animals Research Centre, Türkiye, following receipt of Adıyaman University Experimental Animals Ethics Committee approval (no. 2023/0027 dated 27.12.2023).

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