The Possible Curative Role of Colchicine on Bleomycin-Induced Pulmonary Fibrosis in Rats

Original Article

Sarah A. Arakib[1], Mohamed Abdel Hay Autifi[2], Eman A. El-Sawaf[1], Alsayed A. Abdelhady[1] and Manal H. Al Badawi[1]

[1]Department of Anatomy and Embryology, Faculty of Medicine, [1]Helwan University And [2]Al-Azhar University

ABSTRACT

Background: Pulmonary fibrotic disease is characterized by progressive replacement of the normal pulmonary tissue of collagen fibers leading to loss of transfer oxygen via alveolar spaces. Patients clinically have variable degrees of dyspnea ending in death in severe cases.

Aim of the Work: This study was designed to examine the possible action of colchicine in treating pulmonary fibrosis in rats.

Material and Methods: 24 male adult albino rats were allocated into 4 groups, each one containing 6 rats; GI (control), GII (colchicine), GIII (BLM), and GIV (treated group). Pulmonary fibrosis was developed experimentally by intraperitoneal (I.P) injection of BLM sulfate with 0.5 mg\kg\day 2 times weekly for three weeks. Colchicine and curative groups received the oral colchicine in a single daily dose of 1 mg/kg/day by gavage. At the end of the experiment, rats were anesthetized, and lungs were extracted and processed for H&E sections. Other specimens were processed for examination by transmission electron microscope (TEM).

Results: The BLM group showed destruction of the pulmonary parenchyma with severe damage and collapse of the alveoli, thickening of the interstitial septa, and the whole lung tissue showed severe inflammatory cellular infiltration. By electron microscope, pneumocytes were severely degenerated. The BLM group treated with colchicine showed a marked decrease in these findings.

Conclusion: Colchicine can be used as a treatment for pulmonary fibrosis and reduce its histopathological changes.

Key Words: Colchicine, rats, pulmonary fibrosis.

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Corresponding Author: Sarah A. Arakib, Assistant lecturer of Anatomy and Embryology, Faculty of Medicine, Helwan University, Helwan, Egypt, **Tel.:** 01002433933, **E-mail**: Sarah.arakeeb@med.edu.helwan.eg

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INTRODUCTION

Pulmonary Fibrosis is characterized by inflammatory changes in the lung tissue ending in scarring and fibrosis. The etiology is varied including immune-mediated, infections, side effects of medications, toxic agents, or idiopathic[1].

Bleomycin (BLM) is a chemotherapy used in Hodgkin's lymphoma. It has a common side effect of the development of pulmonary fibrosis due to lung inflammation so it can be used as a model for the progression of pulmonary fibrotic disease in rats[2].

Colchicine is an old medication extracted from plants. It can be used mainly for the treatment of gout and also for some diseases such as coronary heart disease, familial Mediterranean fever, pericarditis, and Behcet's disease[3].

Colchicine can be used in the treatment of lung fibrosis due to its anti-mitotic effect as it disrupts the tubulin, the fibroblast, and the synthesis of collagen, also it can reduce the inflammatory action[4].

During the COVID-19 epidemic, many clinical studies have justified the use of colchicine in patients with severe disease, with pulmonary fibrotic signs in computed tomography (CT), without histopathological confirmation of the drug effect[5].

So, our rationale was to study the possible histological curative effect of colchicine on lung fibrosis in rats.

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MATERIAL AND METHODS

Animals

24 adult male albino rats, each weighing about 150-200 gm, were used. The experiment was done at the Animal House, Al-Azhar University. They were housed in medium-sized cages and left for 1 week for acclimatization and they had an open access to water, and the standard rat diet.

Ethical considerations:

This study was done under the guidelines of the Committee of Animal Research Ethics, Helwan University, College of Medicine (serial number: 43-2022).

Medications:

- **Colchicine:** Was purchased from Sigma-Aldrich Co. Colchicine will be given daily by oral gavage with a dose of 1 mg/kg/day[6].

- **Bleomycin sulfate (BLM sulfate):** Was purchased from Sigma–Aldrich Co. The rats were injected with the BLM intraperitoneally twice weekly for three weeks, with a dose of 0.5 mg\kg\day dissolved in 0.5 ml of saline[7].

Animal groups:

The animals were allocated into 4 groups (6 rats \ each).

- **Group I (Control group):** The animals received saline only.

- **Group II (Colchicine group):** The animals received oral colchicine only.

- **Group III (BLM group):** The animals were injected with I.P BLM sulfate for induction of pulmonary fibrosis for 3 weeks, and the animals didn't receive any other drug.

- **Group IV (BLM + Colchicine group):** After 3 weeks of administration of BLM sulfate and establishment of pulmonary fibrosis, the animals received oral colchicine for 4 weeks later.

The animals were anesthetized after 7 weeks (the end of the study). The chest wall was incised, and the lungs were obtained.

- **Histological studies:**

1. Tissue processing for light microscopic study:

At first, fixation of the specimens was done with 10% formalin for 24 hours. Then they were dehydrated, cleared, and finally, put in paraffin blocks. Thin sections (5um) were cut and stained with Hematoxylin and Eosin (H&E)[8].

2. Tissue processing for electron microscopic study:

Other sections were processed for examination by transmission electron microscope (TEM). The specimens were fixed in 3% fresh glutaraldehyde, then dehydrated, infiltrated, embedded, polymerized, and finally cut into sections (semithin sections then ultrathin sections)[8].

- **Morphometric Study:**

- Measuring the mean weight of the lungs in all groups.

Statistical analysis

The SPSS statistical program was used to estimate the mean and the standard deviation (SD). The significance of the data was determined by the probability value (*P. value*). The difference was non-significant at $P. > 0.05$, significant $P. \leq 0.05$, and highly significant $P. \leq 0.001$.

RESULTS

H&E stained sections of the control group (Group I), showed normal lung tissue shape forming of, alveoli and alveolar sacs. The alveolar walls were seen as having epithelial lining formed of two types of cells called pneumocytes. Type I cells were flattened with flat nuclei, and Type II cells were rounded with rounded nuclei. The interstitial septa between the alveoli were seen as thin (Figure 1A). Group II (Colchicine group) showed the same picture as the control (Figure 1B). The BLM group (group III) showed a loss of normal architecture of the pulmonary tissue, with severe damage of the lung parenchyma and

alveolar collapse. The interstitial septa were thickened with interstitial secretions, marked infiltration by inflammatory cells and hemosiderin deposition. Also, hyaline membrane formation was seen. Many lung sections show intrabronchial debris, and peribronchiolar cellular infiltration, especially lymphocytes. The bronchial arteriolar walls were thickened (Figures 1C, 2A, 2B, 3A). Group IV (treated group) showed regaining of normal pulmonary architecture, and decreased thickness of inter-alveolar septa in this group. The interstitial lymphocytic infiltration and extravasated blood were still present but decreased than the group II (Figures 1D, 3B).

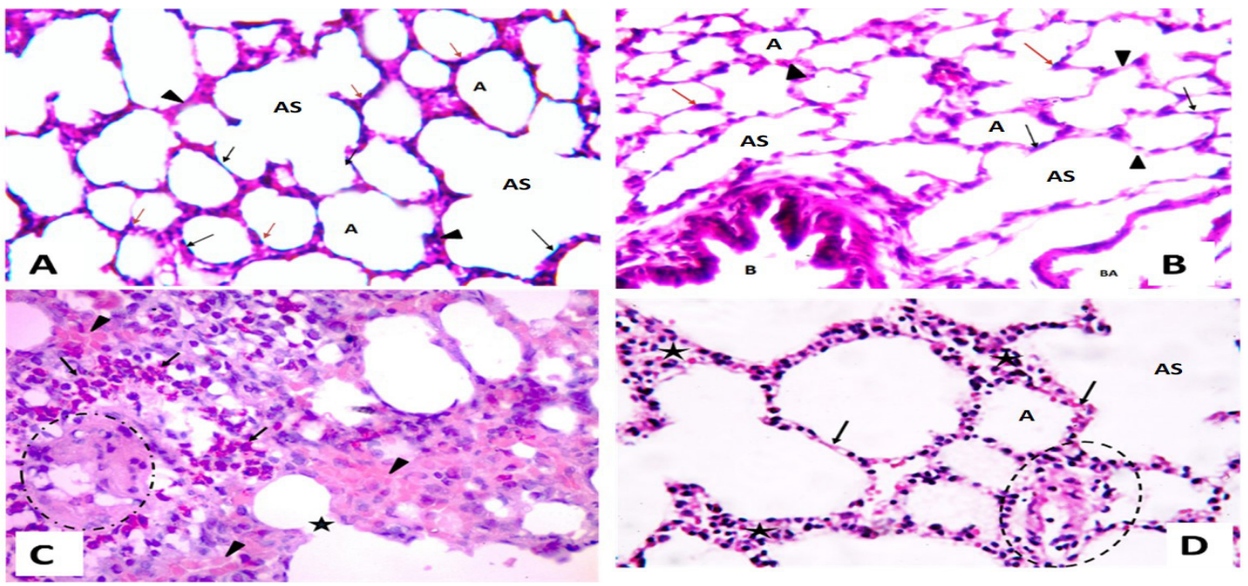

Fig.1 (A-D): Photomicrographs of H&E lung sections of the rats. A; control group showing preserved pulmonary architecture consisting of alveoli and alveolar sacs. The alveolar walls are lined by two types of pneumocytes; type I (black arrow), and type II (Red arrow), and the interstitial septa in-between are thin (arrowhead). B; Colchicine group showing the same appearance as the control. C; BLM group showing marked damage of the lung tissue, alveolar collapse, marked thickening of the interstitial septa, hyaline membrane formation (dotted circle), marked infiltration by inflammatory cells (arrow), destruction of alveolar walls with the formation of emphysematous bullae (star), and extravasated RBCs (arrowhead). D; The treated group showed regaining of normal lung parenchyma, and decreased thickness of interstitial septa (arrows). The interstitial lymphocytic infiltration and extravasated blood are slightly present (star). Notice, minimal area of alveolar collapse and edema (dotted circle).

Alveolar sacs (AS), Alveoli (A)

(H&E x400)

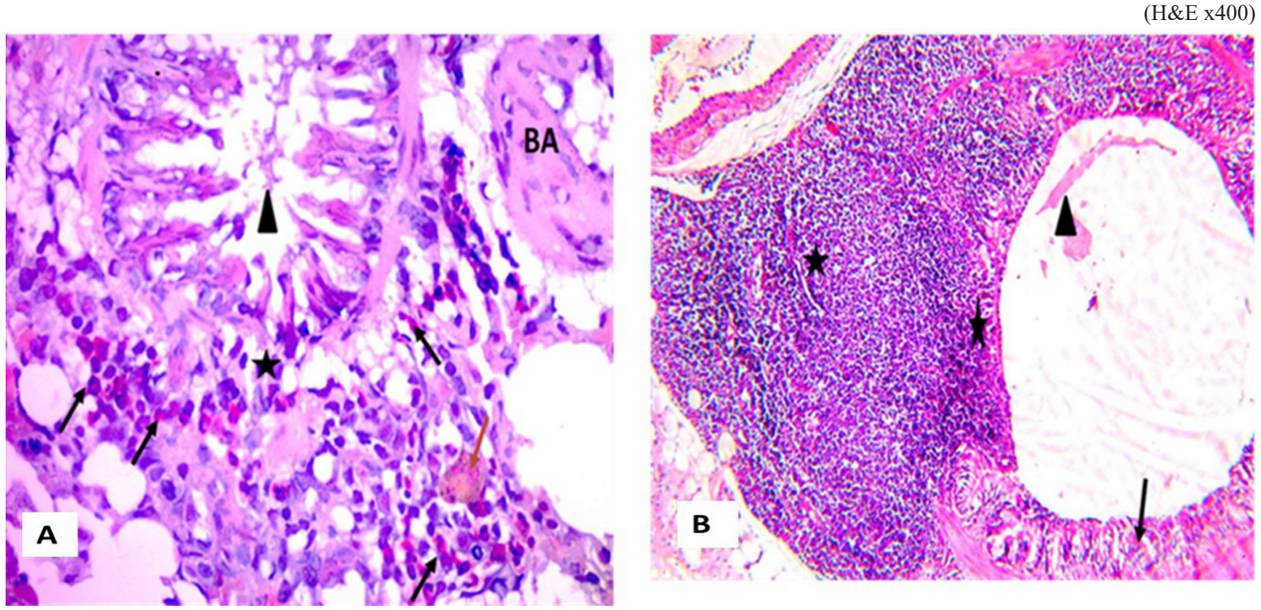

Fig. 2 (A-B): Photomicrographs of H&E lung sections of the rats of the BLM group. A; showing marked peribronchial and bronchial wall inflammatory cells infiltration (arrow), thickened bronchial arteriole wall (BA), and bronchial intraluminal debris (arrowhead) and disrupted muscle layer of the bronchiole (asterisk). Notice, the hemosiderin deposition (red arrow). B; showing marked peribronchial and bronchial wall lymphocytic infiltration (astrex). Notice, the abnormal bronchial epithelial lining (arrow), and intraluminal debris (arrowhead).

(H&E x400)

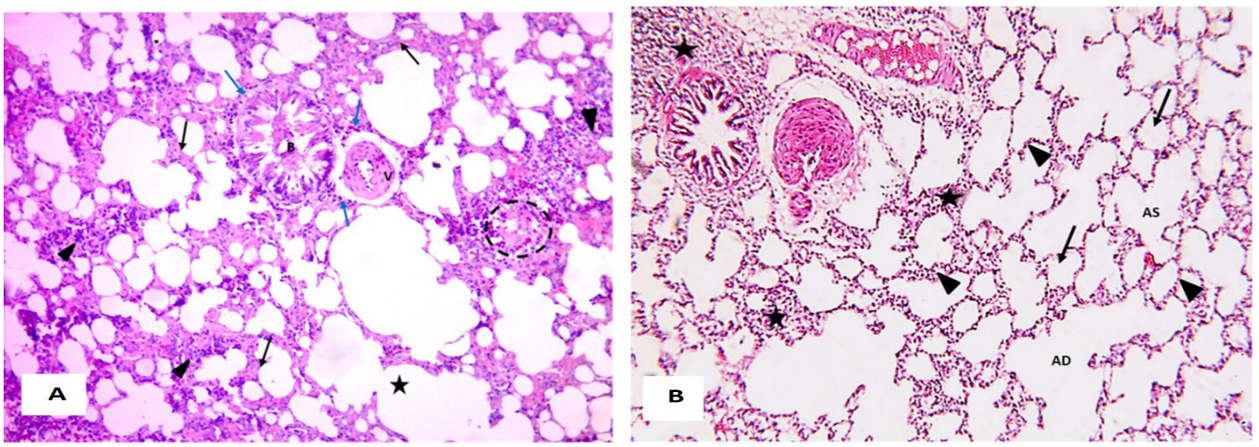

Fig. 3 (A-B): Photomicrographs of H&E-stained lung sections of the rats. A; BLM group showing destruction of pulmonary parenchyma and marked thickening of interstitial septa (black arrow) with severe infiltration by inflammatory cells (arrowhead). Notice, the emphysematous bullae (star), hyaline membrane formation (dotted circle) intrabronchial debris (B), peribronchial and perivascular inflammatory cells (blue arrows), and thickened walled bronchial arteriole (BA). B; the lung section in a treated group showing preserved pulmonary parenchyma forming of alveolar sacs (AS), alveolar ducts (AD), and alveoli (black arrows). The thickness of the interstitial septa is decreased (arrowheads). Notice the lymphocytic infiltration was still present but decreased (star).

(H&E x100)

TEM examination of the lungs of the rats of the control group showed normal alveolar air spaces separated by thin interstitial septa containing blood capillaries, and their walls were seen to have epithelial lining formed by two types of pneumocytes. The type I cells were flattened with flattened euchromatic nuclei and a thin cytoplasmic layer. The type II cells were rounded cells with euchromatic rounded nuclei. Their cytoplasm showed multiple mitochondria and lamellar bodies. The type II cells were characterized by having surface microvilli. The barrier between blood and air was seen to form endothelial cells, basal lamina, and pneumocytes type I (Figures 4, 5). The BLM group showed that the pneumocytes showed severe degeneration. The pneumocytes type I were seen as distorted shapes. Their nuclei were seen dark and shrunken and the blood-air barrier was disrupted. The pneumocytes type II also showed severe degeneration, nuclei were seen as irregular, dark, and shrunken. Their cytoplasm contained empty lamellar bodies. Some specimens showed loss of their microvilli. The interstitial septa were seen markedly thickened with marked collagen fibrils deposition. It was seen infiltrated by multiple inflammatory cells including plasma cells, lymphocytes, and eosinophils (Figures 6-9). The ultrastructure of the lungs of rats in the treated group (Group IV) revealed regaining of normal alveolar cells. The alveoli were lined with nearly normal pneumocytes. The nuclei of pneumocytes type I were seen as euchromatic and surrounded by a cytoplasmic thin rim. The blood-air barrier regained its normal character without any disruption. The nuclei of type II cells were seen as euchromatic, yet slightly irregular. The cytoplasm showed multiple rather normal mitochondria and lamellar bodies. The microvilli were reappeared (Figures 10-12).

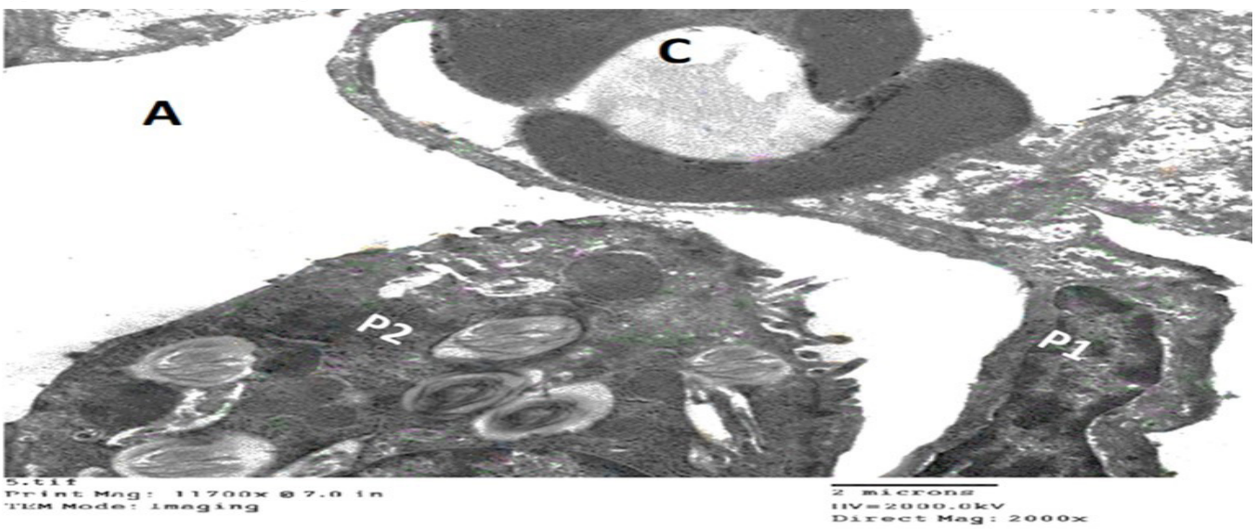

Fig. 4: An electron photomicrograph of the lung section of the control group showing normal air spaces (A) separated by interalveolar interstitial septum containing blood capillaries (C) and lined by two types of normal pneumocytes; type I (P1) and type II (P2).

(TEM x2000)

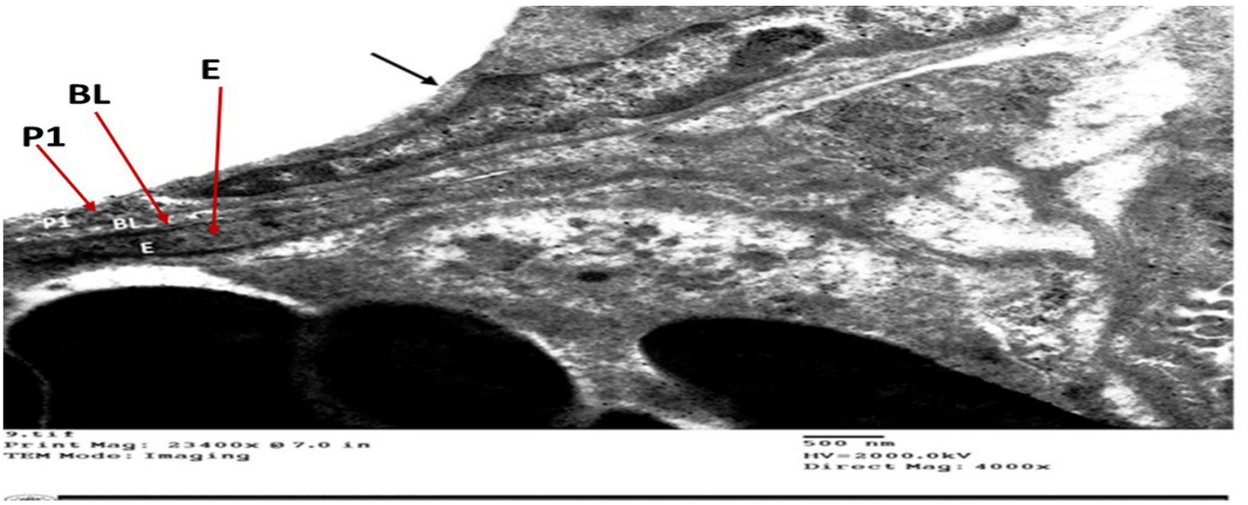

Fig. 5: An electron photomicrograph of the lung section of the control group showing part of normal pneumocyte type I (arrow), and the blood-air barrier formed of three layers; the thinned part of pneumocyte type I (PI), basal lamina (BL), and endothelial cells (E).

(TEM x4000)

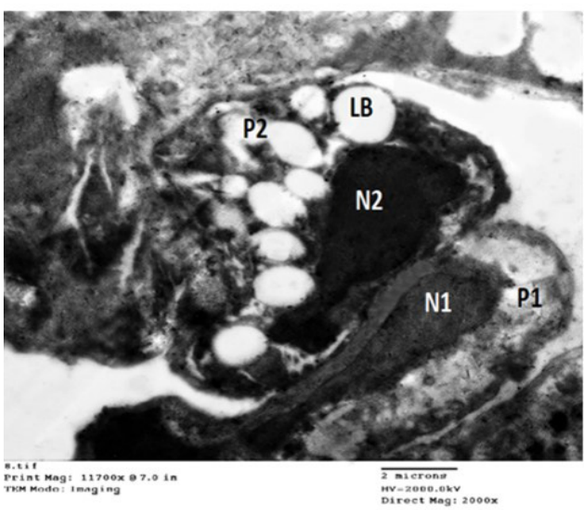

Fig. 6: An electron photomicrograph of the lung section of the BLM group shows the pneumocytes. The pneumocyte type I (P1) appears swollen, with distorted morphology, and with a dark shrunken pyknotic nucleus (N1). The pneumocyte type II (P2) also shows a dark pyknotic nucleus (N2), empty lamellar bodies (LB), and no microvilli.

(TEM x2000)

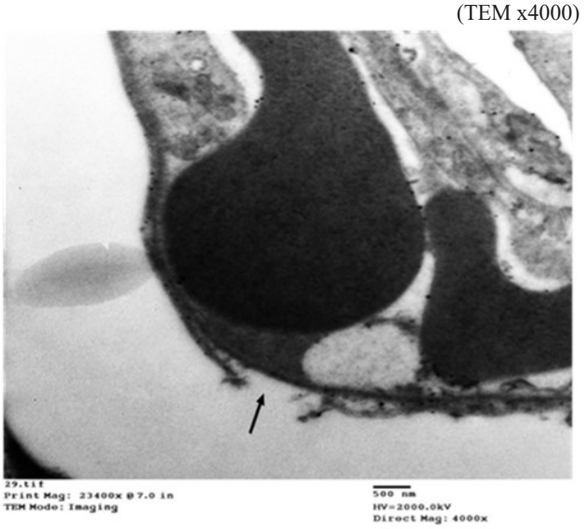

Fig.7: An electron photomicrograph of the lung section of the BLM group shows a disrupted blood-air barrier (arrow).

(TEM x4000)

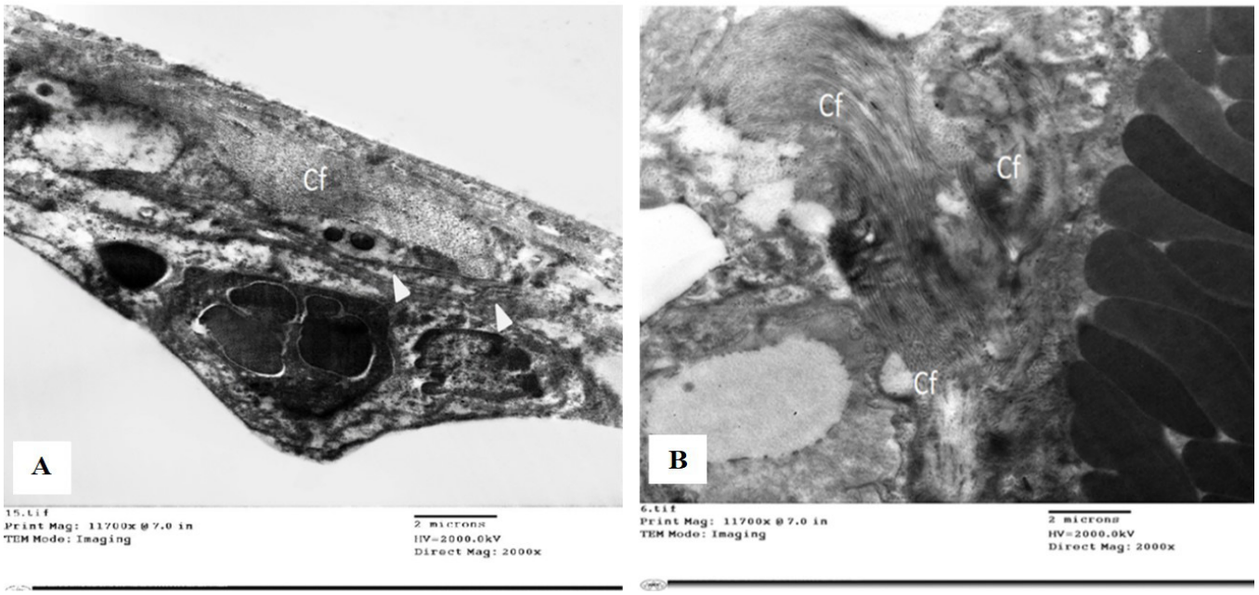

Fig. 8 (A-B): Electron photomicrographs of lung sections of the BLM group. A; showing thickened interstitial septum with a bundle of collagen fibrils (Cf). Note, the collapsed alveolar space (arrowheads). B; showing marked thickening of the interstitial septum with multiple bundles of collagen fibrils (Cf).

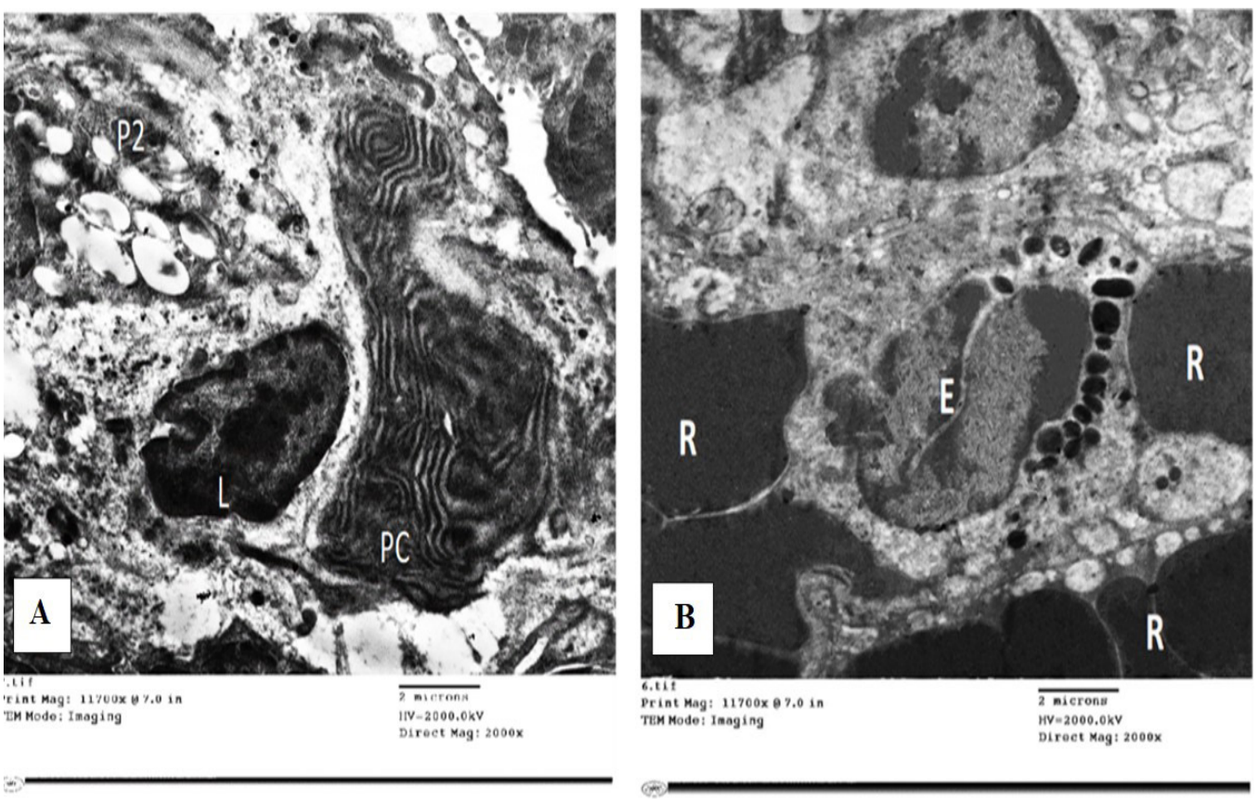

Fig.9 (A-B): Electron photomicrographs of the lung sections of the BLM group. A; showing plasma cell (PC) lymphocyte (L) infiltration in the thickened septum. Note, the degenerated type II pneumocyte (P2). B; showing eosinophil (E) and extravasated RBCs (R) in the interstitium.

(TEM x2000)

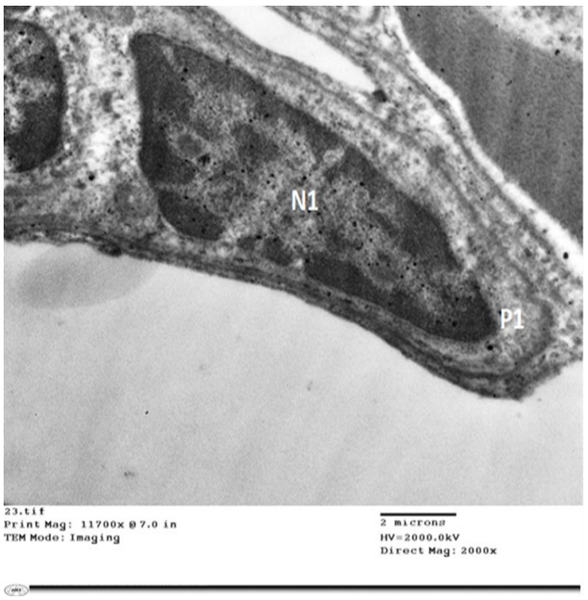

Fig. 10: An electron photomicrograph of the lung section of the treated group shows normal pneumocyte type I (P1). Note the normal appearance of the euchromatic flat nucleus (N1) surrounded by a thin cytoplasmic layer.

(TEM x2000)

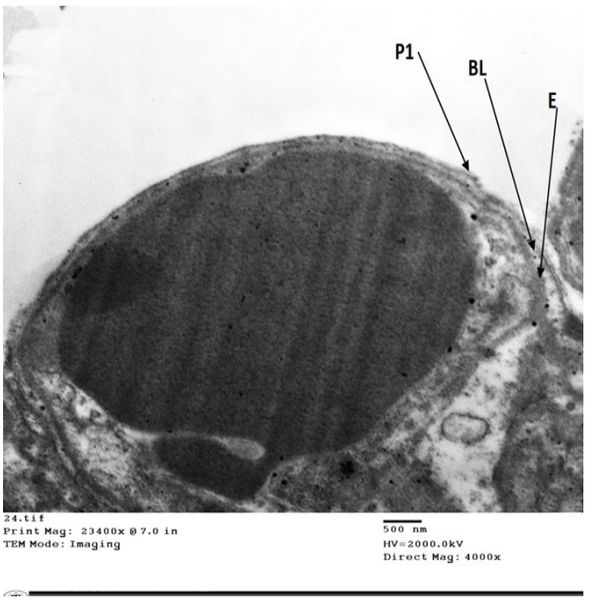

Fig. 11: An electron photomicrograph of the lung section of the treated group shows a normal blood-air barrier, consisting of 3 layers: endothelial cells (E), basal lamina (BL), and pneumocyte type I (PI).

(TEM x4000)

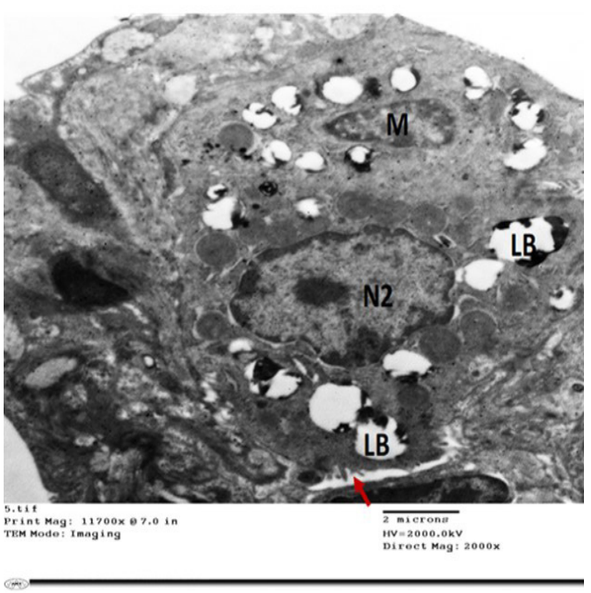

Fig. 12: An electron photomicrograph of a lung section of the treated group showing a type II pneumocyte with a slightly indented euchromatic nucleus (N2) and prominent nucleolus. The cytoplasm contains rather normal lamellar bodies (LB) and numerous mitochondria (M). Note, the presence of surface microvilli (red arrow).

(TEM x2000)

Morphometric results:

Measuring the mean weight of the lung:

The mean weight of the lung was 1.2 ± 0.05 gm in the control group (GI), 1.4 ± 0.24 gm in the colchicine group (GII), 2.3 ± 0.32 gm in BLM group (GIII), and 1.7 ± 0.11gm (GIV).

There was a high significance increase in the mean weight of the lung in the BLM group compared to the control (*P value* <0.001). The treated group (GIV) showed a significant increase in the mean weight of the lung as compared to the control (*P value*=0.023), and a high significance decrease as compared to the BLM group (*P value* <0.001) (Table 1, Figure 13).

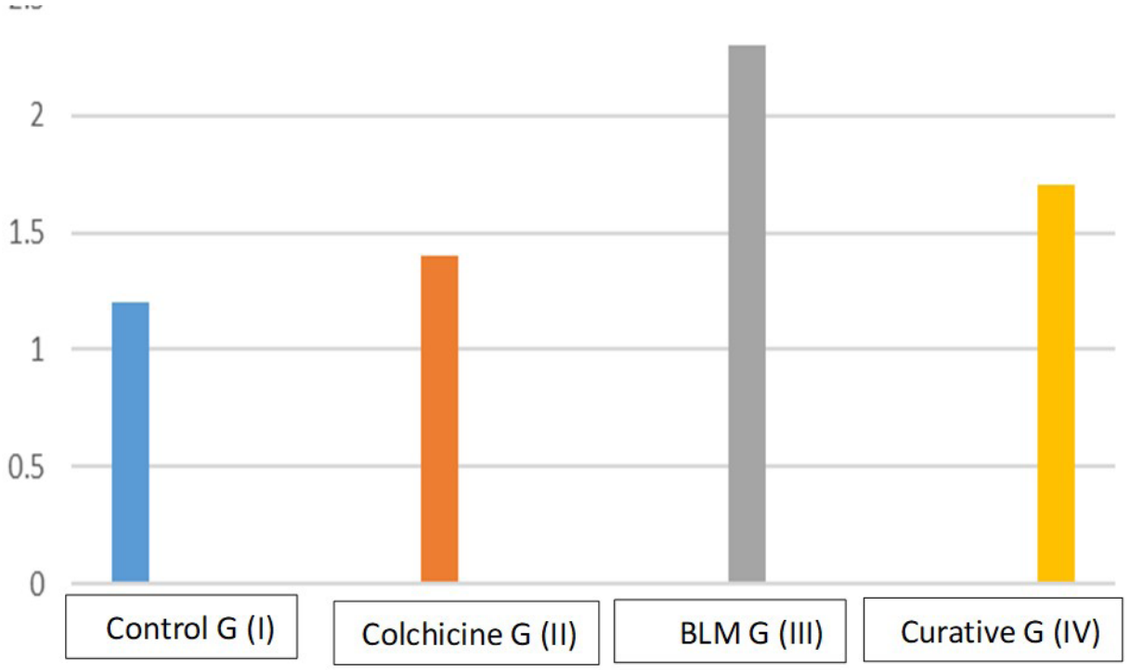

Fig. 13: Bar chart representing the mean weight of the lung in grams in all groups.

Table 1: The mean weight of the lung in grams in all groups.

Group	Mean ± SD.	p[a]	p[b]
G I (control G.)	1.2 ± 0.05		
G II (Colchicine G.)	1.4 ± 0.24	1.000	<0.001**[b]
G III (BLM G.)	2.3 ± 0.32	<0.001**[a]	
GIV (Curative G.)	1.7 ± 0.11	0.023*[a]	<0.001**[b]

F: ANOVA
* Significant $p \leq 0.05$ ** Highly significant $p < 0.001$
a: Compared to the control group b: Compared to the BLM group

DISCUSSION

Pulmonary fibrotic diseases are group diseases affecting lung parenchyma, they are resistant to treatment with a high incidence of mortality rate. They are characterized by irreversible progressive damage of lung tissue ending in the formation of scars leading to gas exchange disruption, multi-organ failure, respiratory failure, and finally death. The commonest and the severest form is idiopathic pulmonary fibrotic disease (IPF), having unknown etiology[9]. Our study aimed to demonstrate the BLM-induced histopathological changes in the lung and the possible curative effect of colchicine. The BLM is the most common medication used to induce experimental pulmonary fibrosis in rats because of its direct and maintained toxicity on the lung[10].

In, the present work, the LM examination of H&E stained sections of the BLM group showed marked destruction of the lung parenchyma, marked thickening of the interstitial septa, hyaline membrane formation, marked interstitial inflammatory cellular infiltration, formation of emphysematous bullae and extravasated RBCs. These findings were agreed with ***Zakaria et al.,*** (2021) who stated that the BLM can cause pneumonitis as it can stimulate the alveolar macrophages leading to the liberation of multiple cytokines, which also stimulate the activation and the proliferations of the fibroblasts, and finally ending by lung fibrosis[10].

Moodley et al., (2009) also added that the BLM intake leads to direct inflammation and fluid exudation in the lung tissue, with infiltration by multiple inflammatory cells and production of many cytokines[11].

In the current work, the bronchioles were seen markedly affected in the BLM group as bronchiolar epithelium was seen as abnormal, the muscle layer was disrupted, and there was intrabronchial debris, and peribronchiolar cellular infiltration, especially lymphocytes. In severely affected sections the lymphocytic infiltration was seen invading most of the bronchiolar wall. These findings were agreed with ***Zakaria et al.,*** (2021) who stated that the peribronchiolar cellular infiltration was due to the chemotactic effect of cytokines[10].

In the present study, the thickening of bronchial arteriolar walls was seen in the H& E stained sections of the BLM group. These findings agreed with ***Schroll et al.,*** (2010) who reported that BLM resulted in pulmonary hypertension due to its fibrotic effect on the lung tissue[12].

In the current work, TEM examination of the BLM group showed marked degeneration of pneumocytes (I and II). Their shape was markedly distorted, the nuclei were shrunken, and type II pneumocytes contained empty lamellar bodies. The blood-air barrier was disrupted. These findings agreed with ***Zakaria et al.,*** (2021) who stated that EM results of the BLM group showed that marked degeneration of the pneumocytes could be due to the binding of BLM to DNA forming a complex, leading to oxidative damage and liberation of free oxygen radicals leading to cellular lipid peroxidation[10].

In the present study, TEM sections showed an infiltration of the lung tissue with inflammatory cells such as plasma cells, lymphocytes, and eosinophils. Also, a marked deposition of collagen fibers was observed in the pulmonary interstitium. This agreed with Wynn (2011) who stated that BLM can cause infiltration of the lung by multiple inflammatory cells leading to its inflammation and finally ending in fibrosis[9]. Also, ***Hapani et al.,*** (2010) added that the BLM can lead to eosinophilic infiltration due to allergic reaction[13].

Colchicine has been repeatedly proposed for use in the treatment of lung fibrotic disease due to its anti-inflammatory and anti-fibrotic actions, but not taken FDA approval yet[14]. In the COVID-19 outbreak, it has been used in the protocol in severe cases of COVID-19 with the risk of developing pulmonary fibrosis[15].

Also, in the present work, the H&E stained sections of the treated group (received BLM followed by treatment with colchicine for 1 month). The pulmonary architecture was rather preserved, focal areas of alveolar exudation and collapse were markedly decreased than the BLM group II, and interalveolar septa thickness and interstitial cellular infiltration were relatively decreased as compared to the BLM group. The bronchial epithelium of the treated group regained its normal continuous folded respiratory epithelium.

The ultrastructure of the lungs of rats in the treated group revealed regaining of the normal morphology of the pneumocytes (I, II). The blood-air barrier regained its normal character. The lamellar bodies in the cytoplasm of pneumocytes type II have become normal. The collagen deposition in the interstitium was markedly decreased as compared to the BLM group. This agreed with ***Esther et al.,*** (2020) who stated that colchicine has anti-inflammatory and anti-fibrotic effects[16].

Leung et al., (2015) said that colchicine has anti-mitotic action as it can obstruct the function of the cytoskeleton by inhibiting the polymerization of β-tubulin into microtubules., thus inhibiting the growth of the microtubule. Also, it can cause depolymerization of microtubules, when increasing its concentration[3].

Furthermore, ***Schlesinger et al.,*** (2020) reported that colchicine can also disturb the neutrophil inflammasome complex, which causes activation of the inflammatory mediators. Colchicine can also decrease the adhesion of the neutrophil and decrease H_2O_2 production[5].

In the current work, statistical analysis results by measuring the mean weight of the lung showed that the BLM group showed a high significance increase compared to the control. The curative group showed a significant increase in the mean weight of the lung as compared to the control, and a high significance decrease as compared to the BLM group. ***Kitzerow et al.,*** 2022 reported similar findings[17].

CONCLUSION

Colchicine can decrease histopathological and ultrastructure changes in lung fibrotic disease, through its anti-inflammatory and anti-fibrotic actions.

No any financial support

The paper isn't published in other journals or presented at a meeting, organization, or any other place

CONFLICT OF INTERESTS

No conflicts of Interest

The study was done under the guidelines of the animal research committee, faculty of medicine, Helwan University (serial No. 43-2022)

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الدور العلاجى المحتمل للكولشيسين على التليف الرئوى الناتج عن البليوميسين فى الجرذان

سارة عبدالمنعم عراقيب[١]، محمد عبد الحى عطيفى[٢]، ايمان احمد الصواف[١]، السيد عبد الرحمن عبد الهادى[١] و منال حمدى البدوى[١]

[١]قسم التشريح والاجنة، كلية الطب، جامعة حلوان

[٢]قسم التشريح والاجنة، كلية الطب، جامعة الازهر

المقدمة: يعتبرمرض التليف الرئوى من الامراض الخطيرة التى يتم فيه استبدال أنسجة الرئة الطبيعية تدريجيًا بالخلايا الليفية والكولاجين مما يتسبب في فقدان القدرة على نقل الأكسجين إلى مجرى الدم عبر الحويصلات الرئوية. يعانى المرضى من ضيقًا تدريجيًا في التنفس يؤدي في النهاية إلى الوفاة.

الهدف من البحث: الهدف من البحث هواثبات دور الكولشيسين في علاج التليف الرئوى فى الفئران.

المادة و طرق البحث: تم استخدام ٢٤ من ذكور الفئران البيضاء في هذه الدراسة حيث تم تقسيمهم عشوائيا إلى ٤ مجموعات (٦ فئران لكل منها): المجموعة الأولى (المجموعة الحاكمة): تلقت محلول محلى فقط، المجموعة الثانية (تلقت الكولشيسين فقط): فى هذه المجموعة الفئران غير مصابة بمرض التليف الرئوى وتلقت الكولشيسين فقط بجرعة ١مجم / كجم بالفم، المجموعة الثالثة (مجموعة البليوميسين):تم حقن الفئران بعقار البليوميسين من أجل اصابتها بمرض التليف الرئوى، بجرعة ٠,٥ مجم / كجم مذاب فى محلول ملحى داخل الغشاء البريتوني كجرعتين اسبوعيا لمدة ٣ اسابيع، المجموعة الرابعة (المجموعة العلاجية): تلقت الفئران فى هذه المجموعة البليوميسين اولا لمدة ٣ اسابيع، وبعد حدوث التليف الرئوى تلقت الكولشيسين بنفس الجرعة السابقة لمدة ٤ اسابيع اخرى.

في نهاية التجربة، تم تخدير الحيوانات وشق جدارالصدر وأخذ عينات من الرئتين وتم تمريرها ومعالجتها ثم فحصها بواسطة المجهر الضوئي، ايضا تم معالجة باقى العينات لفحصها بالميكروسكوب الالكترونى النافذ.

النتائج: لقد أظهر الفحص الهستولوجى للانسجة ان المعالجة باعطاء الكولشيسين قد ادى الى انخفاض نسبة التليف الرئوى الناتج عن البليوميسين وقد اتضح ذلك من خلال استعادة البنية الطبيعية لانسجة الرئة الى حد ما، كما انخفض سمك الحاجزالبينى بين الحويصلات الهوئية بشكل ملحوظ، وانخفض ايضا تخلله بالخلايا الالتهابية وارتشاح السوائل خلاله نسبيًا، وشوهد ايضا استعادة الشعيبات الهوائية شكلها ونمطها الطبيعى، كشف ايضا فحص العينات بالميكروسكوب الالكترونى النافذ في المجموعة العلاجية استعادة الخلايا الرئوية نمطها الطبيعي إلى حد ما مع بدأ ملء الأجسام الصفاحية الموجودة بسيتوبلازم الخلايا الرئوية من النوع الثاني واستعاد حاجز الهواء الدموي طابعه الطبيعي، كما انخفض ترسب الكولاجين بشكل ملحوظ فى النسيج البينى مقارنة بمجموعة البليوميسين.

الاستنتاج: أثبتت هذه الدراسة أن عقار الكولشيسين قد حد من التغيرات المرضية المصاحبة للتليف الرئوي، من خلال تأثيراته المضادة للالتهابات والمضادة للتليف.