



## Doxorubicin toxicity on pulmonary tissue

Saif Salah Abdul Hassan,

Department of Computer, College of Basic Education,  
Al-Mustansiriya University, Baghdad, Iraq

### Abstract

A variety of malignancies can be effectively treated with doxorubicin. It is mostly used to treat leukemias, lymphomas, and a variety of solid cancers, including thyroid, breast, lung, and ovarian cancer. Doxorubicin exhibits dose-dependent cytotoxicity, which is especially harmful to the heart, just as other anti-cancer drugs. As an anthracycline, doxorubicin is an antibiotic that has been researched for many years and is utilized as a cytostatic medication in lung cancer treatment. This study aims to identify damage to lung tissue due to the impact of different doses of doxorubicin. Male albino rats, which weighed between 200 and 250 grams. Laboratory animals were obtained from the Technology Research Center, University of Nahrain, and laboratory rats were bred at the University of Baghdad, College of Science, Department of Biology, Animal House. Three sets of six male rats were used in the investigation. Normal saline was given to Group 1, doxorubicin at a dose of 5 mg/kg body weight was administered intraperitoneally twice a week for four weeks to Group 2, and doxorubicin at a dose of 10 mg/kg body weight was administered intraperitoneal twice a week for four weeks to Group 3. 4% formaldehyde was used to fix the lung tissues for histopathological analysis. Histopathological analysis revealed various effects on the lung tissues. The laboratory animal dosing period is from 2/1/2025 to 3/1/2025 for 4 weeks. In the sections from rats treated with doxorubicin (5 mg/kg body weight), acute pulmonary hemorrhage, diffuse pulmonary emphysema, and pulmonary edema were observed. Conversely, the sections from the rats treated with doxorubicin (10 mg/kg body weight) displayed signs of acute lung necrosis, acute lung abscess, and hemorrhagic infarction.

**Key words:** pulmonary, doxorubicin, toxicity, intraperitoneal, histopathology

## Introduction

With over 6 million deaths annually, cancer continues to be the world's top cause of death (Abullaev, 2000). It works well against many types of cancer and is mostly used to treat solid tumors such as thyroid, breast, lung, and ovarian cancer, as well as lymphomas and leukemias (Gianni, 2007). Similar to the adverse effects of other anti-cancer agents, doxorubicin has its own dose-dependent cytotoxicity on the heart and other organs (Naiyara, 2010). It is one of the established and commonly used antineoplastic agents in treating different types of cancers, including pediatric cancer, leukemia, breast cancer, etc. Dox is an inhibitor of the DNA topoisomerase II enzyme and causes damage to the DNA (Renu, 2018). Doxorubicin (Dox) lipid-binding properties link the body's organs to the cell membrane and nucleotide base insertion. Dox's insertion prevents nucleotide replication, which in turn stops DNA and RNA polymerases from working. Dox appears to have a potent method for killing cells through its interaction with topoisomerase II to generate DNA-reputable complexes (Speth, 1988). Cells treated with Dox have demonstrated notable morphological changes linked to apoptosis, or programmed cell death. Globally, lung cancer continues to be the primary cause of cancer-related fatalities (Dela, 2011). About one million new cases and 900,000 deaths worldwide are attributed to non-small-cell lung cancer (NSCLC), which makes up a sizable fraction of these cases (Song, 2018). For cancer, chemotherapy is still the recommended course of treatment, frequently used in conjunction with surgery (Tan, 2017). Chemotherapy, particularly doxorubicin (DOX), has been used by several studies to treat lung cancer (Srivastava, 2016). DOX, an anthracycline antibiotic, is utilized as a cytostatic agent in lung cancer chemotherapy and has been studied for several decades (Zhang, 2015). But there are still a number of difficulties. One major issue is that treatment with DOX can lead to toxic side effects, including cardiotoxicity and hair loss (Dou, 2018). The aim of this study is to identify lung tissue due to the effects of different doses of doxorubicin.

## Materials and Methods

### Animal preparation

The National Institute of Nutrition (NIN) in Hyderabad provided the Wistar Kyoto breed male albino rats, which weighed between 200 and 250 grams. Laboratory animals were obtained from the Technology Research Center, University of Nahrain, and laboratory rats were bred at the University of Baghdad, College of Science, Department of Biology, Animal House. The rats were kept in cages made of solid-bottom

polypropylene and fed a commercial mash.

### **Drug preparation**

The drug was obtained from pharmacies specializing in the sale of anti-cancer drugs in the Al-Saadoun Street area. Doxorubicin, produced by Baxter International Company (U.S.), was used by injecting 5 mg per kilogram of body weight per week as a low dose and 10 mg per kilogram of body weight per week as a high dose.

### **Study design**

Three groups of six male rats each were kept in the animal house of the department. Group 1 served as the control and received normal saline. Group 2 was administered doxorubicin at a dosage of 5 mg/kg body weight via intraperitoneal injection twice a week for four weeks. Group 3 received Doxorubicin at a dosage of 10 mg/kg body weight. I was dosed with laboratory animals at the University of Baghdad, College of Science, Department of Biology, Animal House.

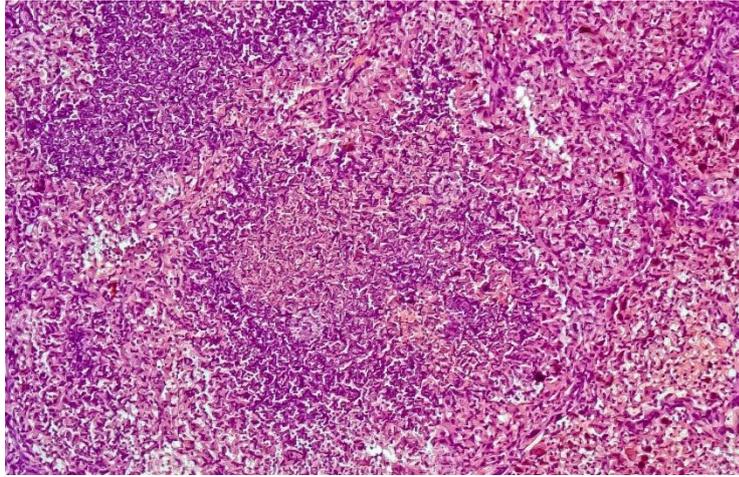
### **Result and discussion**

The lung tissue, 40x zoom. Micrography showing bronchiole and alveoli, histology, micrograph, control animal with normal saline] Figure 1].

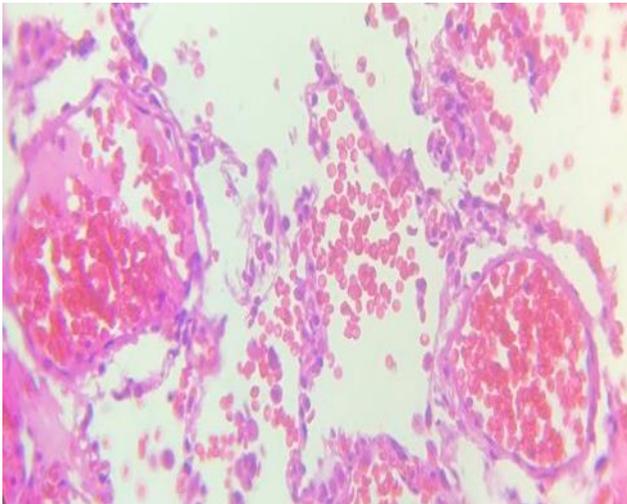
The lung sections exhibited various conditions and treatments across two groups. In group 1, the lung section displayed acute lung hemorrhage treated with doxorubicin at a dosage of 5 mg per kilogram of body weight [Figure 2]. Another section from group 1 revealed diffuse lung emphysema and hemorrhage, also treated with doxorubicin at 5 mg per kilogram of body weight [Figure 3]. Additionally, a lung section showed lung edema and hemorrhage, treated with the same dosage of doxorubicin in group 1 [Figure 4]. In group 2, the lung section demonstrated acute lung necrosis treated with doxorubicin at a higher dosage of 10 mg per kilogram of body weight. [Figure 5]. Another section from group 2 revealed an acute lung abscess treated with doxorubicin at 10 mg per kilogram of body weight. [Figure 6]. Lastly, a lung section showed a hemorrhagic infarct, also treated with doxorubicin at 10 mg per kilogram of body weight in group 2 [Figure 7].

The section in the lung of animals treated with doxorubicin (5 mg per kilogram of body weight) appears to show low damage, and animals treated with doxorubicin (10 mg per kilogram of body weight) appear to show high damage in the tissue of the lung compared with control animals.

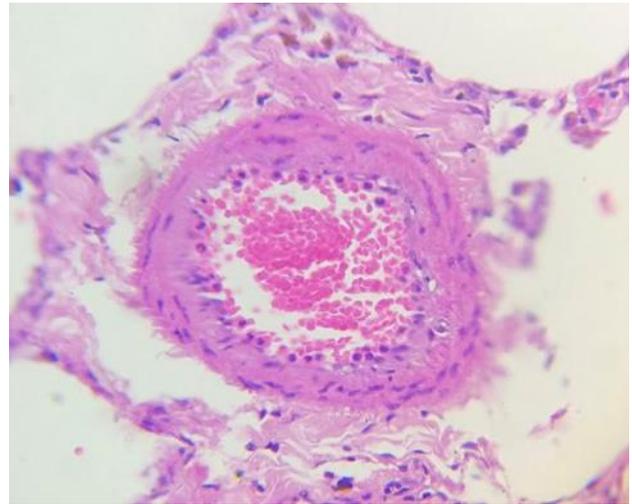
The control group shows normal tissue, 5% lung tissue damage, no inflammation, and no necrosis. The Doxorubicin group (5mg) shows moderate tissue damage, 30% lung tissue damage, moderate inflammation, mild necrosis, and no fibrosis. The doxorubicin group (10mg) shows lung tissue damage of 60% and excessive fibrosis and necrosis in multiple areas. (Table 1).



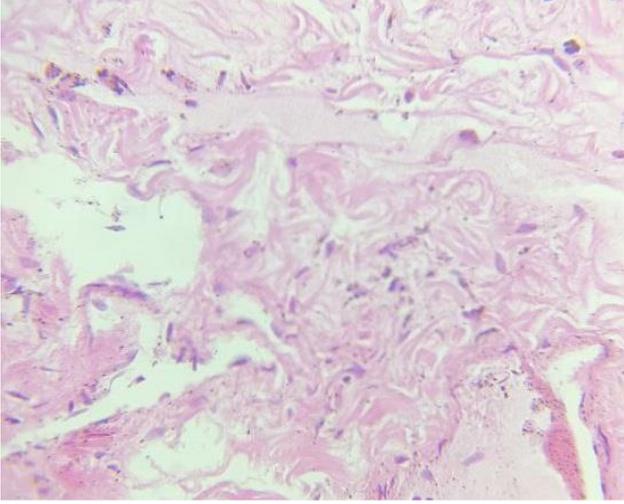
**Figure 1:** Cross-section of rat normal lung tissue, 40x zoom. Micrograph showing bronchiole and alveoli, histology, micrograph, control animal with normal saline H and E, 40X.



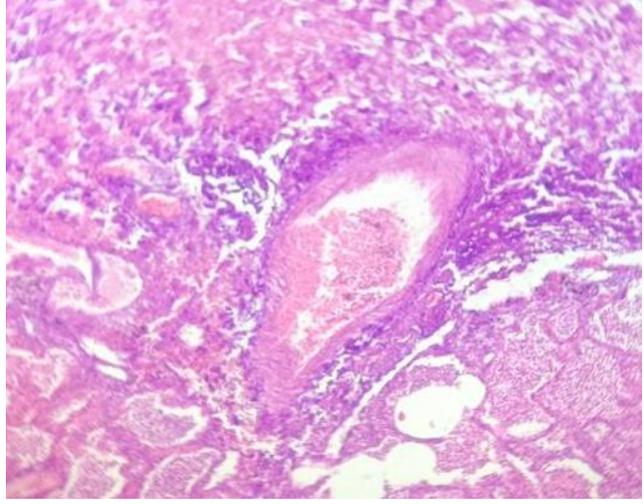
**Figure2:** Photomicrograph of lung showing acute pulmonary hemorrhage treated with doxorubicin (5 mg/kg b.w.) (H and E, 40X).



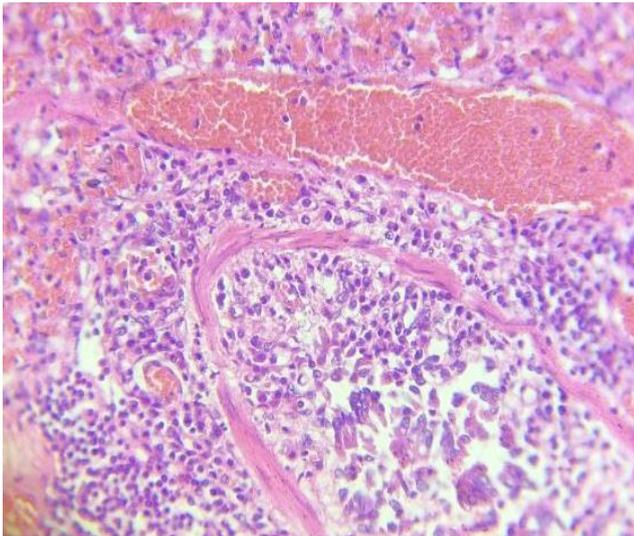
**Figure 3:** Photomicrograph of lung showing diffuse pulmonary emphysema hemorrhage treated with doxorubicin (5 mg/kg b.w.) (H and E, 40X).



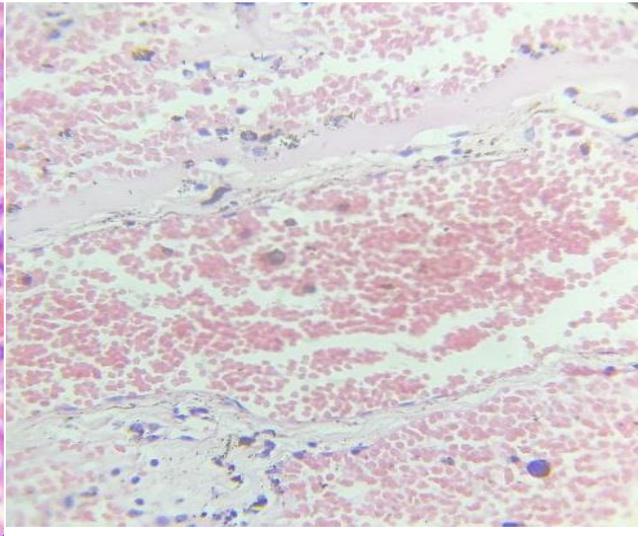
**Figure 4:** Photomicrograph of lung showing pulmonary edema hemorrhage treated with doxorubicin (5 mg/kg b.w.) (H and E, 40X).



**Figure 5:** Photomicrograph of lung showing acute pulmonary necrosis treated with doxorubicin (10 mg/kg b.w.) (H and E, 40X).



**Figure 6:** Photomicrograph of lung showing acute lung abscess treated with doxorubicin (10 mg/kg b.w.) (H and E, 40X).



**Figure 7:** Photomicrograph of lung showing hemorrhagic infarct of lung treated with doxorubicin (10 mg/kg b.w.) (H and E, 40X).

**Table 1: show the percentage effect of doxorubicin on lung tissue.**

Groups	Lung tissue damage %	Severity of inflammation	Presence of necrosis	Presence of fibrosis	Notes
Control	5%	No inflammation	No	No	Normal tissue
5 mg Doxorubicin	30%	Moderate inflammation	Mild	No	Moderate tissue damage
10 mg Doxorubicin	60%	Sever inflammation	Obvious	Present	Excessive fibrosis and necrosis in multiple areas

According to the study's findings, the lungs underwent histological alterations after receiving doxorubicin once a week for four weeks. Oxidative stress brought on by reactive intermediates, particularly doxorubicin semiquinone, which is produced during doxorubicin metabolism, may be the source of the harm to these organs.

Reactive oxygen species are produced when the anthracyclines react with molecular oxygen to create semiquinone radical intermediates. Cytological damage results from these species' interactions with biological macromolecules (De Beer, 2001).

As an anthracycline, DOX is known to have a quinone form that may be reduced by one electron to a semiquinone radical. Then, molecular oxygen is reduced to superoxide anion, which dismutates into H<sub>2</sub>O<sub>2</sub> to recreate this parent quinone once again. By taking electrons from lipids in cell membranes, reactive oxygen species (ROS) cause oxidative stress, lipid peroxidation, and oxidant-induced cell damage. Furthermore, ROS can harm mitochondria both structurally and functionally, which is why our study found such strong apoptotic characteristics (Mubarak, 2018).

Oxidative stress, inflammation, endoplasmic reticulum-mediated apoptosis, and damage to DNA and RNA are among the toxicities associated with doxorubicin (DOX). Cellular membranes may sustain damage as a result of

the hydroxyl radicals and superoxide anions produced when the cytochrome P-450 enzyme breaks down DOX (Abdel-Daim, 2017).

There is little research on doxorubicin-induced lung damage. According to Take et al., doxorubicin and paclitaxel together harm the lungs (Take et al., 2008). In a different research, they showed that fullerene C60(OH)24's antioxidant qualities helped to lessen the lung damage that doxorubicin induced in rats (Srdjenovic et al., 2010).

Thymoquinone has been shown in several studies to have both therapeutic and preventive effects against lung injury. Al-Gabri et al. (2019) documented thymoquinone's protective effects on lung damage, while Yetkin et al. (2020) showed its efficacy in mitigating lung damage caused by smoking. Boskabady et al. (2021) reported that thymoquinone reduced inflammation and pathological changes in the lungs induced by lipopolysaccharide. Additionally, Alzohairy et al. (2021) found that thymoquinone had a protective role against lung damage caused by benzo(a)pyrene in rats.

Studies on the lung injury of that doxorubicin causes lung damage together with paclitaxel in their study (Take et al., 2008). In another study, they showed that fullerenol C60(OH)24 reduced the damage to lungs caused by doxorubicin in rats, thanks to its antioxidant property (Srdjenovic et al., 2010). Studies are showing that thymoquinone has a therapeutic and protective effect on lung damage (Al-Gabri et al., 2019).

In their study, Yetkin et al. showed the protective effect of thymoquinone on lung damage caused by smoking (Yetkin et al., 2020). In the study of Boskabady et al., they reported that thymoquinone reduced inflammation and pathological changes caused by Lipopolysaccharide in the lung (Boskabady et al., 2021).

### Conclusion

The study's findings showed that doxorubicin at a level of 5 mg per kilogram of body weight had a more harmful effect on the pulmonary tissue of male albino rats compared with the dose of doxorubicin of 10 mg/kg.

### References

- Abdel-Daim, M Kilanyany OE, Khalifa HA, Ahmed AA, Allicin M. (2017). ameliorates doxorubicin-induced cardiotoxicity in rats by suppressing oxidative stress, inflammation, and apoptosis. *Cancer Chemother Pharmacol* 745–753. <https://doi: 10.1007/s00280-017-3413-7>.
- Abullaev FI, Luna RR, Roitenburd BV, Espinosa AJ. (2000) Pattern of childhood cancer mortality in Mexico. *Arch Med Res* ;31: 526-31. [https://doi: 10.1016/s0188-4409\(00\)00094-1](https://doi: 10.1016/s0188-4409(00)00094-1)

Al-Gabri, N A, Qaid MM, El-Shaer NH, Ali MH. & Abudabos, AM. (2019). Thymoquinone ameliorates pulmonary vascular damage induced by Escherichia coli-derived lipopolysaccharide via cytokine downregulation in rats. *Environ Sci Pollut Res Int.*, 26(18):18465-18469. <https://doi:10.1007/s11356-019-05229-4>. Epub 2019 May 2.

Al-Gabri, N.A.; Qaid, M.M.; El-Shaer, N.H.; Ali, M.H. & Abudabos, AM. (2019) Thymoquinone ameliorates pulmonary vascular damage induced by Escherichia coli-derived lipopolysaccharide via cytokine regulation in rats. *Environ Sci Pollut Res Int.*, 26(18):18465-18469. <https://doi:10.1007/s11356-019-05229-4>.

Alzohairy MA, Khan AA, Alsahli MA, Almatroodi SA, Rahmani AH. (2021) Protective Effects of Thymoquinone, an Active Compound of Nigella sativa, on Rats with Benzo(a)pyrene-induced Lung Injury through Regulation of Oxidative Stress and Inflammation. *Molecules*, 26(11):3218. <https://doi.org/10.3390/molecules2611>.

Boskabady M, Khazdair MR, Bargi R, Saadat S, Memarzia A, Mohammadian Roshan N, Hosseini M, Askari VR, Boskabady MH. Thymoquinone (2021). Ameliorates Lung Inflammation and Pathological Changes Observed in Lipopolysaccharide-Induced Lung Injury. *Evid Based Complement Alternat Med.*, 6681729.

<https://doi:10.1155/2021/6681729>. collection.

Boskabady M, Khazdair MR, Bargi R, Saadat S, Memarzia A, Mohammadian Roshan N, Hosseini M, Askari VR, Boskabady MH. (2021) Thymoquinone Ameliorates Lung Inflammation and Pathological Changes Observed in Lipopolysaccharide-Induced Lung Injury. *Evid Based Complement Alternat Med.*, 2021: 6681729.

<https://doi:10.1155/2021/6681729>.

De Beer EL, Bottone AE, Voest EE. (2001). Doxorubicin and mechanical performance of cardiac trabeculae after acute and chronic treatment: A review. *Eur J Pharmacol*; 415:1-11.

[https://doi:10.1016/s0014-2999\(01\)00765-8](https://doi:10.1016/s0014-2999(01)00765-8).

Dela Cruz CS, Tanoue, L.T. Matthay, R.A. (2011). Lung cancer: epidemiology, etiology, and prevention, *Clin. Chest Med.* 32 (4) 605–644.

<https://doi:10.1016/j.ccm.2011.09.001>.

Dou XQ, Wang H, Zhang J, Wang F, Xu GL, Xu CC, Xu HH, Xiang SS, J.Fu, Song H.F, (2018) Aptamer-drug conjugate: targeted delivery of doxorubicin in a HER3 aptamer-functionalized liposomal delivery system

reduces cardiotoxicity, *Int. J. Nanomedicine* 13 763–776.

<https://doi:10.2147/IJN.S149887.eCollection> 2018.

Gianni L, Salvatorelli E, Minotti G. (2007) Anthracycline cardiotoxicity in breast cancer patients: Synergism with trastuzumab and taxanes. *Cardiovasc Toxicol*; 7:67-71. [https://doi: 10.1007/s12012-007-0013-5](https://doi:10.1007/s12012-007-0013-5).

Karabulut D, Ozturk E, Kuloglu N, Akin AT, Kaymak E & Yakan B. (2020). Effects of vitamin B12 on methotrexate hepatotoxicity: receptor-interacting protein (RIP) kinase evaluation. *Naunyn Schmiedebergs Arch Pharmacol.*, 393(12):2473-2480.

[https://doi: 10.1007/s00210-020-01992-1](https://doi:10.1007/s00210-020-01992-1). Epub 2020 Oc.

Mubarak S, Abdel Hamid S, Farrag AE, Samir N, Hussein JS. (2018)

Cardioprotective effect of date palm against doxorubicin-induced cardiotoxicity. *Asian J Pharm Clin Res* 11, 141–146.

<https://DOI:10.1038/s41598-024-80197-5>

Naiyara A, Abdul E, Ali AA, Ahmed RA. (2010). Simvastatin cardioprotective effect in doxorubicin-induced cardiotoxicity in rats. *J Basic Appl Sci*; 6:29-38. <https://doi.org/10.54133/ajms.v3i.9>

Renu K, Abilash V G, Tirupathi PB, Arunachalam, (2008) Molecular mechanism of doxorubicin-induced cardiomyopathy - an update, *Eur. J. Pharmacol.* 818241–253. [https:// DOI: 10.1016/j.ejphar.2017.10.04](https://DOI:10.1016/j.ejphar.2017.10.04)

Song Z, Shi Y, Han Q, Dai G. (2018). Endothelial growth factor receptor-targeted and reactive oxygen species-responsive lung cancer therapy by docetaxel and resveratrol encapsulated lipid-polymer hybrid nanoparticles, *Biomed. Pharmacother.* 105 18–26.

[https://doi: 10.1016/j.biopha.2018.05.095](https://doi:10.1016/j.biopha.2018.05.095).

Srdjenovic B, Milic-Torres V, Grujic N, Stankov K, Djordjevic A, Vasovic V. (2010). Antioxidant properties of fullereneol C60(OH)24 in rat kidneys, testes, and lungs treated with doxorubicin. *Toxicol Mech Methods*, 20(6):298-305. [https://doi: 10.3109/15376516.2010.485622](https://doi:10.3109/15376516.2010.485622).

Srdjenovic B, Milic-Torres V, Grujic N, Stankov K, Djordjevic A, Vasovic V. (2010). Antioxidant properties of fullereneol C60(OH)24 in rat kidneys, testes, and lungs treated with doxorubicin. *Toxicol Mech Methods*, 20(6):298-305. [https://doi: 10.3109/15376516.2010.485622](https://doi:10.3109/15376516.2010.485622).

Srivastava A, Amreddy N, Babu A, Panneerselvam J, Mehta M, Muralidharan R, Chen A, Zhao YD, Razaq M, Riedinger N, Kim H, Liu S . Abdel- Mageed, A. Munshi, R. Ramesh (2016). Nanosomes carrying doxorubicin exhibit potent anticancer activity against human lung cancer cells, *Sci. Rep.* 6 38541. [https://doi: 10.1038/srep38541](https://doi:10.1038/srep38541).



Take G, Yamaç D, Ozoğul C, Erdogan D. (2008) Ultrastructural damage in lung tissues in rats treated with doxorubicin and paclitaxel. *Adv Ther.* 25(2):115-22. [https:// DOI:10.1007/s12325-008-0015-0](https://DOI:10.1007/s12325-008-0015-0)

Take G, Yamaç D, Ozoğul C, Erdogan D. (2008). Ultrastructural damage in lung tissues in rats treated with doxorubicin and paclitaxel. *Adv. Ther.* 25(2):115-22. <https://doi:10.1007/s12325-008-0015-0>.

Tan S and Wang G. (2017). Redox-responsive and pH-sensitive nanoparticles enhanced stability and anticancer ability of erlotinib to treat lung cancer in vivo, *Drug Des.Devel. Ther.* 11 3519–3529. <https://DOI:10.2147/DDDT.S151422>. eCollection 2017.

Yetkin NA, Büyükoğlan H, Sönmez MF, Tutar N, Gülmez I, Yilmaz I. (2020) The protective effects of thymoquinone on lung damage caused by cigarette smoke. *Biotech Histochem.*, 95(4):268-275. [https:// doi:10.1080/10520295.2019.1681511](https://doi:10.1080/10520295.2019.1681511).

Yetkin NA, Büyükoğlan H, Sönmez MF, Tutar N, Gülmez I, Yilmaz I.(2020) The protective effects of thymoquinone on lung damage caused by cigarette smoke. *Biotech Histochem.*, 95(4):268-275. [https:// doi:10.1080/10520295.2019.1681511](https://doi:10.1080/10520295.2019.1681511). Epub 2019 Nov 5.

Zhang P, Ghazwani J, Li M, Zhao W, Huang Y, Zhang X, Venkataramanan R S. Li. (2015). Effective co-delivery of doxorubicin and dasatinib using a PEG-Fmoc nanocarrier for combination cancer chemotherapy, *Biomaterials* 67104–114.

[https:// DOI:10.1016/j.biomaterials.2015.07.027](https://DOI:10.1016/j.biomaterials.2015.07.027).

## سمية الدوكسوروبيسين على أنسجة الرئة

سيف صلاح عبد الحسن

كلية التربية الاساسية، الجامعة المستنصرية، قسم الحاسبات، العراق، بغداد

### مستخلص البحث:

علاج مجموعة متنوعة من الأورام الخبيثة بفعالية باستخدام دوكسوروبيسين. ويُستخدم في الغالب لعلاج سرطان الدم والأورام اللمفاوية ومجموعة متنوعة من أنواع السرطان الخطرة، بما في ذلك سرطان الغدة الدرقية والثدي والرئة والمبيض. يُظهر دوكسوروبيسين سمية خلوية تعتمد على الجرعة، وهي ضارة بشكل خاص بالقلب، تمامًا مثل أدوية السرطان الأخرى. دوكسوروبيسين، وهو مضاد حيوي، تم البحث عنه لسنوات عديدة ويُستخدم كدواء تثبيط للخلايا في علاج سرطان الرئة. تهدف هذه الدراسة إلى تحديد الضرر الذي يلحق بأنسجة الرئة بسبب تأثير جرعات مختلفة من دوكسوروبيسين. ذكور فئران بيضاء، يتراوح وزنها بين 200 و250 جرامًا. تم الحصول على حيوانات المختبر من مركز بحوث التقنيات الاحيائية بجامعة النهرين، وتم تربية فئران المختبر في جامعة بغداد، كلية العلوم، قسم علوم الحياة، البيت الحيواني. استُخدمت ثلاث مجموعات من ستة فئران ذكور في البحث. أعطيت المجموعة الأولى محلول ملحي طبيعي، وأعطيت المجموعة الثانية دواء دوكسوروبيسين بجرعة 5 ملغم/كغم من وزن الجسم عن طريق الصفاق مرتين أسبوعيًا لمدة أربعة أسابيع، بينما أعطيت المجموعة الثالثة دواء دوكسوروبيسين بجرعة 10 ملغم/كغم من وزن الجسم عن طريق الصفاق مرتين أسبوعيًا لمدة أربعة أسابيع. استُخدم فورمالدهيد 4% لتثبيت أنسجة الرئة للتحليل النسيجي المرضي. كشف التحليل النسيجي المرضي عن تأثيرات مختلفة على أنسجة الرئة. تتراوح فترة إعطاء جرعات الحيوانات المعملية بين 2025/2/1 و2025/3/1 لمدة أربعة أسابيع. لوحظ في عينات الفئران المعالجة بالدوكسوروبيسين (5 ملغم/كغم من وزن الجسم) نزيف رئوي حاد، وانتفاخ رئوي منتشر، ووذمة رئوية. وعلى العكس من ذلك، أظهرت المقاطع من الفئران المعالجة بالدوكسوروبيسين (10 ملغم/كغم من وزن الجسم) علامات نخر الرئة الحاد، وخراج الرئة الحاد، ونزف داخل الأحشاء.

**الكلمات المفتاحية:** الرئة، دوكسوروبيسين، السمية، داخل الصفاق، علم الأمراض النسيجي