The North African Journal of Scientific Publishing (NAJSP)
مجلة شمال إفريقيا للنشر العلمي (NAJSP)
E-ISSN: 2959-4820
Volume 3, Issue 3, 2025
Page No: 219-226
Website: https://najsp.com/index.php/home/index
SJIFactor 2024: 5.49 **0.71 :2024 (AIF) معامل التأثير العربي** **ISI 2024: 0.696**

Aqueous Extract of *Saussurea lappa* Roots Alleviates Tamoxifen-Induced Oxidative Stress and Inflammation-Mediated Lung Injury in Female Rats

Eman Ali Faraj Hamouda*
Department of Zoology, Faculty of Humanities and Applied Sciences, University of Benghazi, Tocra, Libya

تخفيف المستخلص المائي لجذور القسط الهندي (*Saussurea lappa*) للإجهاد التأكسدي والالتهاب الرئوي الناتج عن عقار التاموكسيفين في إناث الجرذان

إيمان علي فرج حموده *
قسم علم الحيوان، كلية العلوم الإنسانية والتطبيقية، جامعة بنغازي، توكرة، ليبيا

*Corresponding author: eali40411@gmail.com

Received: July 02, 2025	Accepted: August 19, 2025	Published: August 22, 2025

Abstract:
Tamoxifen (TMX), a selective estrogen receptor modulator used for hormone-dependent breast cancer, is therapeutically effective but may induce lung injury with physiological consequences. This study evaluated the protective potential of *Saussurea lappa* root aqueous extract (SLRE) against TMX-induced oxidative stress, inflammation, and lung damage in female rats. Twenty-four female rats were randomly assigned to four groups (n = 6 each): control, SLRE (200 mg/kg/day), TMX (40 mg/kg/day), and TMX + SLRE. Treatments were administered orally for 28 days. Serum levels of malondialdehyde (MDA; marker of lipid peroxidation), superoxide dismutase (SOD), and catalase (CAT) were measured as indices of oxidative stress. Circulating inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), were quantified. Lung histopathology was examined to support biochemical data.TMX administration caused a significant increase in serum MDA levels with a parallel reduction in antioxidant enzymes (SOD, CAT) compared with controls ($p < 0.001$). TMX also markedly elevated IL-6 and TNF-α level ($p < 0.001$). Co-treatment with SLRE significantly reduced oxidative damage, restored antioxidant enzyme activities, suppressed cytokine expression, and improved lung histological architecture compared with TMX alone. TMX induced substantial oxidative and inflammatory lung injury, reflected by increased lipid peroxidation, impaired antioxidant defenses, and heightened cytokine release. SLRE exerted a protective effect by mitigating oxidative stress, restoring antioxidant capacity, and reducing inflammation. These findings suggest SLRE as a promising supportive therapy for limiting TMX-induced pulmonary toxicity.

Keywords: Fibrosis, Pulmonary Physiology, *Saussurea Lappa*, Tamoxifen.

الملخص
يُعد التاموكسيفين من مُعدِّلات مستقبلات الإستروجين الانتقائية المستخدمة على نطاق واسع في علاج سرطان الثدي المعتمد على الهرمونات، ورغم فعاليته العلاجية، إلا أنه قد يُحدث إصابة في الرئة مع آثار فسيولوجية مهمة. تهدف هذه الدراسة إلى استكشاف التأثير المحتمل للمستخلص المائي لجذور القسط الهندي (***S. lappa***)على الإجهاد التأكسدي والإلتهابات الرئوية لدى إناث الجرذان المعالَجة بالتاموكسيفين(TMX). تم تقسيم أربع وعشرون جرذًا أنثى عشوائيًا إلى أربع مجموعات (6 جرذان لكل مجموعة): المجموعة الضابطة، مجموعة المستخلص المائي لجذور القسط الهندي (SLRE، 200 ملغ/كغ/يوم) ، مجموعة التاموكسيفين(TMX، 40ملغ/كغ/يوم)، ومجموعة التامكسوفين مع المستخلص النباتي(TMX

SLRE +)، أُعطيت جميع المعالجات عن طريق الفم لمدة 28 يومًا متتاليًا. تم قياس مستويات المصل من المالونديالديهيد (MDA)؛ كمؤشر على أكسدة الدهون وتلف الغشاء ، إنزيمات الدفاع المضاد للأكسدة (SOD) و (CAT)كمؤشرات للإجهاد التأكسدي. كما تم تحديد مستوى السيتوكينات الالتهابية في الدم، وهي الإنترلوكين 6 (IL-6) وعامل نخر الورم (TNF-α).بالإضافة إلى ذلك، تم تقييم نسيج الرئة لدعم وربط النتائج الحيوية الكيميائية النسيجية .تسببت معالجة TMX في زيادة ملحوظة في مستويات MDA في المصل مع انخفاض في إنزيمات الدفاع المضاد للأكسدة (SOD) و (CAT مقارنة بالمجموعة الضابطة .($p < 0.001$) وعلاوة على ذلك، رفع TMX بشكل واضح التعبير عن السيتوكينات الالتهابية، بما في ذلك TNF-α وIL-6، مقارنة بالمجموعة الضابطة ($p <0.001$) أما المعالجة المشتركة مع SLRE فقد خففت بشكل كبير هذه التغيرات في مؤشرات الإجهاد التأكسدي والسيتوكينات الالتهابية، مع تحسين ملحوظ في المظهر النسيجي للرئة .يسبب التاموكسيفين إجهادًا تأكسديًا وأضرارًا التهابية في نسيج الرئة، في حين أظهر المستخلص المائي لجذور نبات القسط الهندي *S. lappa* تأثيرات وقائية مهمة على بنية ووظيفة الرئة، مما يبرز دوره كعلاج مساعد لتخفيف إصابة الرئة الناتجة عن التاموكسيفين.

الكلمات المفتاحية :التليف، فسيولوجيا الرئة، القسط الهندي، التاموكسيفين.

Introduction

The lungs play a critical physiological role as the primary organs responsible for gas exchange, ensuring oxygen uptake and carbon dioxide elimination, processes essential for maintaining systemic homeostasis and supporting cellular metabolism [1]. Beyond their respiratory function, lungs actively regulate systemic acid-base balance, filter blood-borne microthrombi, and contribute to immune surveillance by defending against inhaled pathogens and environmental toxins [2]. Optimal pulmonary function depends on the integrity of the alveolar-capillary barrier, adequate lung elasticity, and a balanced immune response. Disruption of these physiological parameters can lead to impaired ventilation and compromised oxygen delivery to tissues, resulting in systemic consequences. The lungs, due to their extensive surface area and exposure to the external environment, are susceptible to damage from harmful agents including drugs, pollutants, and reactive oxygen species (ROS), which can trigger inflammation, fibrosis, and loss of lung compliance [3]. Drug-induced lung injury is of concern as it may alter normal lung physiology through cellular toxicity and immune-mediated mechanisms [4].

Tamoxifen (TMX), a selective estrogen receptor modulator widely used in breast cancer therapy, although effective in targeting estrogen-positive tumors, has been associated with adverse effects in multiple organs including the lungs [5]. Pulmonary complications such as inflammation, fibrosis, and pleural effusion have been reported, likely resulting from tamoxifen-induced oxidative stress, mitochondrial dysfunction, and elevated pro-inflammatory cytokines that disrupt alveolar-capillary integrity [6]. Furthermore, tamoxifen upregulates transforming growth factor-beta (TGF-β), a key mediator promoting fibroblast activation and pathological lung remodeling [7].

These pathophysiological changes directly impact lung elasticity and gas exchange efficiency, leading to respiratory insufficiency [8]. Therefore, natural products with antioxidant and anti-inflammatory properties may have an essential role in mitigating oxidative and inflammatory tissue damage linked to drug toxicity. *Saussurea lappa*, (*S. lappa*) commonly known as costus root, is a medicinal herb recognized for its antioxidant and anti-inflammatory constituents [9]. Experimental studies have demonstrated its ability to enhance endogenous antioxidant defenses and mitigate oxidative tissue damage induced by drugs [10]. This study aims to investigate the potential beneficial impact of S *lappa* root extract (SLRE) against oxidative stress and inflammatory lung tissue damage in female rats subjected to TMX therapy. Through correlating the biochemical and histological findings with known physiological implications, this work seeks to contribute to understanding therapeutic strategies against drug-related pulmonary dysfunction.

Material and methods

Drug

Tamoxifen (tamoxifen citrate), commercially marketed as Nolvadex®, and was supplied by AstraZeneca, United Kingdom, in tablet form. For this study, the tablets were suspended in distilled water and administered orally to the experimental animals at a dose of 40 mg/kg body weight. This dose corresponds to the therapeutic dose used in humans and was given once daily for 28 consecutive days, following the protocol described by [11].

Preparation of *Saussurea lappa* Extract

Dried roots of *Saussurea lappa* were procured from a local medicinal plant market in Benghazi, Libya. For aqueous extraction, 1 kg of powdered root material was boiled in 5 L of distilled water for 30 min and then filtered. The filtrate was freeze-dried (lyophilized), yielding approximately 35 g of

dried extract. This extract was reconstituted in distilled water to prepare a stock solution of 50 mg/mL for experimental use [12].

Experimental Animals and Grouping

Twenty-four female albino rats aged eight weeks and weighing 180–190 g, were obtained from the Animal House of the Faculty of Medicine, University of Benghazi. The animals were housed under controlled environmental conditions (temperature 23–25 °C, humidity 50–65%, 12-hour light/dark cycle) with free access to standard diet and water. Following a 7-day acclimatization period, the rats were randomly divided into four groups (n = 6 per group) and treated orally via gastric tube for 28 consecutive days as follows:

- **Group I (Control):** Received normal saline.
- **Group II (SLRE):** Received *Saussurea lappa* root extract (SLRE) at 200 mg/kg/day [12].
- **Group III (TMX):** Received tamoxifen (TMX) at 40 mg/kg/day [11].
- **Group IV (TMX + SLRE):** Received a combined treatment of TMX (40 mg/kg/day) and SLRE (200 mg/kg/day.

Blood sampling and tissue collection

Rats from the different experimental groups were anesthetized for the collection of blood samples, followed by serum separation. Subsequently, lung tissues were harvested from all groups after euthanasia for histopathological examination.

Biochemical serum analysis

Malondialdehyde (MDA), a marker of lipid peroxidation, along with antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) were measured using commercial kits (Biodiagnostic, Cairo, Egypt). Inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), were quantified using rat-specific ELISA kits (ABCAM, UK) according to the manufacturer's instructions.

Histopathological Examination

Lung samples were carefully rinsed with physiological saline and fixed in 10% neutral buffered formalin for 24–48 hours to preserve the delicate tissue architecture. Standard histological processing was performed, and 4–5 µm thick sections were prepared and stained with hematoxylin and eosin (H&E) according to the method described by [13].

Statistical analysis

Data were analyzed by comparing the mean values for different TMX groups with the mean values of controls. Results are expressed as mean ± SD. Significant differences among values were analyzed using one-way analysis of variance (ANOVA) followed by Bonferroni's test post-ANOVA. Values were considered statistically significant at $p < 0.05$.

Results

Serum biochemical results

Oxidative stress markers

The effects of SLRE on serum oxidative stress and antioxidant markers in TMX-treated rats are presented in Table 1. Tamoxifen administration significantly increased serum MDA levels, an index of lipid peroxidation, while concomitantly decreasing the activities of SOD and CAT compared to the control group ($P \leq 0.001$). Co-administration of SLRE with TMX effectively mitigated these alterations, restoring MDA, SOD, and CAT levels toward normal values in the TMX + SLRE group relative to TMX-treated rats ($P \leq 0.001$).

Table1: Effect of *Saussurea lappa* Root Extract (SLRE) on Serum Oxidative Stress Markers in Rats with Tamoxifen-Induced Lung Injury.

Parameters	Control	SLRE	TMX	TMX + SLRE
MDA (nmol/ml)	1.20±0.10	1.20±0.10 ^{b**}	2.90±0.10 ^{a**}	1.93±0.15 ^{a**b**}
SOD (U/L)	5.30±0.10	5.40±0.1 ^{b**}	3.03±0.15 ^{a**}	4.16 ±0.15 ^{a**b**}
CAT (U/L)	45.30±1.50	47.00±1.00 ^{b**}	28.3±1.50 ^{a**}	41.60±1.50 ^{b**}

Values are expressed as mean ± SD of 6 rats, $^{a**}P$=0.001, compared to control, $^{b**}P$= 0.001 compared to TMX.

Inflammatory markers

Table 2 demonstrates an elevation in serum inflammatory cytokines, namely IL-6 and TNF-α, in TMX-treated rats compared to the control group ($P \leq 0.001$). Administration of SLRE along with TMX markedly reduced the levels of these markers in the TMX + SLRE group relative to TMX-treated rats ($P \leq 0.001$).

Table2: Effect of *Saussurea lappa* Root Extract (SLRE) on Serum Inflammatory Markers in Rats with Tamoxifen-Induced Lung Injury.

Parameters	Control	SLRE	TMX	TMX + SLRE
IL-6 (pg/ml)	19.00±1.00	18.00± 1.00 b**	87.60±2.50 a**	51.00± 1.00 a**b**
TNF-α (pg/ml)	13.00±1.00	13.7±0.64 b**	76.63±1.53 a**	43.60 ±1.53 a**b**

Values are expressed as mean ± SD of 6 rats, a**P=0.001 compared to control, b**P= 0.001 compared to TMX.

Histomorphological Analysis of Lung Tissue

The protective role of SLRE against tamoxifen-induced lung histomorphological alterations in rats is illustrated in Figures 1–4. Lung sections from control rats exhibited well-preserved histological architecture, characterized by normal alveoli with thin alveolar septa, each lined by a single layer of squamous epithelium with a thin layer of connective tissue. Normal alveolar ducts and respiratory bronchioles were also evident, lined by ciliated columnar epithelium in larger bronchioles and cuboidal epithelium in smaller bronchioles as illustrated in Figure 1. Similarly, lung sections from SLRE-treated rats displayed intact architecture, comparable to that of control animals as shown Figure 2.

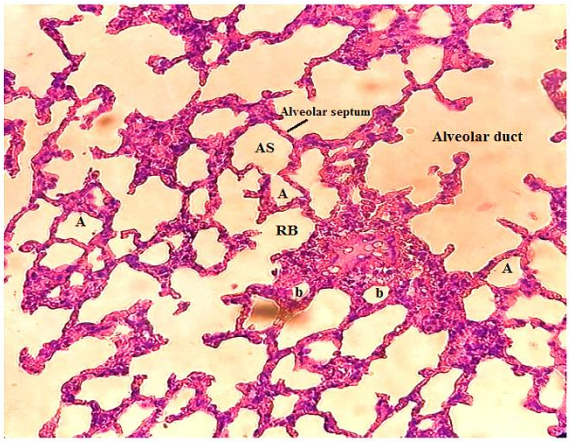

Figure 1: Photomicrograph of lung from a normal rat showing normal alveoli (A), alveolar sac (AS), thin alveolar septa lined by a single layer of squamous epithelium with a thin layer of connective tissue, alveolar duct, and respiratory bronchiole (RB) lined by ciliated columnar epithelium in larger bronchioles or cuboidal epithelium in smaller bronchioles leading to alveoli, as well as blood vessels (b) (H&E, ×400).

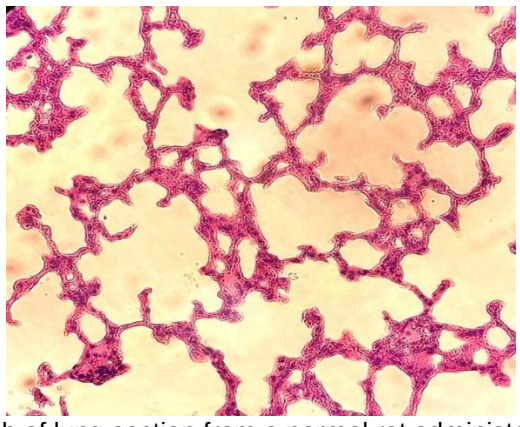

Figure 2: Photomicrograph of lung section from a normal rat administered *Saussurea lappa* root extract (SLRE) showing preserved lung architecture (H&E, ×400).

In contrast, TMX-treated rats demonstrated marked disruption of lung tissue organization, as evidenced by alveolar collapse, infiltration of inflammatory cells, thickening of inter-alveolar septa with fibrosis, and bronchiolar epithelial disruption with cellular debris in the lumina (Figure 3). Co-administration of SLRE with TMX resulted in substantial improvement of lung histomorphology (Figure 4), indicated by reduced infiltration of inflammatory cells, decreased alveolar wall thickness, and limited fibrosis when compared with TMX-intoxicated rats.

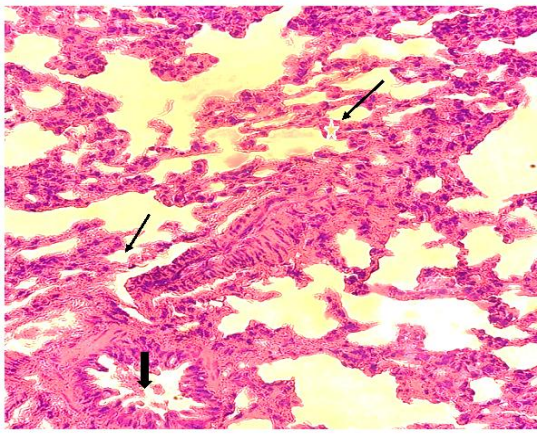

Figure 3: Photomicrograph of lung section from a rat intoxicated with tamoxifen showing disorganized lung architecture, collapsed alveoli (black thin arrows), thickened inter-alveolar septa with fibrosis (yellow star), infiltration of immune cells (blue arrows), and disruption of bronchiolar epithelium with cellular debris in the lumen (black thick arrow) (H&E, ×400).

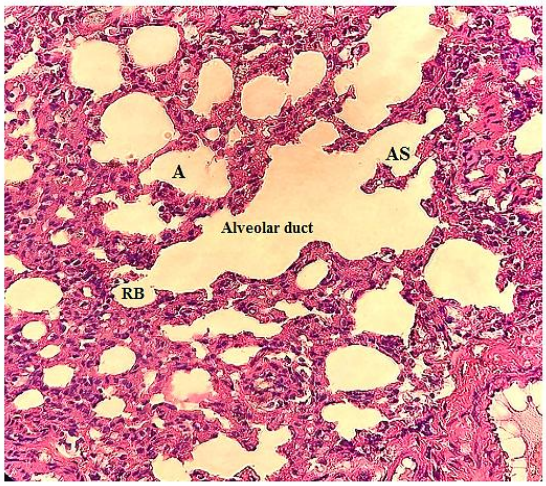

Figure 4: Photomicrograph of lung section from a rat administered tamoxifen along with *Saussurea lappa* root extract (SLRE) showing reduced infiltration of inflammatory cells, decreased alveolar wall thickness, and limited fibrosis. Normal alveoli (A), alveolar sac (AS), alveolar duct, and respiratory bronchiole (RB) are also evident (H&E, ×400).

Discussion

The lungs are vital organs responsible for the essential physiological function of gas exchange, facilitating the entry of oxygen into the bloodstream and the removal of carbon dioxide. This process occurs within the alveoli microscopic sacs with thin and elastic walls surrounded by a dense capillary network enabling rapid diffusion necessary to meet the metabolic demands of body tissues. The structural integrity of alveolar walls, along with the absence of inflammation or fibrosis, is crucial for maintaining lung compliance, optimal ventilation-perfusion balance, and efficient gas exchange. Disruption of this architecture can significantly impair respiratory function, leading to hypoxia and systemic complications. Tamoxifen (TMX), a selective estrogen receptor modulator widely used in breast cancer treatment, has been associated with pulmonary complications, particularly when administered alongside radiation therapy. The present study aimed to investigate the potential protective role of *Saussurea lappa* root extract (SLRE) on serum oxidative stress markers and inflammatory cytokines, as well as on lung histomorphology, in female rats subjected to TMX-induced toxicity.

Oxidative stress has been reported as a key mechanism by which tamoxifen (TMX) promotes tissue damage [14]. In the present study, TMX-treated rats exhibited a significant increase in serum malondialdehyde (MDA), an index of lipid peroxidation, accompanied by a decrease in the activities of antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT), relative to control animals. These findings are consistent with previous studies reporting that TMX administration significantly elevates MDA levels in rat livers while impairing the antioxidant defense system [14, 15]. Moreover, clinical evidence has demonstrated TMX-induced lung injury in a breast cancer patient following surgery [16]. This suggests that TMX toxicity triggers excessive production of free radicals, which attack cellular

components including lipids, proteins, and DNA leading to tissue damage. Cells can generally repair minor oxidative perturbations; however, severe oxidative stress may induce apoptosis, and more intense stress can result in tissue necrosis [17].

Oral administration of *Saussurea lappa* root extract (SLRE) significantly attenuated the TMX-induced increase in serum MDA and restored the activities of SOD and CAT. Similarly, *S. lappa* demonstrated a significant protective effect against triamcinolone acetonide-induced lung oxidative stress by suppressing MDA production and restoring antioxidant enzyme levels [10]. This protective effect may be attributed to the multiple bioactive compounds of *S. lappa*, including phenolic acids and flavonoids, which possess potent antioxidant properties capable of preventing the oxidation of polyunsaturated fatty acids and preserving membrane integrity [18].

Inflammation represents another mechanism by which tamoxifen (TMX) promotes tissue injury and fibrosis. In the present studies [14,15], TMX administration caused a significant increase in the proinflammatory cytokines IL-6 and TNF-α in the serum of treated rats compared to control animals. Clinically, TMX treatment has been reported to induce eosinophilic pneumonia in breast cancer patients [19]. Experimental studies further demonstrated that TMX induces inflammatory tissue damage by stimulating the production of mediators such as TNF-α and IL-1β. The overproduction of these inflammatory molecules can disrupt the balance between pro- and anti-inflammatory cytokines, establishing chronic inflammation and subsequent tissue injury [20].

Oxidative stress and products of lipid peroxidation are additional factors that stimulate lung cells to release inflammatory mediators and cytokines/chemokines, including IL-1β, IL-6, IL-8, and TNF-α, which promote neutrophil chemotaxis and contribute to the histopathological features of lung damage [21]. Oral administration of *Saussurea lappa* root extract (SLRE) concurrently with TMX significantly attenuated the elevation of serum IL-6 and TNF-α in TMX-SLRE treated rat relative to the TMX-only group. This finding is consistent with previous reports demonstrating that *S. lappa* reduces serum levels of inflammatory markers, including CRP, TNF-α, IL-1β, and IL-6, in rats with experimentally induced arthritis [22]. In the present study, the prophylactic effect of *Saussurea lappa* root extract (SLRE) against tamoxifen (TMX)-induced histological lung damage was investigated. In the control group, lung tissue exhibited normal architecture, characterized by thin alveolar walls, patent alveolar spaces, and absence of inflammatory infiltrates, consistent with healthy pulmonary function [23].

By contrast, TMX intoxication induced evident histopathological alterations, including alveolar collapse, inter-alveolar septal thickening with fibrosis, inflammatory cell infiltration, and disruption of the bronchiolar epithelium with cellular debris in the lumen. These observations can be attributed to the oxidative and inflammatory insults elicited by TMX in lung tissue. Consistently, clinical and experimental evidence demonstrated that TMX administration provokes lung injury through inflammation, oxidative stress, and fibrotic remodeling [24,25]. Other investigations further confirmed alveolar septal thickening, collagen deposition, and inflammatory infiltration, which collectively impair lung compliance and gas exchange efficiency [26].

The inflammatory response exacerbates oxidative injury and stimulates fibroblast activation through pro-inflammatory cytokines, particularly TNF-α and IL-6, thereby promoting fibrotic remodeling and tissue stiffening [27]. Such pathological changes decrease lung compliance, elevate the work of breathing, and reduce exercise tolerance, which parallels clinical reports of TMX-associated pulmonary toxicity [28]. Indeed, study [26] demonstrated that TMX-induced histological alterations markedly impair lung function, including reduced oxygen diffusion, defective oxygen uptake, and increased airway resistance, resulting in ventilation–perfusion mismatch. Clinically, these dysfunctions manifest as dyspnea, reduced exercise capacity, and, in severe cases, respiratory failure [28].

Importantly, administration of SLRE alone did not induce any morphological alterations, confirming its pulmonary safety and biocompatibility. The preservation of normal lung histology in this group is consistent with previous reports demonstrating the non-toxic nature of *S. lappa* and its bioactive constituents [29]. Co-administration of SLRE with TMX effectively protected lung tissue from TMX-induced injury. Compared with the TMX group, lungs of SLRE-treated rats showed markedly reduced inflammatory cell infiltration, attenuated alveolar wall thickening, and limited fibrotic remodeling. This protective role is largely attributed to the potent antioxidant and anti-inflammatory properties of *S. lappa* phytoconstituents, including sesquiterpene lactones and phenolic compounds, which scavenge reactive oxygen species and suppress pro-inflammatory cytokine production [30]. By preserving alveolar-capillary membrane integrity and mitigating oxidative and inflammatory insults, SLRE may help maintain lung compliance and efficient gas exchange, which are essential for sustaining respiratory function. These observations align with earlier evidence showing that *S. lappa* attenuates chemically induced pulmonary injury via modulation of oxidative stress and inflammatory pathways.

Conclusion

TMX administration provokes oxidative stress and inflammation that culminate in lung injury, histologically manifested by alveolar wall thickening, inflammatory infiltration, and fibrosis, ultimately impairing pulmonary function and gas exchange. SLRE exerts a pronounced protective effect by counteracting oxidative and inflammatory processes, thereby preserving lung architecture and respiratory physiology. These findings highlight the potential of SLRE as a natural therapeutic adjunct to prevent or alleviate drug-induced pulmonary toxicity. Nevertheless, future investigations incorporating direct pulmonary function assessments and molecular mechanistic studies are warranted to fully elucidate its protective pathways and optimize translational applications.

References

[1] West, J. B. (2012). Respiratory physiology: The essentials. Lippincott Williams & Wilkins.

[2] Hall, J. E., & Guyton, A. C. (2021). Guyton and Hall textbook of medical physiology (14th Ed.). Elsevier.

[3] Barnes, P. J. (2016). Oxidative stress-based therapeutics in COPD. Redox Biology, 10, 148-154.

[4] Spagnolo, P., Bonniaud, P., Rossi, G., Sverzellati, N., & Cottin, V. (2022). Drug-induced interstitial lung disease. European Respiratory Journal, 60(4).

[5] Peng, J., Sengupta, S., & Jordan, V. C. (2009). Potential of selective estrogen receptor modulators as treatments and preventives of breast cancer. Anti-cancer agents in Medicinal Chemistry (formerly current Medicinal Chemistry-Anti-cancer agents), 9(5), 481-499.

[6] Bentzen, S. M., Skoczylas, J. Z., Overgaard, M., & Overgaard, J. (1996). Radiotherapy-related lung fibrosis enhanced by tamoxifen. JNCI: Journal of the National Cancer Institute, 88(13), 918-922.

[7] Babyshkina, N., Dronova, T., Erdyneeva, D., Gervas, P., & Cherdyntseva, N. (2021). Role of TGF-β signaling in the mechanisms of tamoxifen resistance. Cytokine & growth factor reviews, 62, 62-69.

[8] Etori, S., Nakano, R., Kamada, H., Hosokawa, K., Takeda, S., Fukuhara, M., & Sato, K. (2017). Tamoxifen-induced lung injury. Internal Medicine, 56(21), 2903-2906.

[9] Wang, Y. F., Ni, Z. Y., Dong, M., Cong, B., Shi, Q. W., Gu, Y. C., & Kiyota, H. (2010). Secondary metabolites of plants from the genus Saussurea: chemistry and biological activity. Chemistry & biodiversity, 7(11), 2623-2659.

[10] Abd El-Rahman, G. I., Behairy, A., Elseddawy, N. M., Batiha, G. E. S., Hozzein, W. N., Khodeer, D. M., & M. Abd-Elhakim, Y. (2020). Saussurea lappa ethanolic extract attenuates triamcinolone acetonide-induced pulmonary and splenic tissue damage in rats via modulation of oxidative stress, inflammation, and apoptosis. Antioxidants, 9(5), 396.

[11] Bacharach, A. L. (1964). Evaluation of drug activities: pharmacometrics (Vol. 1). Academic Press.

[12] Saleem, T. M., Lokanath, N., Prasanthi, A., Madhavi, M., Mallika, G., & Vishnu, M. N. (2013). Aqueous extract of Saussurea lappa root ameliorate oxidative myocardial injury induced by isoproterenol in rats. Journal of advanced pharmaceutical technology & research, 4(2), 94-100.

[13] Koptev, M., Pronina, O., Danilchenko, S., Avetikov, D., & Stavitskiy, S. (2014). Histological features of rats' normal lung tissue.

[1[14] El-Dessouki, A. M., El Fattah, M. A., Awad, A. S., & Zaki, H. F. (2018). Zafirlukast and vincamine ameliorate tamoxifen-induced oxidative stress and inflammation: Role of the JNK/ERK pathway. Life sciences, 202, 78-88

[15] El-Beshbishy, H. A., Mohamadin, A. M., Nagy, A. A., & Abdel-Naim, A. B. (2010). Amelioration of tamoxifen-induced liver injury in rats by grape seed extract, black seed extract and curcumin. Indian J Exp Biol, 48(3), 280-288.

[16] Etori, S., Nakano, R., Kamada, H., Hosokawa, K., Takeda, S., Fukuhara, M., ... & Sato, K. (2017). Tamoxifen-induced lung injury. Internal Medicine, 56(21), 2903-2906.

[17] Pourzand, C., & Tyrrell, R. M. (1999). Apoptosis, the role of oxidative stress and the example of solar UV radiation. Photochemistry and Photobiology, 70(4), 380-390.

[18] El Sheikh, D. M., El-Kholany, E. A., & Abo-Taleb, H. M. (2025). Utilization of Saussurea costus powder as Antioxidant, Antimicrobial agent, and Anti-Alzheimer's (In vitro study). Egyptian Journal of Chemistry, 68(4), 295-307.

[19] Kwon, E., Kim, M., Choi, E., Park, Y., & Kim, C. (2019). Tamoxifen-induced acute eosinophilic pneumonia in a breast cancer patient. International Journal of Surgery Case Reports, 60, 186–190.

[20] Chavda, V. P, Bezbaruah, R., Ahmed, N.Alom, S., Bhattacharjee, B., Nalla, L. V., Rynjah, D Gadanec, L. K., & Apostolopoulos, V. (2025). Proinflammatory Cytokines in Chronic Respiratory Diseases and Their Management Cells, 14(6), 400.

[21] Lee, I. T., & Yang, C. M. (2012). Role of NADPH oxidase/ROS in pro-inflammatory mediators-induced airway and pulmonary diseases. Biochemical pharmacology, 84(5), 581-590.

[22] Tag, H. M., Khaled, H. E., Ismail, H. A., & El-Shenawy, N. S. (2016). Evaluation of anti-inflammatory potential of the ethanolic extract of the Saussurea lappa root (costus) on adjuvant-induced monoarthritis in rats. Journal of basic and clinical physiology and pharmacology, 27(1), 71-78.
[23] Weibel, E. R. (2017). Lung morphometry: the link between structure and function. Cell and tissue research, 367(3), 413-426.
[24] Katayama, N., Sato, S., Katsui, K., Takemoto, M., Tsuda, T., Yoshida, A., ... & Kanazawa, S. (2009). Analysis of factors associated with radiation-induced bronchiolitis obliterans organizing pneumonia syndrome after breast-conserving therapy. International Journal of Radiation Oncology* Biology* Physics, 73(4), 1049-1054.
[25] Ahmed, S., & Shahid, R. K. (2009). Acute interstitial pneumonitis following adjuvant tamoxifen therapy. Journal of Clinical Oncology, 27(15_suppl), e11637-e11637.
[26] Stone, J. P., Ball, A. L., Crichley, W., Yonan, N., Liao, Q., Sjöberg, T., ... & Fildes, J. E. (2020). Ex vivo lung perfusion improves the inflammatory signaling profile of the porcine donor lung following transplantation. Transplantation, 104(9), 1899-1905.
[27] Kim, J. M., Stewart, R., Kim, J. W., Kang, H. J., Bae, K. Y., Kim, S. W., ... & Yoon, J. S. (2018). Changes in pro-inflammatory cytokine levels and late-life depression: A two year population based longitudinal study. Psychoneuroendocrinology, 90, 85-91.
[28] Bentzen, S. M., Skoczylas, J. Z., Overgaard, M., & Overgaard, J. (1996). Radiotherapy-related lung fibrosis enhanced by tamoxifen. JNCI: Journal of the National Cancer Institute, 88(13), 918-922.
[29] Attallah, N. G., Kabbash, A., Negm, W. A., Elekhnawy, E., Binsuwaidan, R., Al-Fakhrany, O. M., & Fawzy, H. M. (2023). Protective potential of Saussurea costus (falc.) Lipsch. Roots against cyclophosphamide-induced pulmonary injury in rats and its in vitro antiviral effect. Pharmaceuticals, 16(2), 318.
[30] Kaur, R., Kaur, R., Singh, R., Bhardwaj, U., & Sharma, P. (2024). Isolation and derivatization of bioactive compounds from Saussurea lappa roots with antifungal efficacy against plant pathogenic fungi. Journal of Biologically Active Products from Nature, 14(5), 551-566.