BioBacta

Journal of Medical and Life Science
https://jmals.journals.ekb.eg/

SPBH

Corn Silk Alleviates Paclitaxel –Induced Lung Toxicity in Rats.

Aml I. Barakat[1]; Sobhy H. El-Nabi[2]; Mohamed S.A. El-Gerbed[1]

Zoology Department, Faculty of Science, Damanhur University, Egypt.[1]

Zoology Department, Faculty of Science, Menoufiya University, Egypt.[2]

Corresponding author: Dramlbarakat123@gmail.com Amal.barkat@sci.dmu.edu.eg

DOI: 10.21608/jmals.2024.356324

Abstract

Background: Corn silk is a yellow, silky substance that arises from the stigma of a female flower at the tip of the corn cob in the maize plant. The chemotherapeutic drug paclitaxel (PTX) is used to treat lung, esophagus, and ovarian cancer. **The aim of the work:** Estimate the impact of Paclitaxel (PTX) toxicity on the rat's lung and the potential protective effect of corn silk extract (CSE). **Materials and Methods:** The experimental groups were designed as (1) control group, (2) CSE group was given corn silk extract (CSE) (400 mg/kg) for 7 days orally, (3) PTX group was given PTX **(**2 mg/kg PTX (i.p) (in 0, 2nd, 4th, 6th days) and (4) PTX+ CSE group was given corn silk extract (CSE) and PTX as in the second and third groups, respectively. At the end of the experiment, the lung tissues were processed for biochemical and histological studies.

Results: The PTX-treated group possessed higher levels of MDA, NO, hydroxyproline, collagen type-1, and MMP-7 in lung tissue. Meanwhile, the concentrations of SOD, CAT, and GSH in lung tissue were decreased. Co-administration of CSE restores antioxidative systems through amelioration of the antioxidant enzyme activity in the lung tissue. In addition, histopathological changes occurred in lung tissue in the PTX-treated group. Collapsed alveoli, cellular infiltration, and perivascular fibrosis were observed. CSE administration improves lung damage induced by PTX.

Conclusion: Corn silk extract has a beneficial impact on lung fibrosis.

Keywords: *Paclitaxel- Corn silk extract – Lung- Oxidative stress - Fibrosis*

---

1. Introduction

Cancer is genetic mutations in abnormal cells. Paclitaxel (PTX) is extracted from the Taxus brevifolia tree's trunk crust. It is among the most potent chemotherapeutics and anticancer medications available. Although it has hazardous consequences, it is utilized in the treatment protocol for numerous types of solid tumors, including malignancies of the head, neck, lung, ovary, and prostate (1). PTX has anticancer properties (2). The antitumor ability of PTX is due to the polymerization of tubulin monomer, leading to a mitotic arrest by inhibiting spindle fiber function and promoting the phosphorylation process of B cell lymphoma-2 (Bcl-2) and apoptotic cell death inducer protein. Medication with chemotherapeutic agents raises the life span of cancer patients. Using these medications to treat a patient might have severe side effects that negatively impact life quality. Treatment of protective drugs concurrently with chemotherapy is one technique to reduce the riskiness of its negative effects (3). Structurally paclitaxel is a diterpenoid pseudoalkaloid with a taxane ring as its nucleus ($C_{47}H_{51}NO_{14}$). Because of its hydrophobic

Received: February 1, 2024. Accepted: April 22, 2024. Published: June 4, 2024

characteristics, it must be administered properly via a vehicle. Typically, a 50/50 mixture of polyethoxylated castor oil and dehydrated ethanol (4). Additionally, it can cause acute hypersensitivity reactions, which include angioedema, dyspnea, flushing, rash, tachycardia, hypotension, and chest discomfort (5).

Many researchers have indicated that chemotherapeutic medications impede the formation of malignant tissue by stimulating cell death (6). Paclitaxel triggers cell death through diverse signal pathways in distinct cell types, such as the mitogen-activated protein kinase (MAPK) pathway. This signal plays an important role in the redox-sensitive signaling system (7).

Lung cancer is a highly malignant kind of cancer that regrettably results in a substantial number of cancer-related fatalities. Many patients with lung cancer develop resistance to chemotherapy, which is a significant characteristic of the disease. Additionally, some individuals show inherent disruptions in the mechanisms that control cell death (8). Paclitaxel is a powerful drug used in cancer treatment. It works by binding to microtubules and preventing their depolarization during cell division. While it is a commonly used treatment for advanced lung cancer with promising results, the effectiveness of this therapy is hindered by the development of resistance, leading to suboptimal clinical outcomes. A thorough comprehension of the molecular foundation of apoptotic deregulation is crucial (9).Several mechanisms of resistance to paclitaxel-induced lung cancer, apoptosis, and fibrosis have been reported (10).

The complex process of fibrogenesis involves the interaction of signals that stimulate the production and accumulation of extracellular matrix, as well as processes that break down this matrix and remove the cells responsible for its formation (11). Lung fibrosis (LF) is a serious and progressive lung damage characterized by the gradual formation of lesions in the pulmonary parenchyma, along with inflammatory infiltration and interstitial fibrosis. Excessive accumulation of collagen and cellular matrix components results in substantial alterations in the structure of the alveoli (12). Pulmonary fibrosis biomarkers refer to the results of respiratory function tests, imaging, or biochemical substances that can be detected in blood, bronchoalveolar lavage, or lung tissue (13).

During the metabolic processes of the human body, the production of molecules such as reactive oxygen species and free radicals, which have potent oxidizing characteristics, have occurred. If these compounds are not promptly eliminated, they will cause damage to biological membranes and cell processes, leading to the development of aging, cardiovascular disease, and cancer (14). Antioxidants can eliminate free radicals, therefore diminishing their detrimental effects on the human body. Nevertheless, the research focus has shifted towards the production of natural antioxidants that are low-toxic, safe, and efficient, owing to the potential safety risks associated with synthetic antioxidants (15).

Corn silk refers to the filamentous stigmas of female maize flowers that are typically thrown as byproducts during maize cultivation (13). The primary byproduct resulting from maize processing is accumulated in significant amounts and disposed of as agricultural waste. Throughout time, it has been used to treat various medical conditions. It has pharmacological properties, which include antioxidant, anti-diabetic, anti-fatigue, and anti-inflammatory activities. In addition to proteins, carbohydrates, and bioactive compounds such as pigments, phenolic acids, flavonoids, and aromatic oils, corn silk is abundant in protein. The presence of these essential nutritional constituents qualifies it for integration into therapeutic diets to mitigate the onset of chronic ailments (16). Flavonoids, which are significant secondary metabolites, have been discovered by numerous studies to be broadly distributed in plant tissues in recent years (17).

Using corn silk can improve overall health, enhance farmers' economy, and be marketed as a value-added functional food product. The latest research covered in the current study confirms the practical use of maize silk, even though it is typically considered a waste. It may be utilized in food-grade goods, cosmetics, and herbal medicine. This presents several potential to create functional and therapeutic food items with additional value (18). The present work focuses on investigating the anti-cancer properties of corn silk extract (CSE) and its bioactive constituents, specifically polyphenols, flavonoids, and sterols. The anticancer impact of several chemicals, such as polyphenols and flavonoids (including quercetin, rutin, apigenin, and beta-sitosterol), derived from maize silk, has been studied (19).

2 Materials and Methods

2.1 Drugs and Chemicals

Paclitaxel (Unitaxel 150 mg/25 ml) 0.05 ml was completed to 0.5 ml with saline for each rat. Paclitaxel solution in a vial for infusion was purchased from Hikma Specialized Pharmaceuticals Company (Cairo, Egypt). Corn silk extract (CSE) purchased from MAKIN T9CRNS, batch no. 22CRNS6043 (Spain). All chemicals used were of the highest purity and analytical grade.

2. 2 Animals and Diets

Pathogen-free forty healthy adult male Wister albino rats, aged 6-7 weeks, weighing approximately 160±4 g, used for this experiment were purchased from the Animal House of the National Research Center in Dokki, Cairo, Egypt. Animals were acclimatized for 1 week before experimentation in a specific-pathogen-free environment and housed in clean well-ventilated plastic cages under natural photo-conditions: room temperature (23 ± 2°C) and 55 ± 5% relative humidity. Rodent pellet diet and water were allowed *ad-libitum*, and beddings were daily changed (20). This study protocol received approval under the designation (DMU-SCI-CSRE-23-11-04).

2.3 Experimental Procedure

Experimental rats were randomly assigned into four groups (each group n=10). Rats of the first group I (Control group) were given 0.2 ml of isotonic 0.9% NaCl solution were administered intraperitoneal (i.p.) and kept control. Rats of the second group II (CSE group) were given orally corn silk extract (CSE) at a dose of (400 mg/kg) for 7 days (21). Rats of the third group III (PTX group) were given PTX at a dose (2 mg/kg in 0.2 ml saline) (i.p) (in 0, 2nd, 4th, 6th days) and the final cumulative dose of 8 mg/kg (22). Rats of the fourth group IV (PTX+ CSE group) were given corn silk extract (CSE) and PTX as in the second and third groups, respectively.

2.4 Biochemical and Histological Sample Preparation

At the end of the experiment period, the animals were euthanized by administering an intraperitoneal injection of sodium pentobarbital. Lung tissue samples were collected and washed using an ice-cold saline solution, and then they were cut into small pieces. The first part for homogenates was homogenized in potassium phosphate buffered (pH 7.4), then centrifuged to obtain the supernatants which were kept at -800 C for further biochemical estimations. The remaining part of the lung tissues was fixed in a 10% neutral formalin solution for histopathological analysis.

2.5 Biochemical assays

Malondialdehyde (MDA), Nitric oxide (NO), superoxide dismutase (SOD), Catalase (CAT), and reduced glutathione (GSH) levels were measured according to the manufacturer's protocol.

The concentration of malondialdehyde (MDA) was used as an index of Lipid peroxidation (LPO). The level of MDA at 534 nm was expressed as nmol/g tissue (23) and NO was performed using the methods of (24) (Cat. No. 10009055 and 780001, respectively, Cayman Chemical Company, USA).

Moreover, SOD assay relies on the ability of the SOD to inhibit the phenazine methosulphate-mediated reduction of nitro-blue tetrazolium dye (25). CAT assay colorimetric method depends on the measurement of hydrogen peroxide (H_2O_2) substrate using a redox dye. The change in color intensity at 570 nm is directly proportional to the CAT activity (25) as well as GSH activity was measured according to (26) (Cat No. 707002, 706002, and 703102, respectively).

2.5 Fibrosis lung markers

The lung tissue homogenates were performed to a colorimetric-based hydroxyproline assay (Cat NO. ab222941) and for collagen type-1 content (Cat NO. ab222942) determination according to (27) and (28), respectively. Matrix metalloproteinase-7 (MMP-7) was measured using an ELISA kit (Cat. NO.ab314459) (29).

2.6 Histopathological Examination

Freshly collected lung tissue samples from each group were fixed in 10% normal formalin at room temperature for 24 h, processed, and embedded in paraffin. Lung tissue blocks were cut at 4 µm thick by using a rotary microtome. Paraffin sections were stained with hematoxylin and eosin dye and examined using a digital light microscope (Olympus, Tokyo, Japan) (30).

The specimens were examined in the Department of Zoology, Faculty of Science, Damanhur University.

2.7 Statistical analysis

Data analysis was performed using SPSS v20.0. All data were expressed as means ± SEM. Significant differences between different groups were evaluated using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. The mean values were considered significantly varied to $p < 0.05$.

3. RESULTS

3.1 Biochemical evaluation

3.1.1 The effect of CSE on lipid peroxidation

Shown in Fig 1, group III (PTX-treated group) demonstrated a highly significant increase ($p<0.001$) in the concentration of MDA and NO as lipid peroxidation markers when compared to control rats and group II (CSE group). Group IV that treated with the combination of PTX and corn silk extract displayed significant decrease in the level of MDA ($p<0.01$) in comparison with PTX-treated animals and control rats. Moreover, group IV recorded significant decrease in the level of NO ($p < 0.05$) when compared with the control rats while revealing significant decrease ($p< 0.01$) in the concentration of NO in comparison with the PTX-treated group.

3.1.2 The effect of CSE on antioxidant enzymes

The changes in sodium dismutase, catalase, and glutathione activities of the lung tissues are summarized in Fig. 2. It was determined that group III (PTX-treated group) with highly significantly decreased the antioxidant enzyme activities (CAT and GSH) compared to the control group and corn silk extract group (group II) ($p < 0.001$) and significantly decreased ($p < 0.01$) in the level of SOD in compared to control rats. A significant increase of the level of SOD in the experimental group (group IV) treated with PTX and corn silk extract ($p < 0.05$) when compared to corn silk extract group (group II). Moreover, A significant increase in the concentration of CAT and GSH in group IV ($p < 0.01$) when compared with PTX rats.

3.1.3 The effect of CSE on lung fibrosis markers

The activity of hydroxyproline, collagen type-1, and MMP-7 were higher concentrations ($P < 0.001$) in the lung tissue content of PTX-treated rats relative to the control and corn silk extract experimental group (Fig. 3). Co-treatment of PTX and corn silk extract in group IV highly significantly reduces ($p < 0.001$) the tissue activity of hydroxyproline relative to the treated group III. Meanwhile, the concentration of collagen type-1 recorded a highly significant decrease ($p < 0.001$) in the PTX+CSE –treated group when compared to the corn silk group (group II) in

addition significant decrease ($p < 0.01$) in comparison with group III which treated with PTX animals. Treatment with corn silk extract significantly decreased MMP-7 concentration in rats ($p < 0.01$) (group IV) when compared to group III.

3.2 Histopathological examination of lung tissue

Representative sections of the lungs from experimental rats are presented in Figures 4 and 5. Sections from the control group (**Figs. 4A&5A**) and corn silk extract group (group II) **(Figs. 4B&5B)** revealed normal lung features and architecture in the components of the bronchioles, alveolar ducts, alveolar sacs, alveoli, and bronchial arteriole. The bronchiolar passages appeared lined by normal respiratory epithelium. The adjacent alveolar spaces and septa exhibited no pathological abnormality. Moreover, normal pleural mesothelium, bronchioles pulmonary arterioles, and alveolar canals were observed in the lung tissues of laboratory animals.

On the other hand, the lung tissue of rats which were exposed to PTX revealed an increase in thickness of the alveolar wall, infiltration of inflammatory cells, collapse, and vacuole in the wall of alveoli. In addition, in PTX (group III) there are ruptured interalveolar septa with large irregular emphysematous air spaces **(Figs. 4C&5C).** The present study also noted that corn silk extract also improved the histopathological conditions in the lung tissue of the PTX group, except for mild interstitial inflammation **(Figs. 4D&5 D)**.

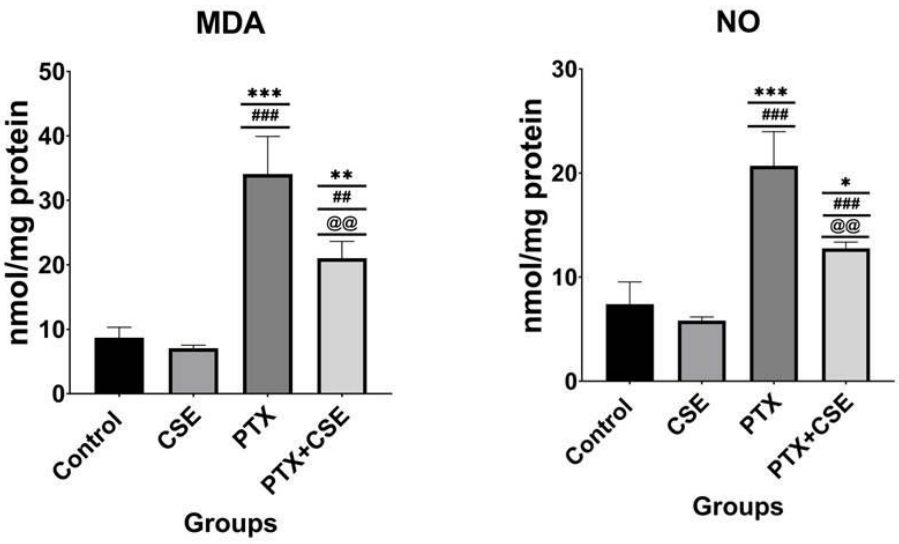

Figure (1):- Effect of CSE on the levels of MDA and NO contents in lung tissues. Values are presented as mean ± SEM of six independent observations in each group. *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ indicate significant differences compared with the control group; $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$ with CSE group and $^{@@}p < 0.01$ and $^{@@@}p < 0.001$ with PTX group. MDA: Malondialdehyde and NO: Nitric oxide.

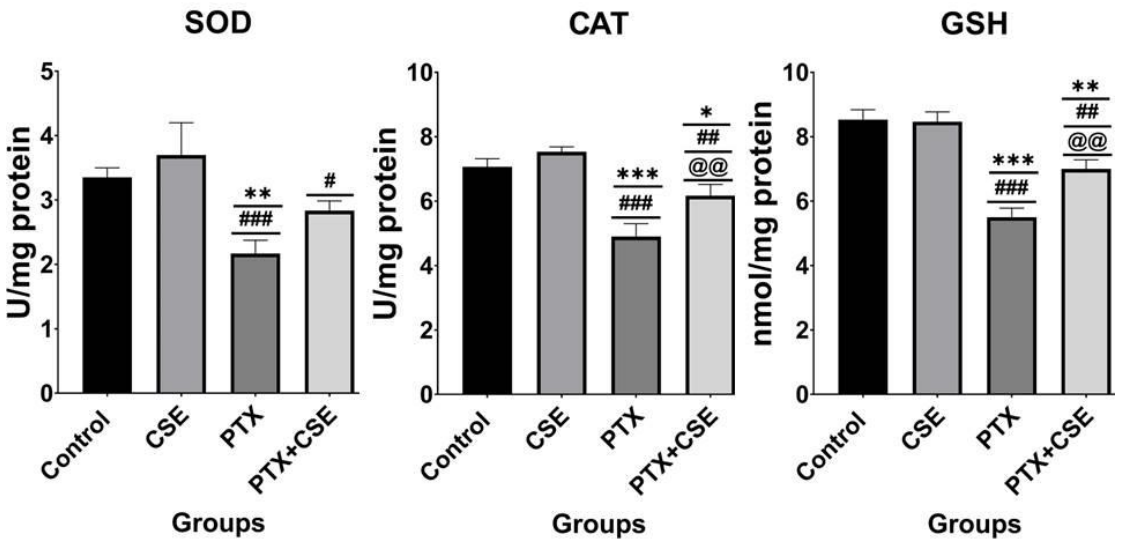

Figure (2):- Effect of CSE on the levels of SOD, CAT, and GSH contents in lung tissues. Values are presented as mean ± SEM of six independent observations in each group. *p < 0.05, **p < 0.01 and ***p < 0.001 indicate significant differences compared with the control group; $^{\#\#}$p < 0.01 and $^{\#\#\#}$p < 0.001 with CSE group and $^{@@}$ p< 0.01 and $^{@@@}$ p < 0.001 with PTX group. SOD: Sodium dismutase, CAT: Catalase, and GSH: Glutathione.

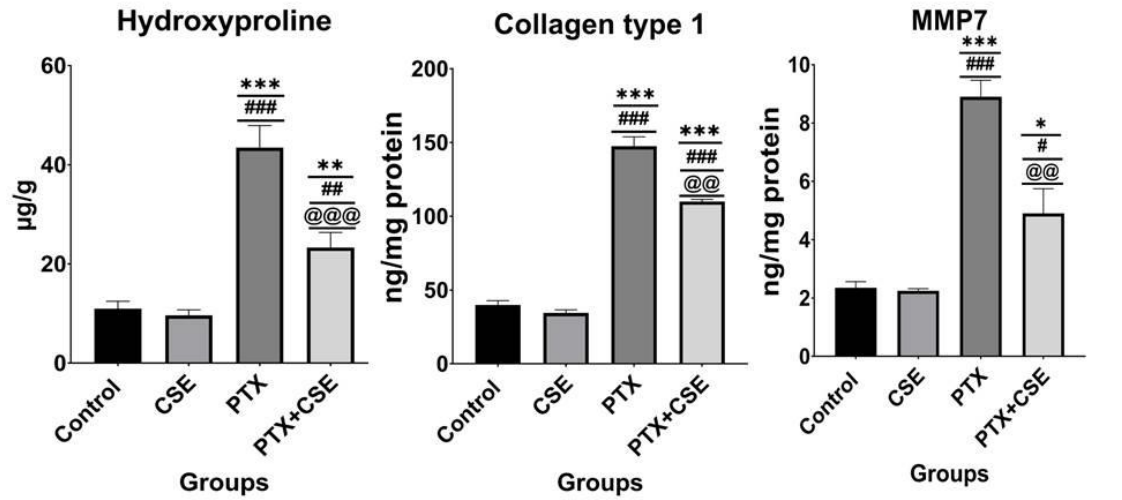

Figure (3):- Effect of CSE on the levels of hydroxyproline, **collagen Type-1, and MMP-7** contents in lung tissues. Values are presented as mean ± SEM of six independent observations in each group. *p < 0.05, **p < 0.01and ***p < 0.001 indicate significant differences compared with the control group; $^{\#\#}$p < 0.01 and $^{\#\#\#}$p < 0.001 with CSE group and $^{@@}$ p < 0.01 and $^{@@@}$ p < 0.001 with PTX group. MMP-7: Metalloproteinase-7.

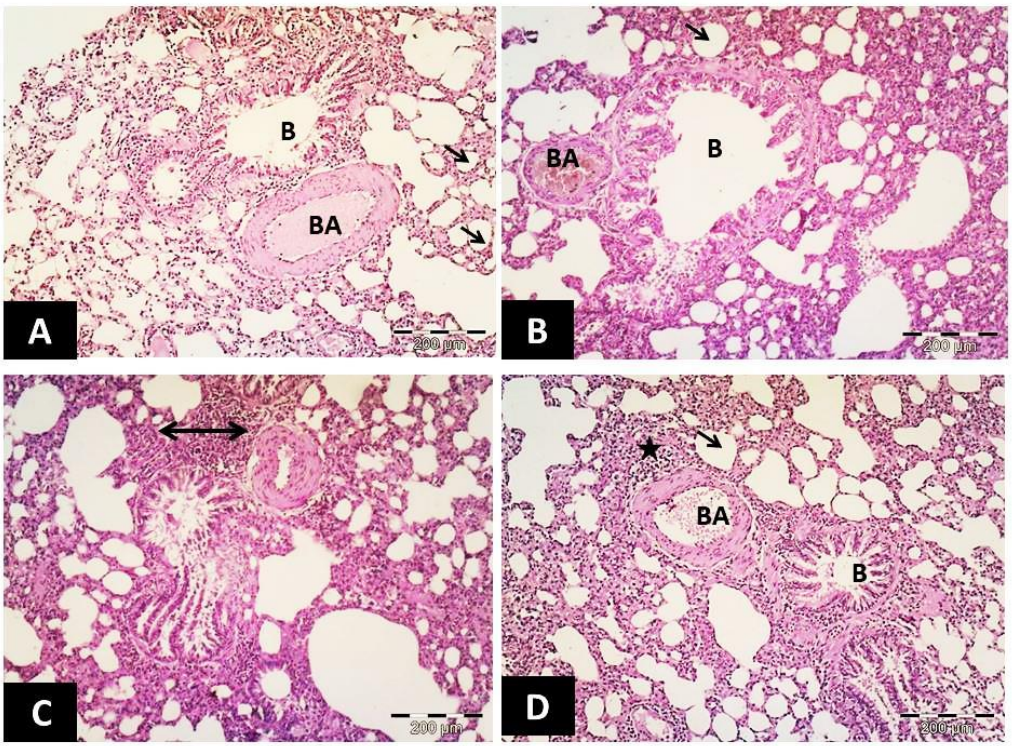

Figure (4):- photomicrograph sections of the rat lungs (A&B) Control (group I) and corn silk extract group (group II) respectively showing the typical architectures and intact cellular morphology of lungs with no pathologic changes. Notice: normal bronchiole (B) is accompanied by thin-walled bronchial arteriole (BA), Alveoli (arrow), and normal bronchiole (B). (C) PTX group (group III) showing persistent and progressive inflammatory cell infiltration. Note, that there was an increase in the thickness of the alveolar wall with an increase in the alveoli ulceration and massive peribronchial infiltration of mononuclear cells (double arrow). (D) PTX+CSE group (group IV) showing normal alveolar ducts and alveolar sacs with moderate alveolar and interstitial inflammation (star) (H&E, X200).

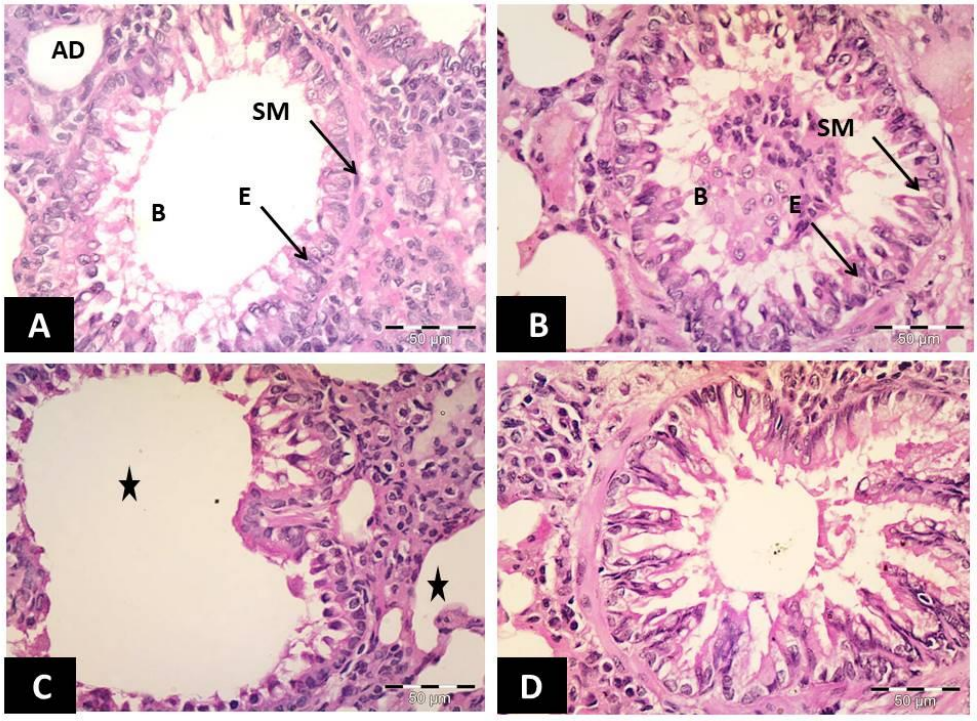

Figure (5):- Photomicrograph sections of the rat lungs (A&B) Control group (group I) and corn silk extract group (group II) respectively showing normal bronchioles (B), which lined by simple columnar epithelial cells (E) and surrounded by smooth muscle layer (SM), alveolar ducts (AD) and alveolar sacs. (C) PTX group (group III) showing ruptured interalveolar septa with large irregular emphysematous air spaces (star). Increase in thickness of the bronchiole wall. Note, that inflammatory infiltrates in the perivascular connective tissue. (D) PTX+ CSE group (group IV) showing obvious positive treatment with extract of corn silk (H&E, X400).

4. Discussion

Anticancer drugs are extensively utilized in chemotherapeutic protocols for cancer patients owing to their potent activity against a broad range of tumor types. To mitigate the deleterious effects of chemotherapeutic drugs, numerous authors have advocated for the utilization of natural products (31). Paclitaxel is widely recognized as a prevalent chemotherapeutic agent (32). A recent study was conducted to investigate whether the extract from corn silk may operate as a protective agent against lung damage caused by the chemotherapeutic medication PTX.

Despite the control group, the current research showed that PTX caused an increase in lipid peroxidation markers in lung tissue. This was demonstrated by an unexpected rise in MDA and NO concentrations, as well as a simultaneous decrease in SOD, CAT, and GSH levels. Oxidative stress is a crucial contributing factor linked to several human diseases (33).

Reactive oxygen species (ROS), which are potentially reactive oxygen derivatives, are perpetually produced within the human body due to excessive exposure to exogenous compounds (34). ROS produced are normally detoxified by the antioxidants present in the body, and the body maintains an equilibrium between ROS production and antioxidant presence. As a result of excessive ROS production and/or insufficient antioxidant defense, this equilibrium is disrupted in favor of the ROS influx, which ultimately leads to oxidative stress. Further, ROS readily influence and induce oxidative harm in a wide range of biomolecules, such as DNA, lipids, proteins, and lipoproteins (35).

An excess of ROS and inadequate antioxidant defense result in oxidative cell injury, both of which contribute to the development and advancement of cancer. The principal ROS source in living organisms is the respiratory transport chain, which generates O_2^- (26). Many chemotherapy treatments produce free radicals, which damage cancer cells irreversibly, and overproduction of ROS in cancer cells may deplete SOD and other adaptive antioxidant defenses. Research indicates that paclitaxel may boost intracellular H_2O_2 levels by increasing O_2^- levels. Paclitaxel therapy increases ROS, which are essential to oxidative stress. Paclitaxel increases ROS and decreases SOD and GSH peroxidase antioxidant enzyme activity (5).

According to the present study, the harmful impacts of PTX on lung tissue may be explained by the rise in oxidative stress indicators that occur when the drug is taken. Additionally, elevated ROS generation, such as H_2O_2, may cause PTX pulmonary damage. To disrupt redox signaling and potentially activate NADPH oxidase, PTX binds to microtubules and prevents its assembly. This allows PTX to promote the release of H_2O_2, GSSG, and DNA-oxidation adducts and disrupts redox signaling (2).

In the current investigation, the experimental group IV that received PTX and corn silk extract treatment showed a rise in SOD, CAT, and GSH and a decrease in MDA and NO. This study examined the relationship between the functional components in corn silk extracts and their antioxidant activity. Corn silk extract consists of proteins, vitamins, carbohydrates, calcium, potassium, magnesium, sodium salts, volatile oils, and flavonoids, which belong to the class of steroids. The phenolic compounds included in CSE comprise anthocyanins, p-coumaric acid, vanillic acid, protocatechuic acid, derivatives of hesperidin and quercetin, along with conjugated forms of hydroxycinnamic acid composed of p-coumaric and ferulic acid. Additionally, there are data on the antioxidant properties of CSE (36). The volatile extract and extracts obtained using petroleum ether, ethanol, and water from corn silk demonstrated evident antioxidant properties (37).

Flavonoids have been acknowledged for their antioxidant properties and significant impact on human nutrition and health and exert their effects via participating in scavenging or chelating activities. Corn silk extract comprises phenolic compounds, which are a class of antioxidants that act as scavengers for free radicals (38). According to this study, the contents of these phytochemicals in CSE can explain its antioxidant activity.

The present study examined the fibrosis lung markers, including hydroxyproline, collagen type-1, and MMP-7 in lung tissue. The results showed an elevation of these markers in the experimental rats that were treated with PTX. Pulmonary illnesses caused by chemotherapy create specific difficulties for pulmonary and critical care specialists. The pulmonary responses can be intense and quickly lethal. Furthermore, it is crucial to promptly and accurately distinguish the manifestations of drug-induced lung disease from alternative factors, such as pulmonary infection (31). The occurrence of lung illness as a result of chemotherapy was initially identified in the early 1960s. In the last 15 years, these responses have emerged as a significant issue, especially in regards to treatment plans using bleomycin, methotrexate, cyclophosphamide, and paclitaxel (39).

Almost all patients who consume these medications experience immune suppression, both due to their underlying illness and the chemotherapy medicines they receive. These individuals are prone to a range of common and uncommon illnesses, and the reappearance of their underlying lung disease. These conditions are significant alternative diagnoses that must be ruled out (40). Paclitaxel is a versatile anticancer medication that is primarily used to treat a wide range of solid cancers. Nevertheless, the practical use of it is greatly limited due to its low solubility, tendency to recrystallize when diluted, and the toxicity caused by the solvent (41).

Significant adverse reactions were found following infusions, necessitating the development of formulations with fewer side effects that do not necessitate the use of corticosteroids as a pre-medication. PTX induces the activation of genes that regulate apoptosis, leading to the programmed death of tumor cells. Additionally, the treatment of tissue with PTX results in the production of cancer cells **(42).** This is also connected with the transcription of genes that trigger inflammation, DNA damage response proteins, and cytokines that contribute to cellular proliferation in lung tissue. The rate of programmed cell death of tumor cells, known as apoptosis, is influenced by both the duration of exposure and the dose of the PTX medication **(43).** It can cause sudden and severe allergic responses characterized by symptoms such as difficulty breathing, reddening of the skin, skin rash, chest pain and rapid heartbeat, low blood pressure, swelling of the skin and mucous membranes, and widespread hives. Paclitaxel is a potent chemotherapy drug that exerts its effectiveness by stabilizing microtubules in cancer cells. Nevertheless, this stabilization also impacts the microtubules of sensory neurons (44).

Paclitaxel therapy hampers the response to oxidative stress, hence exacerbating the ATP deficiency. Reactive oxygen species (ROS) play a critical role in the oxidative stress mechanism. After treatment with paclitaxel, which leads to lung fibrosis and death, there is an increased expression of ROS (45). Fibrosis is a prevalent characteristic of numerous systemic inflammatory disorders and can also manifest as a primary progressive disease, resulting in organ failure and substantial morbidity (46). As well as characterized by a formation of activated fibroblasts and excessive deposition of fibrotic extracellular matrix proteins, particularly collagen type I, which is the primary cause of death in developed countries (47). Generous I collagen is a kind of collagen that forms fibrils and serves as the primary structural component in many tissues. It is present in all connective tissues and is an important

constituent of the interstitial membrane. Collagen type-1 mutations play significant roles in several disorders, especially those affecting bone and lung tissue (48). Elevated levels of serum collagen-type indicators have been shown to serve as an early indicator of fibrosis in the lung (49). Matrix metalloproteinase (MMP)-derived fragments of type I collagen have demonstrated an effective association with systemic inflammation and pulmonary fibrosis (50).

There is also data indicating that epidermal matrix-metalloproteinase (MMP) contributes to the degeneration that occurs after paclitaxel treatment (32). Exposure to paclitaxel in zebrafish leads to an increase in H_2O_2 reactive species in basal keratinocytes, which originate from damaged mitochondria (51). Matrix-metalloproteinases (MMPs) are often controlled by reactive oxygen species (ROS). Specifically, the expression of MMP-7 has been observed to rise in a cancer cell line following exposure to a mitochondrial ROS inducer. H_2O_2 enhanced MMP-7 expression in lung cancer cells (52). Moreover, collagen Type-I is a structured molecule found in the interstitial matrix, forming ordered fibrils. Furthermore, the increased lung hydroxyproline content following injury not only indicates an increase in collagen formation, but also suggests a potential impairment in the overall collagen turnover in the lung tissue (53). These results are consistent with our research findings.

The administration of CSE supplementation partially mitigated the adverse effects of PTX in the experimental group, as evidenced by a notable enhancement in lung fibrosis indices.

The use of corn silk showed a protective effect in the treatment of PTX. The study found that chemicals derived from corm silk specifically affect the responses of immune cells, cause cell death, and the markers associated with fibrosis (19). Corn silk-derived flavonoids improve the immunological response mediated by T cells and reduce the levels of inflammatory factors and fibrosis indicators. The beneficial chemicals present in corn silk were discovered to mitigate the adverse effects of cancer treatment. The presence of antioxidants such as quercetin and rutin in corn silk aids in mitigating the harmful effects on the lungs caused by chemotherapy medicines (54).

Chemotherapy drugs have been shown to produce pulmonary toxicity, resulting in histopathological signs in lung tissue (55). The reported injuries include lung parenchymal disease, pleural symptoms, airway disorders, pulmonary vascular abnormalities, changes in the mediastinum, and neuromuscular effects. Pulmonary toxicity is rare with most chemotherapy medications and typically presents as damage to the lung tissue, commonly referred to as "pneumonitis" or interstitial lung disease. The magnitude of severe pulmonary injury can be substantial, at times resulting in progressive respiratory failure and death (56).

The degree of pulmonary toxicity resulting from PTX treatment varies and can manifest during the first cycle, later in the course of treatment, and correlation with lung fibrosis. The histopathology features observed in these cases are distinct to this type of lung injury and typically involve different interstitial patterns such as nonspecific interstitial, organizing pneumonia, and diffuse alveolar damage. The histopathological patterns are observable in a diverse range of clinical situations (57). Acute lung injury (ALI) typically results in acute respiratory distress syndrome (ARDS), which is the main cause of mortality in patients with serious illnesses who have been administered PTX (58). Regarding the histopathological findings in the ongoing investigation of lung tissue. An improvement was recorded in the experimental rats that received a combination of PTX and corn silk, compared to the group that only received PTX supplementation. The protective action of corn silk extract is attributed to its high content of polysaccharides, which play a significant role in several biological activities involved in tissue healing (59). In addition, the corn

silk extract contains antioxidants that function as electron donors and counteract reactive oxygen radicals, so decreasing the formation of tumors in lung tissue (60). Flavonoids are bioactive substances that have a significant role in maintaining overall human health. Corn silk has been found to include a range of flavonoids and their glycosides, which have the ability to improve lung tissue and possess strong antioxidant properties, which suggest that it may have the ability to prevent and treat many diseases. Flavonoids provide several beneficial properties, including anti-inflammatory, anti-fibrotic, diuretic, antioxidant, antidiabetic, lung protecting and antidepressant effects (61). Other researchers have been notified about the beneficial effects of corn silk extract in reducing the harmful effects of PTX on lung tissue.

5. Conclusion

A comprehensive analysis has been conducted to evaluate the anti-cancer characteristics, mechanism, and function of corn silk extract in managing the adverse effects of PTX. This research has shown new possibilities for utilizing maize silk in cancer treatment.

Ethical approval:

This study protocol received approval under the designation (DMU-SCI-CSRE-23-11-04).

Source(s) of support: Nil

Conflicting Interest: Nil

6. Reference

1. Sarli S, Kalani MR, Moradi A. A potent and safer anticancer and antibacterial taxus-based green synthesized silver nanoparticle. International Journal of Nanomedicine. 2020:3791-801.
2. Ileriturk M, Kandemir O, Akaras N, Simsek H, Genc A, Kandemir FM. Hesperidin has a protective effect on paclitaxel-induced testicular toxicity through regulating oxidative stress, apoptosis, inflammation and endoplasmic reticulum stress. Reproductive Toxicology. 2023;118:108369.
3. Ruggiero A, Ariano A, Triarico S, Capozza MA, Romano A, Maurizi P, et al. Cisplatin-induced nephrotoxicity in children: what is the best protective strategy? Journal of Oncology Pharmacy Practice. 2021;27(1):180-6.
4. Sharifi-Rad J, Quispe C, Patra JK, Singh YD, Panda MK, Das G, et al. Paclitaxel: application in modern oncology and nanomedicine-based cancer therapy. Oxidative medicine and cellular longevity. 2021;2021.
5. Klein I, Lehmann HC. Pathomechanisms of paclitaxel-induced peripheral neuropathy. Toxics. 2021;9(10):229.
6. Shanshan W, Hongying M, Jingjing F, Yiming Y, Yu R, Rui Y. CircDTL functions as an oncogene and regulates both apoptosis and ferroptosis in non-small cell lung cancer cells. Frontiers in Genetics. 2021;12:743505.
7. Yu-Wei D, Li Zs, Xiong Sm, Huang G, Luo Yf, Huo Ty, et al. Paclitaxel induces apoptosis through the TAK1–JNK activation pathway. FEBS Open Bio. 2020;10(8):1655-67.
8. Min H-Y, Lee H-Y. Mechanisms of resistance to chemotherapy in non-small cell lung cancer. Archives of pharmacal research. 2021;44(2):146-64.
9. Cui H, Arnst K, Miller DD, Li W. Recent advances in elucidating paclitaxel resistance mechanisms in non-small cell lung cancer and strategies to overcome drug resistance. Current medicinal chemistry. 2020;27(39):6573-95.
10. Wattanathamsan O, Thararattanobon R, Rodsiri R, Chanvorachote P, Vinayanuwattikun C, Pongrakhananon V. Tubulin acetylation enhances lung cancer resistance to paclitaxel-induced cell death through Mcl-1 stabilization. Cell Death Discovery. 2021;7(1):67.
11. Li L, Fu H, Liu Y. The fibrogenic niche in kidney fibrosis: components and mechanisms. Nature Reviews Nephrology. 2022;18(9):545-57.

12. Savin IA, Zenkova MA, Sen'kova AV. Pulmonary fibrosis as a result of acute lung inflammation: molecular mechanisms, relevant in vivo models, prognostic and therapeutic approaches. International Journal of Molecular Sciences. 2022;23(23):14959.
13. Stankovic S, Stjepanovic M, Asanin M. Biomarkers in Idiopathic Pulmonary Fibrosis. Idiopathic Pulmonary Fibrosis: IntechOpen; 2021.
14. Lushchak VI. Free radicals, reactive oxygen species, oxidative stress and its classification. Chemico-biological interactions. 2014;224:164-75.
15. Tian S, Sun Y, Chen Z. Extraction of flavonoids from corn silk and biological activities in vitro. Journal of Food Quality. 2021;2021:1-9.
16. Abdulrasaq KO. Physicochemical Composition and Bioactivities of Gluten-Free Cookies Made from Yellow Maize and Brachystegia eurycoma Blends: Kwara State University (Nigeria); 2022.
17. Shen N, Wang T, Gan Q, Liu S, Wang L, Jin B. Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity. Food chemistry. 2022;383:132531.
18. Kaur P, Singh J, Kaur M, Rasane P, Kaur S, Kaur J, et al. Corn silk as an agricultural waste: A comprehensive review on its nutritional composition and bioactive potential. Waste and Biomass Valorization. 2023;14(5):1413-32.
19. Gulati A, Singh J, Rasane P, Kaur S, Kaur J, Nanda V. Anti-cancerous effect of corn silk: a critical review on its mechanism of action and safety evaluation. 3 Biotech. 2023;13(7):246.
20. Atta MS, Almadaly EA, El-Far AH, Saleh RM, Assar DH, Al Jaouni SK, et al. Thymoquinone defeats diabetes-induced testicular damage in rats targeting antioxidant, inflammatory and aromatase expression. International journal of molecular sciences. 2017;18(5):919.
21. Okon A, Etim D, Daniel A, Bobson P, Asuquo A. Effect of ethanolic extracts of Persea americana seed and Zea mays silk on blood glucose levels, body and organ weights of alloxan-induced hyperglycemic albino Wistar rats. Global Journal of Pure and Applied Sciences. 2018;24(2):153-68.
22. Faheem M, Khan A-u, Saleem MW, Shah FA, Ali F, Khan AW, et al. Neuroprotective effect of natural compounds in paclitaxel-induced chronic inflammatory pain. Molecules. 2022;27(15):4926.
23. Legaz I, Barrera-Pérez E, Sibón A, Martínez-Díaz F, Pérez-Cárceles MD. Combining oxidative stress markers and expression of surfactant protein a in lungs in the diagnosis of seawater drowning. Life. 2023;13(1):159.
24. Zhang P, Li Y, Tang Y, Shen H, Li J, Yi Z, et al. Copper-based metal-organic framework as a controllable nitric oxide-releasing vehicle for enhanced diabetic wound healing. ACS applied materials & interfaces. 2020;12(16):18319-31.
25. Kheradmand A, Alirezaei M, Asadian P, Rafiei Alavi E, Joorabi S. Antioxidant enzyme activity and MDA level in the rat testis following chronic administration of ghrelin. Andrologia. 2009;41(6):335-40.
26. Zińczuk J, Maciejczyk M, Zaręba K, Pryczynicz A, Dymicka-Piekarska V, Kamińska J, et al. Pro-oxidant enzymes, redox balance and oxidative damage to proteins, lipids and DNA in colorectal cancer tissue. Is oxidative stress dependent on tumour budding and inflammatory infiltration? Cancers. 2020;12(6):1636.
27. Kliment CR, Englert JM, Crum LP, Oury TD. A novel method for accurate collagen and biochemical assessment of pulmonary tissue utilizing one animal. International journal of clinical and experimental pathology. 2011;4(4):349.
28. Chen S, Wei Y, Liu H, Gong Y, Zhou Y, Yang H, et al. Analysis of Collagen type X alpha 1 (COL10A1) expression and prognostic significance in gastric cancer based on bioinformatics. Bioengineered. 2021;12(1):127-37.

29. Oggionni T, Morbini P, Inghilleri S, Palladini G, Tozzi R, Vitulo P, et al. Time course of matrix metalloproteases and tissue inhibitors in bleomycin-induced pulmonary fibrosis. European Journal of Histochemistry. 2006;50(4):317-26.
30. Koptev M, Pronina O, Danilchenko S, Avetikov D, Stavitskiy S. Histological features of rats' normal lung tissue. 2014.
31. Spagnolo P, Bonniaud P, Rossi G, Sverzellati N, Cottin V. Drug-induced interstitial lung disease. European Respiratory Journal. 2022;60(4).
32. Staff NP, Fehrenbacher JC, Caillaud M, Damaj MI, Segal RA, Rieger S. Pathogenesis of paclitaxel-induced peripheral neuropathy: A current review of in vitro and in vivo findings using rodent and human model systems. Experimental neurology. 2020;324:113121.
33. Vona R, Pallotta L, Cappelletti M, Severi C, Matarrese P. The impact of oxidative stress in human pathology: Focus on gastrointestinal disorders. Antioxidants. 2021;10(2):201.
34. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nature reviews Molecular cell biology. 2020;21(7):363-83.
35. Unsal V, Dalkıran T, Çiçek M, Kölükçü E. The role of natural antioxidants against reactive oxygen species produced by cadmium toxicity: a review. Advanced pharmaceutical bulletin. 2020;10(2):184.
36. Liu Q, Liu J, Fan S, Yang D, Wang H, Wang Y. Rapid discovery and global characterization of multiple components in corn silk using a multivariate data processing approach based on UHPLC coupled with electrospray ionization/quadrupole time-of-flight mass spectrometry. Journal of separation science. 2018;41(21):4022-30.
37. Shalaby EA, Shanab SM, Hafez RM, El-Ansary AE. Chemical constituents and biological activities of different extracts from ginger plant (Zingiber officinale). Chemical and Biological Technologies in Agriculture. 2023;10(1):14.
38. Naeem MM. Protective effect of Corn silk (Zea mays L.) on kidney and liver functions of rats. Bulletin of the National Nutrition Institute of the Arab Republic of Egypt. 2022;60(2):122-53.
39. Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, et al. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. Genes & Diseases. 2022.
40. Behranvand N, Nasri F, Zolfaghari Emameh R, Khani P, Hosseini A, Garssen J, et al. Chemotherapy: a double-edged sword in cancer treatment. Cancer immunology, immunotherapy. 2022;71(3):507-26.
41. Wileński S, Koper A, Śledzińska P, Bebyn M, Koper K. Innovative strategies for effective paclitaxel delivery: Recent developments and prospects. Journal of Oncology Pharmacy Practice. 2024:10781552231208978.
42. Faria RS, de Lima LI, Bonadio RS, Longo JPF, Roque MC, de Matos Neto JN, et al. Liposomal paclitaxel induces apoptosis, cell death, inhibition of migration capacity and antitumoral activity in ovarian cancer. Biomedicine & Pharmacotherapy. 2021;142:112000.
43. Diab T, AlKafaas SS, Shalaby TI, Hessien M. Dexamethasone simulates the anticancer effect of nano-formulated paclitaxel in breast cancer cells. Bioorganic Chemistry. 2020;99:103792.
44. Baldo BA, Pham NH, Baldo BA, Pham NH. Non-targeted Drugs for Cancer Therapy. Drug Allergy: Clinical Aspects, Diagnosis, Mechanisms, Structure-Activity Relationships. 2021:645-82.
45. Kozak J, Jonak K, Maciejewski R. The function of miR-200 family in oxidative stress response evoked in cancer chemotherapy and radiotherapy. Biomedicine & Pharmacotherapy. 2020;125:110037.
46. Antar SA, Ashour NA, Marawan ME, Al-Karmalawy AA. Fibrosis: types, effects,

markers, mechanisms for disease progression, and its relation with oxidative stress, immunity, and inflammation. International Journal of Molecular Sciences. 2023;24(4):4004.

47. Blokland KE, Pouwels SD, Schuliga M, Knight DA, Burgess JK. Regulation of cellular senescence by extracellular matrix during chronic fibrotic diseases. Clinical Science. 2020;134(20):2681-706.
48. Halper J. Basic components of connective tissues and extracellular matrix: fibronectin, fibrinogen, laminin, elastin, fibrillins, fibulins, matrilins, tenascins and thrombospondins. Progress in heritable soft connective tissue diseases. 2021:105-26.
49. Jessen H, Hoyer N, Prior T, Frederiksen P, Karsdal M, Leeming D, et al. Turnover of type I and III collagen predicts progression of idiopathic pulmonary fibrosis. Respiratory Research. 2021;22:1-8.
50. Luchian I, Goriuc A, Sandu D, Covasa M. The role of matrix metalloproteinases (MMP-8, MMP-9, MMP-13) in periodontal and peri-implant pathological processes. International Journal of Molecular Sciences. 2022;23(3):1806.
51. D'Iglio C, Famulari S, Capparucci F, Gervasi C, Cuzzocrea S, Spanò N, et al. Toxic Effects of Gemcitabine and Paclitaxel Combination: Chemotherapy Drugs Exposure in Zebrafish. Toxics. 2023;11(6):544.
52. Moreno-Q G, Herrera-R A, Yepes AF, Naranjo TW, Cardona-G W. Proapoptotic Effect and Molecular Docking Analysis of Curcumin–Resveratrol Hybrids in Colorectal Cancer Chemoprevention. Molecules. 2022;27(11):3486.
53. Singh D, Rai V, Agrawal DK. Regulation of collagen I and collagen III in tissue injury and regeneration. Cardiology and cardiovascular medicine. 2023;7(1):5.
54. Wang Y, Mao J, Zhang M, Liu L, Zhu Y, Gu M, et al. An Umbrella Insight into the Phytochemistry Features and Biological Activities of Corn Silk: A Narrative Review. Molecules. 2024;29(4):891.
55. Dhamija E, Meena P, Ramalingam V, Sahoo R, Rastogi S, Thulkar S. Chemotherapy-induced pulmonary complications in cancer: Significance of clinicoradiological correlation. Indian Journal of Radiology and Imaging. 2020;30(01):20-6.
56. Finder JD. Respiratory Complications in neuromuscular disorders. Neuromuscular Disorders: Treatment and Management. 2021:40.
57. Renzoni EA, Poletti V, Mackintosh JA. Disease pathology in fibrotic interstitial lung disease: is it all about usual interstitial pneumonia? The Lancet. 2021;398(10309):1437-49.
58. Li X, Berg NK, Mills T, Zhang K, Eltzschig HK, Yuan X. Adenosine at the interphase of hypoxia and inflammation in lung injury. Frontiers in immunology. 2021;11:604944.
59. Zhang Y, Yao L, Liu Y, Chen B, Wang C, Gong K, et al. Acidic polysaccharide from corn silk: Structural & conformational properties and hepatoprotective activity. International Journal of Biological Macromolecules. 2023;236:123851.
60. Sanjay SS, Shukla AK. Potential therapeutic applications of nano-antioxidants: Springer; 2021.
61. Mady M. The Antioxidant and Antimicrobial Activities of Cornsilk Extract Encapsulated in Polysaccharide Nanoparticles. 2021.