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Effect Of Taxol on the Level of Interleukin 8 and Histopathological Changes of the Liver in Male Rats

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ABSTRACT: Cancer is an increasingly significant health issue globally, resulting in a rise in the use of chemotherapy, which remains the primary and most common treatment for malignant tumors. This study aims to examine the histopathological changes and immunological responses to assess the toxic effects of Taxol. Specifically, it investigates how the anti-cancer drug Taxol impacts the histological and immunological characteristics in laboratory rats. The rats were randomly divided into three groups, each group containing 12 laboratory rats, as follows Control group: Consists of 12 rats. This group was injected with 0.5 ml of distilled wat Low dose group: Consists of 12 rats injected with a concentration of 2mg/kg of TAXOL intraperitoneally High dose group: Consists of 12 rats injected with a concentration of 4mg/kg of TAXOL intraperitoneally. Histological examination of tissue sections revealed pathological changes in the livers of laboratory rats. Specifically, liver samples from rats treated with Taxol exhibited necrosis and degeneration of hepatic cells, along with infiltration of inflammatory cells. Some hepatic cells showed distorted and enlarged nuclei, as well as hyperpigmentation of the cytoplasm. Additionally, there was an expansion and congestion of the hepatic portal vein and hepatic sinusoids. Laboratory analyses conducted using ELISA indicated that the low-dose group experienced a significant increase in IL-8 levels, whereas the high-dose group showed a notable decrease in interleukin 8 levels in the blood serum. The current study revealed that Taxol has a significant effect on liver tissue, leading to noticeable changes and differing immune responses based on the dosage administered.

Keywords: Cancer, Taxol, Histopathology, Hepatotoxicity, IL-8

INTRODUCTION

Cancer is a condition characterized by the uncontrolled growth of certain cells in the body, which can then spread to other areas. It can arise in virtually any part of the human body, which consists of billions of cells (Garcia Diaz et al., 2018). In a healthy individual, cells divide and multiply as needed. Over time, aging or injured cells eventually die off (Saini et al., 2020). However, there are instances when this process goes awry, leading to the growth and multiplication of abnormal or damaged cells. These cells can cluster together to form tumors, which are masses of tissue that can be either malignant (cancerous) or benign (non-cancerous) (Organization, 2018). Chemotherapy primarily involves the use of cytotoxic agents to eliminate malignant cells or inhibit their growth (Kikuchi et al., 2019). Chemotherapy aims to prevent tumor invasion and metastasis by inhibiting cell proliferation and tumor growth. However, it can also have detrimental effects on normal cells. Tumor progression can be halted at various levels within the cell and its environment (Chidharla et al., 2022). Traditional chemotherapy drugs typically disrupt the production and function of molecules in tumor cells by interfering with DNA, RNA, or protein synthesis, or by inhibiting the proper functioning of existing molecules (Peng et al., 2020).

Paclitaxel, commonly known by its brand name Taxol, is a cancer treatment that inhibits the growth and spread of cancer cells. It is used to treat breast cancer, ovarian cancer, and lung cancer, as well as Kaposi's sarcoma associated with AIDS (Davidoff et al., 2021). Paclitaxel was first isolated

from the Pacific yew in 1971 and received medical approval in 1993. Paclitaxel (Taxol) is listed among the World Health Organization's (WHO, 2019) Essential Medicines (Szok et al., 2019) and is recognized as a significant natural anticancer agent used in clinical settings (Altmann and Gertsch, 2007). However, side effects are prevalent, affecting over 30% of patients. Common issues include low red blood cell levels, temporary reductions in both white and red blood cell counts, hair loss, joint and muscle pain, and general discomfort in these areas. These side effects typically last for only 2 to 3 days following treatment with Taxol. Patients may also experience nausea, vomiting, and diarrhea (Sakai et al., 2020). The drug is marketed under several trade names, including Taxol, Onxol, Anzatax, Epetaxel, Benzenepropanoic, Abaxane, and Abraxis Bioscience (Vishnu and Roy, 2011).

MATERIALS AND METHODS

Experimental animals

Thirty rats, each weighing around 200-250 grams, were acquired for the study. They were housed in standard plastic cages, with five rats per cage, under controlled conditions at room temperature and natural daylight. The cage floors were lined with sawdust, which was regularly changed and sterilized throughout the experimental period. The rats were allowed a 10-day acclimatization period before the experiment commenced. They had access to a standard rodent diet and fresh water as needed.

Experimental design

Male and female laboratory rats were separated into three groups, each comprising 12 rats. The first group served as the control and was administered a normal saline solution. The second group, known as the low dose group, received intraperitoneal injections of Taxol at a concentration of 2 mg/kg for six weeks. The third group, referred to as the high dose group, was injected with Taxol at a concentration of 4 mg/kg, administered twice weekly over the same six-week period.

Blood and tissue sampling

After the six-week experimental period, the animals were anesthetized with ether. Blood was collected directly from the heart through cardiac puncture using 5 ml medical syringes. A portion of 3 ml of the blood was placed in air-evacuated GEL TUBE containers and left at room temperature for one hour to allow clotting. The serum was then separated by centrifugation at 3000 rpm for 15 minutes. It was stored in small plastic tubes at -20°C until testing. The animal was secured on a plastic plate with pins, and a longitudinal incision was made on the abdominal side. The liver tissue was extracted, rinsed in saline to remove blood, and then placed in 10% formalin for storage over a 24-hour period.

Histopathological examination

Liver samples from each group were freshly collected and fixed in 10% normal formalin at room temperature for 24 hours. After processing, the samples were embedded in paraffin. Using a rotary microtome, liver tissue blocks were sliced into 4 µm thick sections. These paraffin sections were then stained with hematoxylin and Masson stain and analyzed with a digital light microscope. The examination took place in the Department of Life Sciences at the College of Education for Pure Sciences.

Immunological parameters of serum

The level of cellular motility represented by interleukin 8 was determined using the ELISA technique

Statistical analysis

The data were statistically analyzed using Version 25 of the Statistical Package for the Social Sciences (SPSS). A One-way ANOVA was conducted to evaluate the data, and the means were compared using the Least Significant Difference (L.S.D) test at a significance level of $P < 0.05$.

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RESULTS

Immunological results

Measuring the level of interleukin 8 in the serum of laboratory rats

Table 1: Effect of Taxol on Level of Il-8 in rats' serum

Groups	IL-8 (µg/dI)
Control groups	10.50 ± 1.88 [b]
Low dose of drug Taxol (2mg/kg)	21.16 ± 3.71[a]
High dose of drug Taxol(4mg/kg)	4.58 ± 2.02 [c]

[a–c] Different letters indicate significant difference (P< 0.05)

The statistical analysis results, presented in Table 1, revealed significant differences among the studied groups. The second group (low dose group) exhibited the highest interleukin 8 level, measuring 21.16±3.71, in comparison to the other groups. Conversely, the third group (high dose group) showed a significant decrease, with a level of 4.58±2.02.

Histological results

Histological analysis of liver tissue sections from untreated rats revealed a typical structure, featuring a central blood vessel with normally arranged hepatocytes, as shown in Figure 1. In contrast, rats treated with a drug concentration of 2 mg for six weeks exhibited notable changes in liver tissue, including mild degeneration and necrosis of hepatic cells, along with inflammatory infiltration surrounding the hepatic vein and signs of blood vessel congestion, as illustrated in Figure 2. Furthermore, histological examination of the livers from rats treated with a 4 mg concentration indicated a worsening of the condition, characterized by increased necrosis and degeneration, significant blood congestion within the central vein, a reduction in glycoprotein granules, and heightened inflammatory infiltration, as depicted in Figure 3.

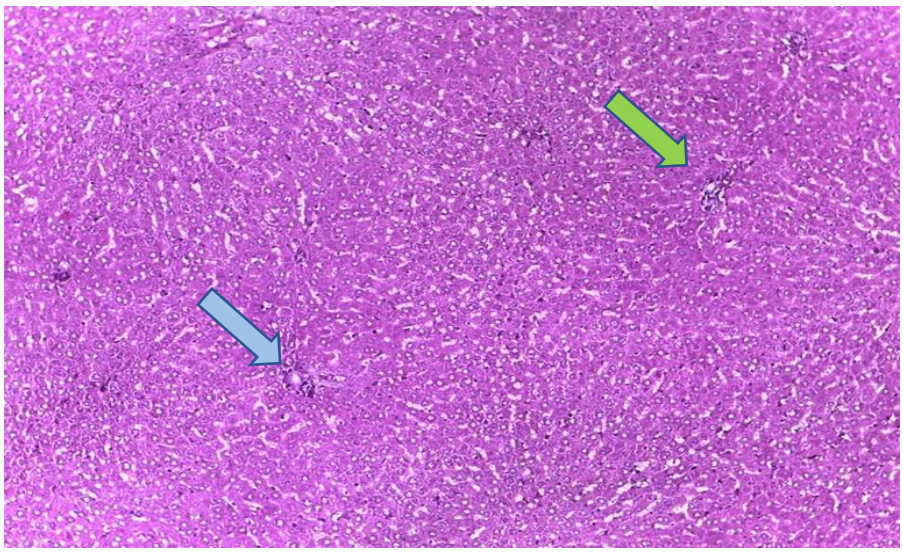

Figure 1: Histological section of the liver of a control rat showing a central blood vessel (blue .arrow) and normally arranged hepatocytes (green arrow)

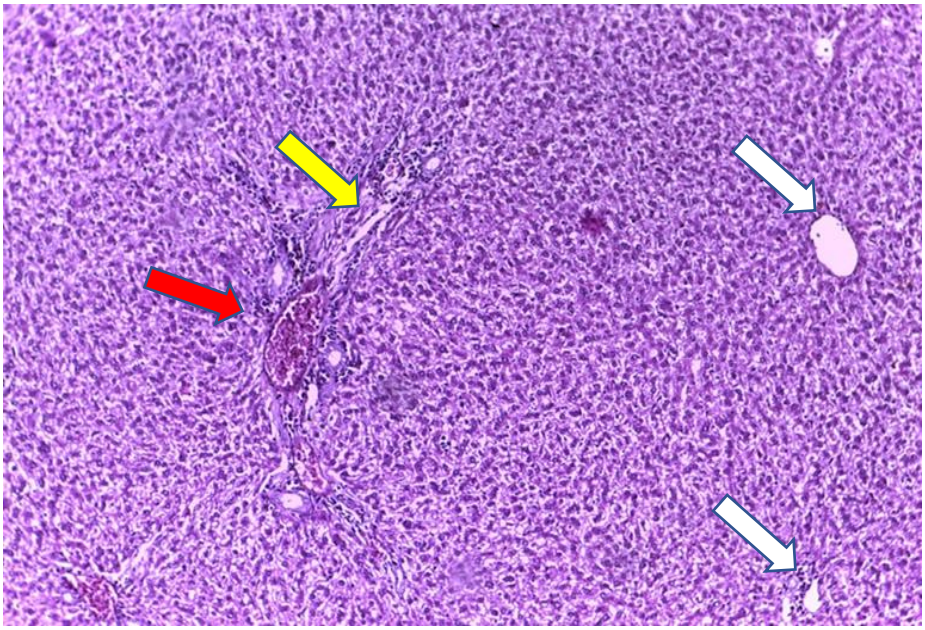

Figure 2: Histological section of the liver of rats treated with the dose (2 mg/kg). It shows venous congestion (red arrow), cell degeneration (white arrow), and inflammatory infiltrate (yellow arrow)

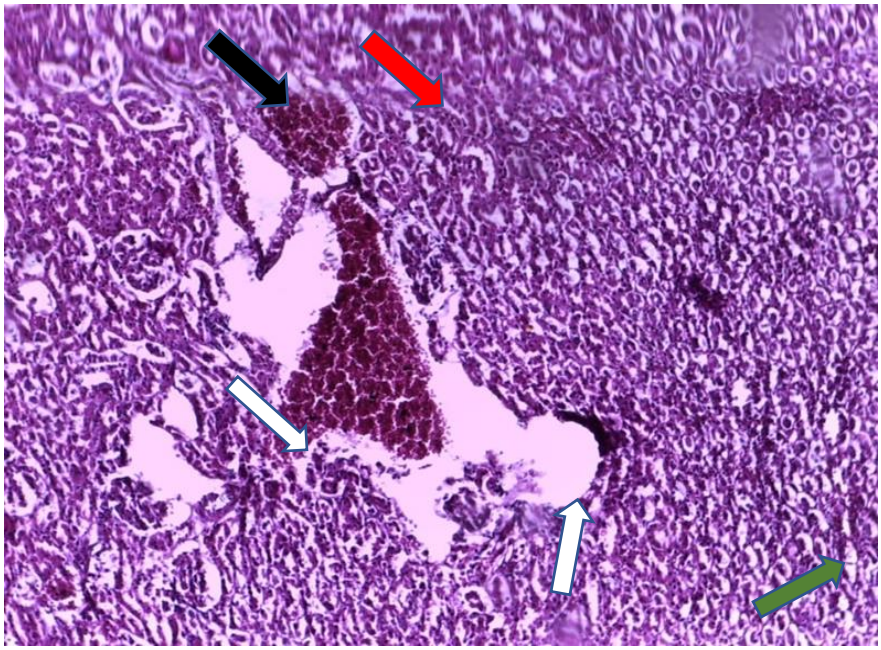

Figure 3: Histological section of the liver of rats treated with the dose (4 mg/kg). It shows venous congestion (red arrow), cell degeneration (white arrow), necrosis (black arrow), and a decrease in glycoprotein granules (orange arrow)

DISCUSSION

Histological analysis of the livers of rats injected with Taxol at doses of 2 and 4 mg/kg revealed significant pathological changes, characterized by the infiltration of inflammatory cells. This infiltration is attributed to increased blood vessel permeability, which occurs when endothelial cells contract in response to certain chemicals or due to the loss of adhesion molecules between these cells. This process allows blood cells to pass through (Cotran et al., 1999). The dilation of blood vessels facilitates the movement of large numbers of inflammatory white blood cells from the affected area. These cells tend to aggregate and move in a circular pattern as they migrate from the center to the periphery, adhering to the endothelial cells lining the blood vessels. This movement is made possible by the increased gaps between endothelial cells, a result of the external factor's influence (Kumar et al., 2007). The blood congestion frequently observed in the tissue sections of this study may be linked to damage to the inner lining of blood vessels, which can lead to bleeding and clot formation. This, in turn, narrows the hepatic blood vessels, resulting in ischemia that adversely affects blood supply to hepatic cells and causes the loss of many cytoplasmic components. The degeneration of hepatic cells may be due to the impact of chemotherapy drugs on the endoplasmic reticulum, leading to its vesiculation and the atrophy of mitochondria within these cells, which are essential components of the cytoplasm (EL-Sayyad et al., 2009). CXCL8, also known as interleukin (IL-8), is one of the most extensively studied chemokinesIL-8 was first identified in the late 1980s and was originally referred to as neutrophil activating factor (NAF) because of its involvement in neutrophil secretion and oxidative stress (Walz et al., 1987). This 6-8 kDa protein is produced by a variety of cell types, including blood monocytes, alveolar macrophages, fibroblasts, endothelial cells, and epithelial cells (Ha et al., 2017). The expression of IL-8 is triggered by several cytokines (such as IL-1, IL-6, CXCL12, and TNF-α), as well as by hypoxic conditions, reactive oxygen species (ROS), bacterial components, and other environmental stressors (Ha et al., 2017). IL-8 binds to its receptors, CXCR1 and CXCR2, to carry out its primary physiological functions, which include promoting a pro-inflammatory response and stimulating angiogenesis. As a potent chemoattractant, IL-8 primarily recruits neutrophils, but it can also attract monocytes to sites of inflammation (Charo and Ransohoff, 2006). Furthermore, IL-8 plays a role in resolving inflammation by acting mainly on neutrophils and enhancing neutrophil-mediated processes. Besides its role in promoting inflammation, IL-8 also supports angiogenesis by enhancing the proliferation, survival, and migration of endothelial cells, which leads to the formation of new blood vessels. This pro-angiogenic characteristic aids in the healing of tissues following inflammation (David et al., 2016). The current study revealed a dose-dependent variation in interleukin 8 levels. Specifically, the low dose resulted in a significant increase in IL-8 levels in the blood serum of rats treated with the drug compared to the control samples. Conversely, the high dose led to a decrease in IL-8 levels. These findings suggest that the effects may vary based on the treatment dosage. This aligns with previous research indicating changes in cytokine levels in response to taxeme chemotherapy. One study examined 30 patients with metastatic breast cancer who underwent multiple treatments with either paclitaxel or docetaxel. A separate study examined 30 patients with ovarian cancer who underwent a combination therapy for three weeks. Blood and peritoneal fluid samples were collected 24 hours post-treatment to measure cytokine levels (Penson et al., 2000). The researchers found elevated levels of IL-6 and IL-8 in both the blood and peritoneal fluid after this period. These findings indicate that systemic chemotherapy with paclitaxel can influence inflammatory cytokine levels in some patients. Our current research also indicates that the response varies based on dosage. Extensive studies have shown that IL-8 is crucial in the development of chemo-resistant cancer cells within the context of chemotherapy. In two preclinical studies, doxorubicin (Dox)-resistant cell lines were created in vitro using colorectal cancer (CRC) models (Du et al., 2018) and osteosarcoma (Cheng et al., 2018). In both studies, IL-8

was the only cytokine that exhibited increased levels in doxorubicin-resistant cells. This pathway has been previously associated with drug resistance. In colorectal cancer (CRC) cell line models, IL-8 enhances the downstream phosphorylation of p65, which then binds to the ABCB1 promoter. When IL-8 is targeted using siRNA or inhibitors of CXCR1/2 or NFkB signaling, a downregulation of ABCB1, along with reductions in MDR1 mRNA and protein levels, has been observed (Du et al., 2018). In osteosarcoma, IL-8 similarly regulates downstream ABCB1, and preliminary analyses indicated that HDAC6 contributes to the increased expression of IL-8 in doxorubicin-resistant osteosarcoma cells. Targeting p65 or HDAC6 led to the upregulation of ABCB1 and IL-8 expression in osteosarcoma cells, respectively (Cheng et al., 2018). Additionally, a study on gastric cancer identified the same p65/ABCB1 mechanism as a mediator of chemoresistance to cisplatin. Notably, the clinical findings of this research revealed that elevated serum IL-8 not only predicted a poor response to platinum-based chemotherapy but also indicated high levels of resistance. Beyond the studies mentioned, numerous other investigations have shown that elevated levels of IL-8 contribute to chemoresistance in various cancers, such as pancreatic, colorectal, breast, and melanoma (Dabkeviciene et al., 2015; Imafuji et al., 2019; Sootichote et al., 2018). Together, these results indicate that targeting IL-8 could enhance the effectiveness of chemotherapy in multiple cancer types

CONCLUSION

The current study found that Taxol significantly impacts liver tissue, resulting in observable effects and varying immune responses depending on the dosage.

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