

Histopathological Studies on the Effect of Taurine Against Etoposide-Induced Acute Liver and Kidney Toxicity in Female Albino Rats

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Abstract

Etoposide (ETP) is a topoisomerase II (TOP II) inhibitor and one of the leading chemotherapeutic drugs for treating a wide variety of tumors. However, ETP induced hepatotoxicity and nephrotoxicity limits its clinical use. This study aims to investigate the protective potential of taurine (Tau) to mitigated histopathological changes in the liver and kidneys of female albino rats treated with ETP. A total of 18 female rats were divided into three groups; control group, ETP-exposed group received intraperitoneal injection of ETP on the first 3 days of the study for a total cumulative dose of 44 mg/kg to induce hepatotoxicity and nephrotoxicity, ETP + Tau group received ETP as stated previously with 400 mg/kg/day of Tau via oral gavage for 15 days. Sections from the liver and kidney were evaluated under light microscope and ETP-exposed group revealed vascular congestion, chronic inflammatory cell infiltration predominantly lymphocytes, edema, vacuolar degeneration, atypical cells, pyknosis, and necrosis while liver and kidney sections of rats treated with combination of ETP + Tau group exhibited marked alleviation of the histopathological damage. The study concludes that treatment with ETP induced marked structural damages in the liver and kidney and such morphological damages are effectively diminished by administering Tau.

Keywords: Etoposide, Taurine, Liver, Kidney, Toxicity.

1. Introduction

Chemotherapeutic drugs have undergone many positive advancements and their use in the oncologic settings resulted in better tumor prognosis and improved overall survival. However, administration of chemotherapy is still considered a “double-edged sword” with severe adverse effects in multiple organs (Mudd & Guddati, 2021; Perazella, 2012; Torri et al., 2021). Hepatotoxicity and nephrotoxicity associated with variety of anticancer therapies are relatively common and significant clinical manifestations which limit the efficacy of life-saving therapies and further reduce cancer patients’ quality of life (Mudd & Guddati, 2021; Santos et al., 2020). The liver has a major function in the metabolism, detoxification and clearance of many drugs and their toxic metabolites. Therefore, it is susceptible to toxicity induced by these toxic metabolites and production of reactive oxygen species which can further result in oxidant/antioxidant imbalance and release of inflammatory cytokines (Maor & Malnick, 2013; Thatishetty et al., 2013) while the kidneys are major pathways for drugs and their metabolites to be eliminated from the body, and renal toxicity results from drugs toxic metabolites

causing injury through oxidation as well as direct interaction of the drug with DNA (Malyszko et al., 2017; Perazella, 2012).

Etoposide (ETP) is a topoisomerase II (TOP II) inhibitor derived from podophyllotoxin that is naturally found in roots and rhizomes of *podophyllum peltatum linnaeus* and *podophyllum emodi wallichii* (Shah et al., 2021). It is one of the leading chemotherapeutic drugs for treating a wide variety of tumors, and it is considered as an important component of chemotherapy regimens. Thus, it improves the response rate when combined with other antineoplastic agents (Meresse et al., 2004). However, ETP-induced hepatotoxicity and nephrotoxicity limit the drugs' clinical use (Nemade et al., 2018; Rjiba-Touati et al., 2018).

Despite numerous animal and human studies reported on ETP-induced hepato- and nephrotoxicity, and the remarkable advance made in understanding the mechanism of toxicity (Almakhatreh et al., 2019; Barnoud et al., 2018; Kwon et al., 2015; Rjiba-Touati et al., 2018; Tran et al., 1991), management and treatment of these toxicities are largely supportive (Lee et al., 2021). However, in the last few decades, novel strategies and effective protective approaches have been developed to prevent or minimize the toxicity of chemotherapeutic drugs. One of the strategies is the use of natural therapeutic agents possessing antioxidant and anti-inflammatory effects together with chemotherapeutic agents (Ibrahim Fouad & Ahmed, 2021; Saleh et al., 2012). In this study, we examined the combinational effect of ETP and taurine (Tau) on liver and kidneys.

Tau (2-aminoethanesulfonic acid) is a major semi-essential amino acid found in most body tissues. It is mainly synthesized in the liver and kidneys, however the intracellular concentration of Tau is largely maintained by its dietary intake (Jakaria et al., 2019; Miyazaki et al., 2009). Tau is considered as a cytoprotective molecule and plays several important pharmacological and physiological functions in the body, including maintenance of calcium homeostasis, bile acid conjugation, osmoregulation, neuromodulation, membrane stabilization, detoxification, antiapoptotic, anti-inflammation and antioxidation (Baliou et al., 2021; Cavdar et al., 2017; Hagar, 2004). It has been shown that Tau administration markedly ameliorated hepatotoxicity induced by cyclosporin (Hagar, 2004), thioacetamide (Dođru-Abbasođlu et al., 2001), and carbon tetrachloride (Dinçer et al., 2002) by scavenging reactive oxygen species. In addition to that, Tau supplementation inhibited inflammation and apoptosis in doxorubicin-induced renal toxicity (Kim et al., 2017). It has also been reported that exogenous Tau effectively reduces cisplatin-induced nephrotoxicity by reducing oxidative stress and accumulation of platinum within kidney tissue (Saad & Al-Rikabi, 2002).

In consequence of these beneficial effects of Tau, this study aimed to investigate the ability of Tau to mitigate histopathological alterations in the liver and kidneys of female albino rats treated with ETP.

2. Materials and Methods

This section outlines materials and the animal model used to conduct the study. Furthermore, it describes the study procedure performed on the animal model.

2.1. Animal model

18 female albino rats, weighing 160-200 grams and 10-12 weeks old, were acquired and housed in polypropylene cages (6 rats in each) on sawdust in the experimental animal house of the college of pharmacy at Hawler Medical University in Erbil, Iraq. They were kept at room temperature, with a 12-h light and dark cycle and 40 to 60% humidity and were allowed to acclimatize to the housing environment for at least one week before carrying out the experimental procedure. The rats had free access to tap water and were supplied with rodent chow. This experiment followed the recommendations of the National Institute of Health "Guide for Care and Use of Laboratory Animals" provided by National Academy of Science (Publication No. 85-23, revised 1985) and was approved by the Hawler Medical University-college of pharmacy's ethics committee on 22 August 2021, with the approval number 26042022.

2.2. Drugs

Etopex vial (Etoposide 100 mg/5 ml injectable solution), Xyla vial (xylazine 20 mg/ml injectable solution), Ketamin Fresenius vial (ketamin 50 mg/ml injectable solution), and Taurin (taurine 500 mg tablet) were manufactured by Deva pharmaceuticals (Istanbul, Turkey), Interchemie (Venray, Netherlands), Fresenius Kabi (Midrand, South Africa), and Warnke Vitalstoffe GmbH (Wetzlar, Germany), respectively and were purchased from a licensed and verified pharmacy. Tau tablet was ground and dissolved in distilled water every day prior to administration. The doses of both ETP and Tau were carefully selected depending on previous studies (Bregman et al., 1994; Wenting et al., 2014).

2.3. Study design

In this study the animals were randomly divided into three groups of 6 rats each as follows: Group I (Control): Rats received intraperitoneal injection of 0.1 ml saline solution (0.9% NaCl) on the first three days of the experiment and 1 ml of sterile water for 15 consecutive days via oral gavage needle. Group II (ETP): Rats received intraperitoneal injections of ETP (14.7 mg/kg/day) on the first three days of the experiment for a total dose of (44 mg/kg) to induce hepatotoxicity and nephrotoxicity along with 1 ml of sterile water for 15 consecutive days via oral gavage needle. Group III (ETP + Tau): Rats received ETP as stated previously along with Tau (400 mg/kg/day) for 15 consecutive days via oral gavage needle.

The rats were anesthetized with xylazine 10 mg/kg and ketamine 100 mg/kg injections administered intraperitoneally three hours following the last treatment (Konecny, 2021) to render them unconscious. Afterward, the liver and kidneys were harvested and grossly examined for any abnormalities developed in the organs. They were then fixed in buffered formaldehyde solution for less than 24 hours for further histopathological analysis.

2.4. Histopathological analysis

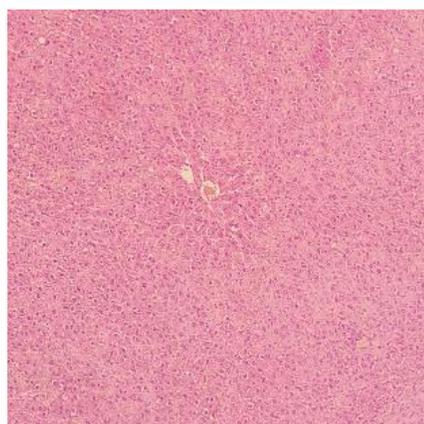
Specimens of liver and kidneys were embedded in molten paraffin and were serially sectioned at 4 μ m thickness using a microtome (Thermo Scientific™ HM E340 Automated Microtome, Germany). The sections were then put on clean slides, deparaffinized and rehydrated using automated tissue processor (Sakura Histo-Tek® VP1™, Netherlands). Next, the slides were stained with hematoxylin and eosin (H&E). After that, the slides were dehydrated, cleared, and the cover slipped. Finally, the slides were observed under a light microscope (Olympus Light microscope, Germany) for histopathological evaluation and their photomicrographs were captured. Random numbers were used to code the slides for a blind investigation by a skillful pathologist.

3. Results

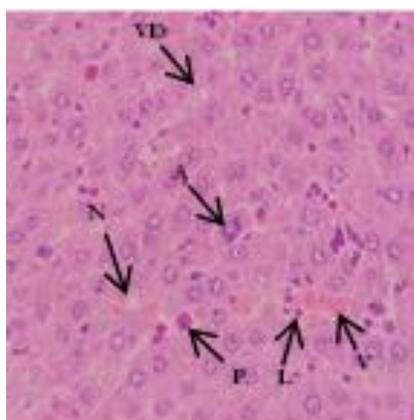
This section describes the main findings of the histopathological analysis of liver and kidneys.

3.1. Effect of Tau on ETP-induced histopathological alterations in liver

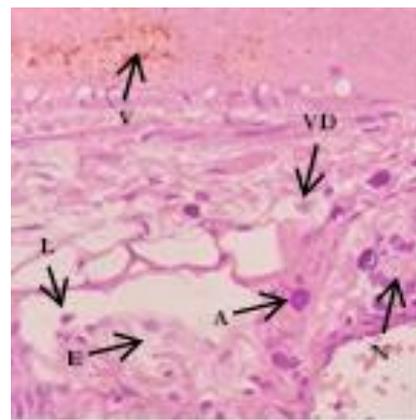
No macroscopic alterations were observed in the livers of all groups. Light microscopic evaluation revealed that the hepatic parenchyma of rats in the control group exhibited normal histological structure (Figure 1a). Meanwhile, in the liver of ETP-exposed rats marked histopathological alterations were noted, which were described by vascular congestion with scattered red blood cells (RBCs), chronic inflammatory cell infiltration predominantly lymphocytes, edema, vacuolar degeneration of hepatocytes, atypical cells, pyknosis of hepatocytes, and necrosis (Figure 1b-d). On the contrary, rats treated with combination of ETP + Tau exhibited marked alleviation of the histopathological damages in the liver and the most encountered injuries were: vascular congestion with scattered RBCs, chronic inflammatory cell infiltration predominantly lymphocytes, and vacuolar degeneration of hepatocytes (Figure 1e-g).



(a)



(b)



(c)

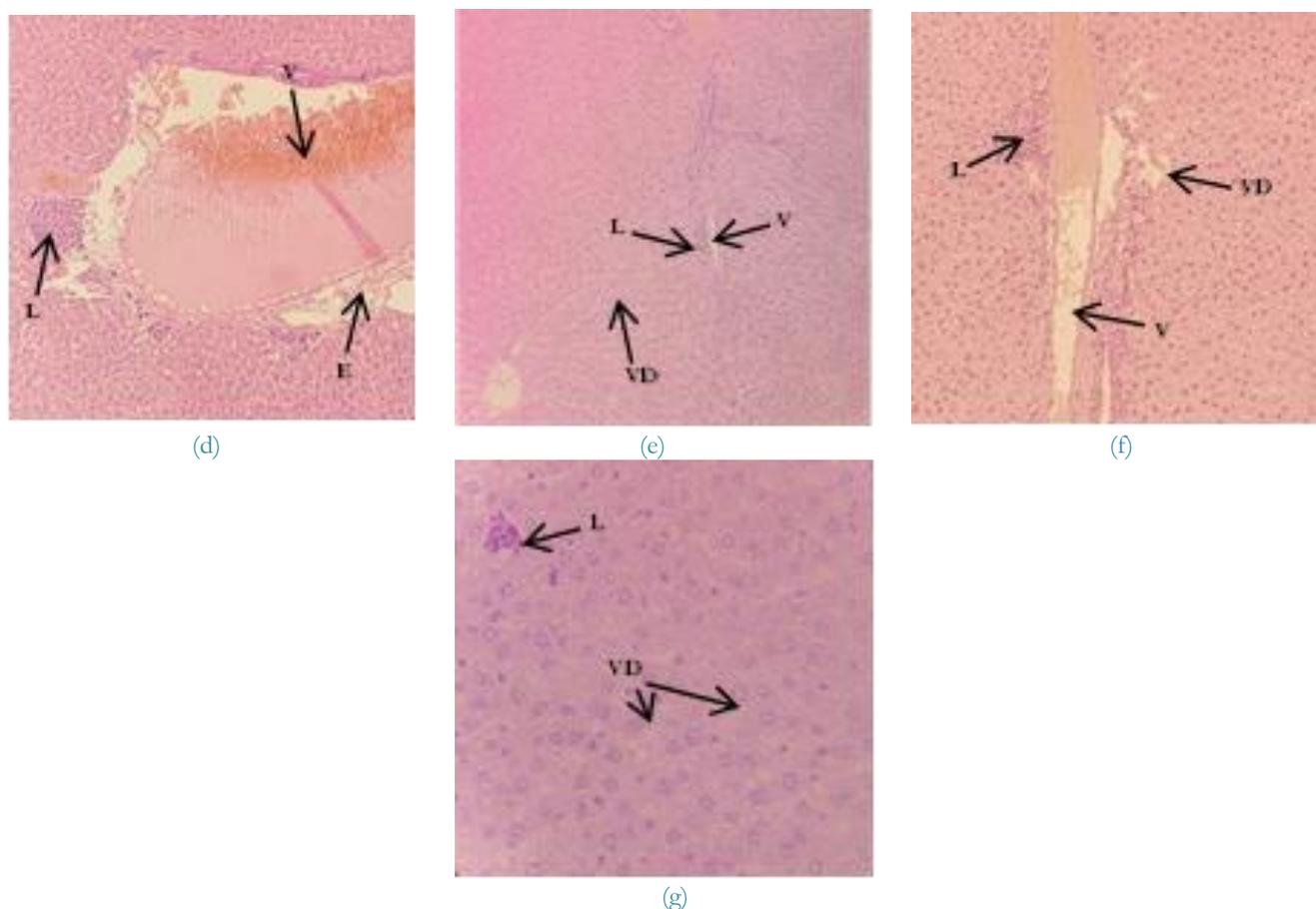


Figure 3. Micrographs of liver sections stained with H&E: a) Liver section of control group showing normal liver structure, b) Liver section of ETP- exposed group showing pyknosis of hepatocytes (P), necrosis (N), vacuolar degeneration of hepatocytes (VD), atypical cells (A), vascular congestion with scattered RBCs (V), and chronic inflammatory cell infiltration predominantly lymphocytes (L), c) Liver section of ETP- exposed group showing necrosis (N), vacuolar degeneration of hepatocytes (VD), atypical cells (A), vascular congestion with scattered RBCs (V), edema (E), and chronic inflammatory cell infiltration predominantly lymphocytes (L), d) Liver section of ETP- exposed group showing vascular congestion with scattered RBCs (V), edema (E), and chronic inflammatory cell infiltration predominantly lymphocytes (L), e) Liver section of ETP + Tau cotreated group showing vascular congestion with scattered RBCs (V), vacuolar degeneration of hepatocytes (VD), and chronic inflammatory cell infiltration predominantly lymphocytes (L), f) Liver section of ETP + Tau cotreated group showing vascular congestion with scattered RBCs (V), vacuolar degeneration of hepatocytes (VD), and chronic inflammatory cell infiltration predominantly lymphocytes (L), and g) Liver section of ETP + Tau cotreated group showing vacuolar degeneration of hepatocytes (VD), and chronic inflammatory cell infiltration predominantly lymphocytes (L).

3.2. Effect of Tau on ETP-induced histopathological alterations in kidneys

No significant gross lesions were conducted in the kidneys of all groups. Histopathological evaluation of the kidneys of rats in control group exhibited normal histological structure of renal parenchyma (Figure 2a). whereas in the ETP-exposed kidneys severe histopathological alterations were noticed, which were described by vascular congestion with scattered RBCs, chronic inflammatory cells infiltration predominantly lymphocytes and fibroblast, marked vacuolar degeneration in renal tubules, and atrophic glomeruli (Figure 2b-d). In kidneys of rats treated with combination of ETP + Tau, the atrophied glomeruli were no longer present. Furthermore, the renal parenchyma maintained a better morphology with mild vascular congestion, chronic inflammatory cell infiltration predominantly lymphocytes, and vacuolar degeneration of renal tubular epithelial cells (Figure 2e-g).

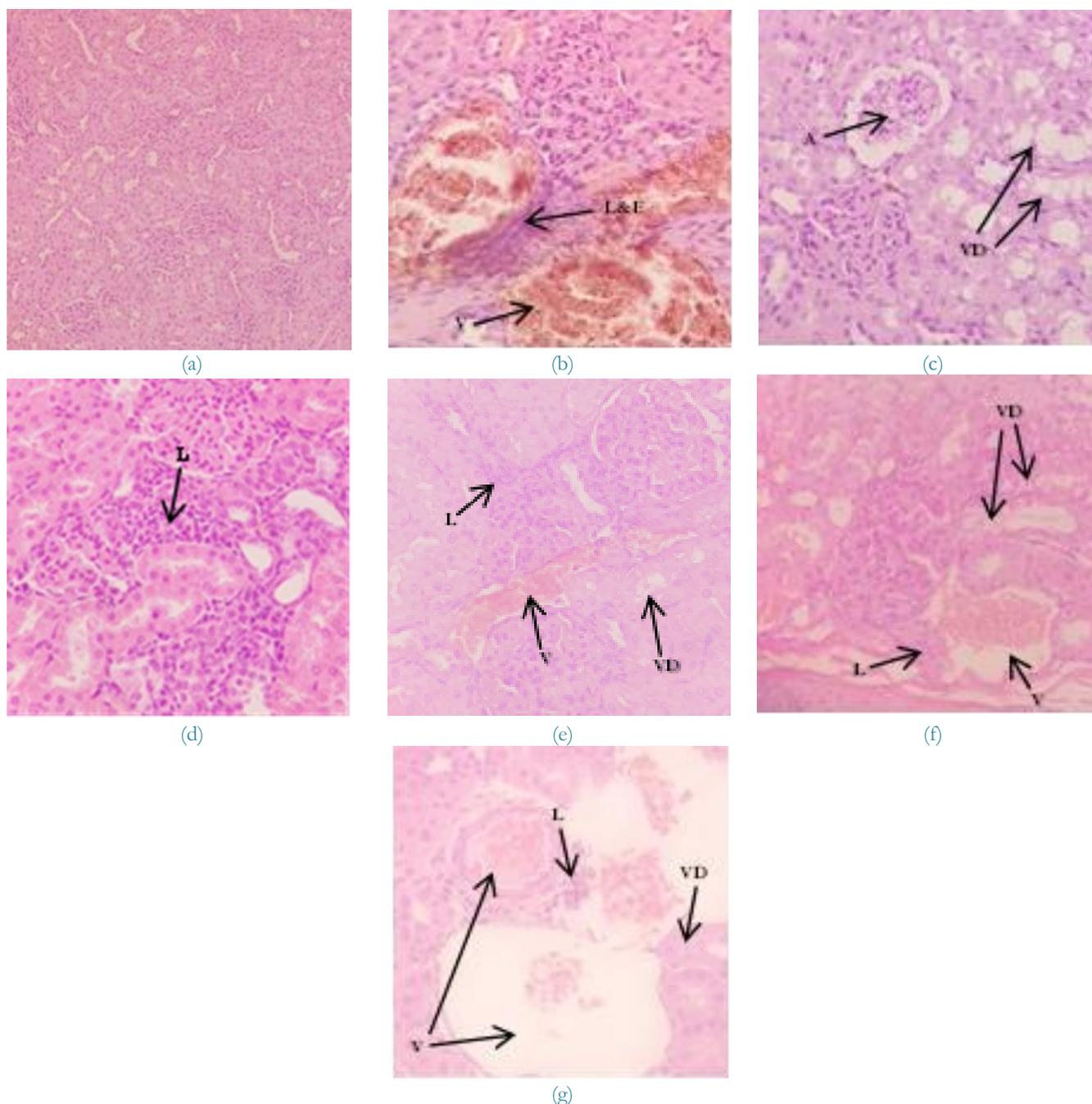


Figure 4. Micrographs of kidney sections stained with H&E: a) Kidney section of control group showing normal kidney structure, b) Kidney section of ETP-exposed group showing chronic inflammatory cell infiltration predominantly lymphocytes and fibroblasts (L&F), and prominent vascular congestion with scattered RBCs (V), c) Kidney section of ETP-exposed group showing atrophic glomeruli (A), and vacuolar degeneration of renal tubular epithelial cells (VD), d) Kidney section of ETP-exposed group showing chronic inflammatory cell infiltration predominantly lymphocytes (L), e) Kidney section of ETP + Tau cotreated group showing vascular congestion with scattered RBCs (V), chronic inflammatory cell infiltration predominantly lymphocytes (L), and vacuolar degeneration of renal tubular epithelial cells (VD), f) Kidney section of ETP + Tau cotreated group showing vascular congestion with scattered RBCs (V), chronic inflammatory cell infiltration predominantly lymphocytes (L), and vacuolar degeneration of renal tubular epithelial cells (VD), and g) Kidney section of ETP + Tau cotreated group showing vascular congestion with scattered RBCs (V), chronic inflammatory cell infiltration predominantly lymphocytes (L), and vacuolar degeneration of renal tubular epithelial cells (VD).

4. Discussion

The present study was conducted to examine the ability of Tau to alleviate histopathological alterations in the liver and kidneys of rats treated with ETP.

It has been demonstrated in a previous study that intraperitoneal injection of 1 mg/kg of ETP daily for four weeks induced hepatotoxicity evidenced by moderate atrophy and vacuolar degeneration of hepatocytes, pyknosis, marked cellular infiltrations, as well as marked congestion in hepatic veins (Tousson et al., 2019). These findings were in accordance with our results in which ETP administered intraperitoneally over a period of three days (14.7 mg/kg/day) for a total cumulative dose of 44 mg/kg and an observation period of 15 days resulted in hepatotoxicity characterized by congestion of hepatic blood vessels, chronic inflammatory cell infiltration predominantly lymphocytes, edema, vacuolar degeneration of hepatocytes, atypical cells, pyknosis of hepatocytes, and necrosis. Furthermore, in our histopathological analysis of kidneys we found that ETP administration caused congestion of renal blood vessels, chronic inflammatory cell infiltration (predominantly lymphocytes and fibroblast), marked vacuolar degeneration of renal tubular epithelial cells, and atrophic glomeruli. These observations are in accordance with an earlier study that revealed long-term treatment with ETP resulted in histological alterations in kidneys that are characterized by dilation and enlargement of the proximal convoluted tubules lumen and vacuolar degeneration in their epithelium around nucleus, glomerular atrophy, necrosis, and marked congestion of the glomeruli (Kamble et al., 2013).

The possible mechanism of ETP-induced toxicity is suggested to be due to its highly reactive metabolites. ETP is metabolized in liver cells through cytochrome P450- monooxygenase-dependent system, horseradish peroxidase, and tyrosinase to generate *ortho*-quinone, short live intermediate free radicals (phenoxy and semiquinone) and catechol. These metabolites, mainly *ortho*-quinone, exert biochemical alterations in the cells through free radical formation and can lead to lipid peroxidation, protein oxidation, and many inflammatory changes which furthermore affects other organs including kidney, brain, and heart (Kluska and Woźniak, 2021; Rao et al., 2019; Zhang et al., 2021). Doxorubicin is also a TOP II inhibitor and studies approved that it induces similar histopathological changes to the liver and kidney in laboratory animals through similar manner. This is by formation of semiquinone-type free radicals, and reacting with molecular oxygen to form reactive oxygen species that cause injury to plasma membranes and intracellular macromolecules (Gökçe et al., 2021; Ibrahim Fouad and Ahmed, 2021; Shivakumar et al., 2012).

In this study, we found that supplementation of rats with Tau for 15 consecutive days at the dose of 400mg/kg with ETP treatment considerably reduced ETP-induced histopathological lesions in the liver and kidneys. However, the protection was not complete to the degree of the rats in the control group. The use of Tau has been studied in reducing toxicity in several organs induced by chemotherapeutic agents including, methotrexate, tamoxifen, 5-fluorouracil, cyclophosphamide, and doxorubicin. It has been suggested that its protective effect is mainly related to its antioxidant activity (Alam et al., 2011; Alhumaidha et al., 2016; Barış et al., 2019; Nagai et al., 2016; Yousef and Aboelwafa, 2017). Furthermore, it has been demonstrated that Tau enhances cell proliferation and promotes neurogenesis in the brain (Hernández-Benítez et al., 2012). In this study, histopathological findings revealed that Tau prevented ETP- induced necrosis in both hepatocytes and renal tubular epithelial cells and this might be due to the ability of Tau to stimulate cellular proliferation.

5. Conclusion

Results of the present investigation concluded that treatment with ETP at a given dose induced marked structural lesions in the liver and kidneys, evidenced by histopathological examination. Oral administration of Tau effectively diminished the severity of the morphological damage induced by ETP. Further investigations are required on the molecular level to understand the exact mechanism underlying the reno- and hepatoprotective effect of Tau and whether the use of combined administration of Tau mitigates this toxicity without compromising the therapeutic efficacy of ETP.

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