DOI: 10.14744/ejmi.2019.14740
EJMI 2019;3(4):315–321

Research Article

Effects of Paclitaxel on Lipid Peroxidation and Antioxidant Enzymes in Tissues of Mice Bearing Ehrlich Solid Tumor

Mustafa Nisari,[1] Emin Kaymak,[2] Tolga Ertekin,[3] Dilek Ceylan,[4] Neriman Inanc,[1] Saim Ozdamar[5]

[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Nuh Naci Yazgan University, Kayseri, Turkey
[2]Department of Histology and Embryology, Faculty of Medicine, Bozok University, Yozgat, Turkey
[3]Department of Anatomy, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyon, Turkey
[4]Genome and Stem Cell Center, Erciyes University, Kayseri, Turkey
[5]Department of Histology and Embryology, Pamukkale University Facuty of Medicine, Denizli, Turkey

Abstract

Objectives: Cancer is the second most common cause of death in the world. Several chemotherapeutic drugs have been studied for their anticancer features. Paclitaxel is one of these chemotherapeutic drugs with high medicinal interest. This study was conducted in order to investigate effects of paclitaxel on lipid peroxidation and antioxidant enzymes in tissues of mice bearing solid-form Ehrlich tumors.

Methods: In this study, 36 Balb/C male mice aged 8-10 weeks and weighing 25-30 g were used. Six mice were kept as cancer stock to produce Ehrlich Ascites Tumor (EAT) cells. Thirty mice were distributed into three groups as healthy control, tumor control and paclitaxel treatment. 0.1 ml physiologic saline solution was administered into mice in healthy control subcutaneously (s.c.) for 15 days. The animals in tumor control and Paclitaxel treatment groups received 1x106 EAT cells s.c. through nape skin on the first day of the experiment. After the application of EAT cells, 10 mg/kg Paclitaxel was injected intraperitoneally on days 4, 9 and 14. At the end of the study (on day 15), animals were sacrificed and liver, kidney, brain and testis tissues were excised and analyzed for Malondialdehyde (MDA), by using TBARS method, superoxide dismutase (SOD) and catalase (CAT) activities spectrophotometrically.

Results: Compared to the results of healthy control group, tumor increased kidney and liver MDA levels development slightly but not significantly. Paclitaxel treatment significantly reduced the increased MDA levels in kidney and liver ($p<0.001$). Paclitaxel had no effect on testis MDA but brain MDA level reduced with the help of EAT cell injection and Paclitaxel returned the brain MDA level close to the level of healthy control ($p<0.001$). EAT cell injection reduced catalase activity in kidney and liver ($p<0.001$) and Paclitaxel had no effect on catalase activities in these tissues. In EAT cell injected mice; testis and brain catalase activities were higher than that of healthy control group that were returned to control levels by Paclitaxel treatment. Paclitaxel had no significant effect on decreased kidney and liver SOD activities whereas it significantly reduced the increased SOD activities in testis ($p<0.05$) and in brain ($p<0.01$).

Conclusion: Paclitaxel alleviated the lipid peroxidation in kidney and liver but had no effect on antioxidant status in these tissues of solid-Ehrlich tumor-bearing mice.

Keywords: Antioxidant enzymes, lipid peroxidation, paclitaxel, solid-form Ehrlich tumor

Cite This Article: *Nisari M, Kaymak E, Ertekin T, Ceylan D, Inanc N, Ozdamar S. Effects of Paclitaxel on Lipid Peroxidation and Antioxidant Enzymes in Tissues of Mice Bearing Ehrlich Solid Tumor. EJMI 2019;3(4):315–321.*

Address for correspondence: Mustafa Nisari, MD. Nuh Naci Yazgan Universitesi, Saglik Bilimleri Fakultesi, Beslenme ve Diyetetik Bolumu, 38090 Kayseri, Turkey
Phone: +90 532 645 52 12 **E-mail:** mnisari@nny.edu.tr

Submitted Date: June 17, 2019 **Accepted Date:** September 25, 2019 **Available Online Date:** October 10, 2019

Cancer, a genomic disease, is a worldwide public health problem. Cancer, which is accepted among chronic diseases, is frequent and has the second leading mortality score following cardiovascular diseases.[1–3] Cancer is one of the most important health problems in Turkey as it is in the whole world. In Turkey, the standardized cancer rate for age in 2013 is 186.5 per hundred thousand for women and 267.9 for men. Total cancer incidence is 227.2 per hundred thousand. In 2002, deaths caused by cancer in our country constituted 12% of all deaths whereas this rate increased up to 21% in 2009. When the 2012 data is evaluated, over 175.000 new cancer cases have emerged in our country within a year. If a similar course continues, it is expected to be 22 million new cases annually in 2030.[2]

A number of experimental cancer models have been developed for use in cancer-related studies and Ehrlich solid carcinoma is a commonly used tumor model among them.[4–5] Ehrlich ascites carcinoma is a spontaneous murine mammary adenocarcinoma adapted to ascites form and carried in outbred mice by serial intraperitoneal (i.p.) passages.[6]

Ehrlich solid carcinoma is an undifferentiated tumor.[5] It was reported that Ehrlich ascites tumor (EAT) cells undergo rapid proliferation in almost any mouse host because they lack H-2 histocompatibility antigens.[4] Morphological and metabolic changes occur following implantation of EAT cells. It was shown that subcutaneous implantation of EAT cells into mice causes changes in oxidant and antioxidant status in the tissues.[5]

Several chemotherapeutic drugs have been studied for their anticancer activities. Paclitaxel, aka Taxol, is a chemotherapeutic drug with high medicinal interest. Paclitaxel is one of the most commonly used chemotherapeutics in clinical studies. It is a broad-spectrum anticancer drug effective in various solid tumors such as ovarian and breast cancer, lung cancer, melanoma, head and neck cancer and bladder cancer.[7–9] Paclitaxel has potent anti-proliferative action against tumor cells[10] and this agent shows its functions by stabilizing microtubules, blocking mitosis and inducing apoptosis.[9–11]

Antioxidants are naturally present in many fruits and vegetables and can be synthesized in laboratories. They delays or improves cellular oxidative damage, so there are various health benefits in the prevention and treatment of diseases. They can be used alone or in combination with other drugs as adjuvant therapies. The study of free radicals and antioxidants includes promising new solutions in disease and health management. Many original studies aim to eliminate this toxicity by the antioxidants of the drug's healing effect and the toxicities associated with chemicals.[12] Reactive oxygen species (ROS) are produced continuously in the body because of aerobic metabolism as well as external factors[13] and these are balanced by antioxidant defense systems. When ROS are produced in excess, they cause tissue damage. Cellular damage resulting from oxidative stress is involved in the initiation and progression of cancer.[14] Cancer cells increase production of ROS compared to normal cells[15] and it is speculated that tumorigenic signaling also increases expression of antioxidant proteins to balance the high ROS production to maintain redox homeostasis.[16, 17] Studies indicated that the levels of oxidative stress markers increase in cancer cases.[18–21] Several adverse effects of chemotherapy treatments have been reported and most of these effects are associated with oxidative metabolism.[19] Anti-cancer drugs can also cause oxidative stress as a side effect.[14] Previous studies investigating the effects of Taxol on lipid peroxidation and antioxidant status in different cancer types in animal models and human have revealed distinct results.[22–24] Therefore, this study was performed to investigate the effects of Paclitaxel on tissue MDA levels and antioxidant enzyme activities in mice bearing Ehrlich solid carcinoma.

Methods

Animals, Management and Experimental Design

In this study, 42 Balb/C male mice aged 8-10 weeks and weighing 25-30 g were obtained from Erciyes University Experimental and Clinical Research Center (DEKAM). The study was held at DEKAM with the permission of Erciyes University Experimental Animals Local Ethics Committee, Approval No. 15/03 and dated 14.01.2015.

Animals were maintained in polycarbonate cages sized 42x26x15 cm (five mice in each) at this center that provides appropriate standard conditions (21±2 ºC room temperature, 50±5% humidity, environmental ventilation systems providing air flow rotation of 12 per hour and 12 hours light/dark light cycle) for highest health status throughout the study. A commercially available pellet diet containing 24% crude protein, 3.85% crude cellulose, 5% fat, 6.98% ash as well as amino acids and vitamin-mineral mix that met the daily nutritional requirement of the mice (routinely used in DEKAM) was provided throughout the experiment. Water and feed were supplied ad libitum during the study.

In the beginning of the study, all animals were weighed. Before initializing the experiment, 12 mice were kept as cancer stocks to obtain sufficient EAT cells. The remaining 30 animals were assigned into three experimental groups consisting of 10 mice in each. Five individually labeled mice were maintained in one cage.

Group I was kept as healthy control and a-0.1 ml injection

of physiologic saline solution was done subcutaneously (s.c.). On the first day of the experiment, a single dose of 1x106 EAT cells in 0.1 ml of phosphate buffer saline (PBS) was injected s.c. through nape skin to each animal in Group II and Group III for solid tumor development. Mice in Group II were kept as solid tumor control following the EAT injection. Mice in Group III received 10 mg /kg Paclitaxel i.p. on days 4, 9 and 14. The animals in Control Group also received physiologic saline solution i.p. on the same days (Fig. 1).

Sample Collection and Preparations

At the end of the experiment (on day 15), all of the animals were sacrificed with ketamine-xylazine under general anesthesia, and the liver, kidney, brain and testis tissues from each animal were collected into sterile plastic bags for determination of MDA levels, SOD and CAT activities. The samples were transferred to the laboratory under cold chain and stored at -80 ºC until biochemical analyses immediately.

Homogenization of Tissues

Tissue samples (500 mg) were thawed and homogenized in a glass homogenizer with physiological saline solution (pH=7.4) (1/10, w/v). The homogenates were centrifuged at 12.000 rpm for 20 minutes under 4 °C. Some parts of the supernatants were kept for MDA and CAT analyses. The remaining supernatants were mixed with ethanol/chloroform mixture [5/3 (v/v)] at 1/1 ratio and they were centrifuged again at 12.000 rpm for 20 minutes in a refrigerated centrifuge. The supernatants were separated for SOD enzyme activity.

Determination of MDA Level, CAT and SOD Activities

Malondialdehyde, a secondary product of lipid peroxidation, is an important indicator of lipid peroxidation. Malondialdehyde forms a pink complex with thiobarbituric acid (TBA) under aerobic conditions at pH=3.4 following the incubation at 95 °C. The absorbance of this complex was measured at 532 nm by using a UV-Visible spectrophotometer (Shimadzu, UV 1601, United states) through freshly prepared 10, 20, 40, 60, 80, 100 nMol/ml 1,1,3,3-tetramethoxypropane (density: 0.99 g/ml) solutions according to the method described by Ohkawa et al.[25] Briefly, 100 µl tissue homogenate was mixed with 8.1% of sodium dodecyl sulfate (SDS), 20% of acetic acid (HAc) (pH=3.5) and 0.8% of TBA (pH=3.5) and incubated at 95 °C for 30 minutes. Then they were cooled and n-Butanol-pyridine (nBu-Pri) solution and distilled water were added in the vortex-mixed solution. The supernatant was separated following the centrifugation at 4.000 rpm for 10 minutes and the absorbance was monitored. The result was recorded in nMol/mg protein.

The activity of SOD was measured spectrophotometrically according to the method described by Sun et al.[26] This method is based on reduction of nitrobluetetrazolium (NBT) by superoxide radicals which are formed by the enzymatic reaction of xanthine oxidase (XO). The colorless NBT ion is transformed into a blue formazan giving maximum absorbance at 560 nm when reduced with the superoxide radical. The tissue was homogenized with the help of 1/10 of distilled water. The sample was mixed with the chloroform/ethanol mixture 1/1 (v/v) and centrifuged at 12.000 rpm for 2 hours at +4 ºC. The supernatant was separated to determine SOD activity. 50 µl tissue supernatant and 50 µl XO in 2 M ammonium sulfate solution (1/100, v/v) were added 2.9 ml of the reagent mixture consisting of xanthine solution + NBT + Na_2CO_3 + BSA. After incubation at 25 °C for 20 minutes, 1 ml of 0.8 mM $CuCl_2$ was added to the tube and optical density of the sample was recorded at 560 nm. The SOD activity was displayed in Unit/mg protein (1 unit=50% inhibition of NBT reduction) and % inhibition was calculated with the following formula: % inhibition = [(blank abs-tissue abs)/blank abs] x 100.

Catalase enzyme catalyzes the conversion of H_2O_2 to H_2O. This conversion can be monitored by a decrease in absorbance at 240 nm. The decrease in absorbance at 30th sec-

Figure 1. (a) Solid tumor on the back of the rat, **(b)** Solid tumor removed from the back of the rat **(c)** Solid tumor.

ond is related to catalase activity. The CAT activity was determined as described previously by Aebi.[27] The CAT assay was performed briefly as follows: Tissue homogenate was mixed with H_2O_2 solution (30 mM) + freshly prepared PBS (50 mM, pH=7.0) then the absorbance was measured spectrophotometrically at 240 nm after 30 seconds against blank. The extinction coefficient was 0.004 (0.0039) mM-1mm-1. The CAT activity was expressed in U/mg protein/min for tissue.

Histopathological Examination

After the experiment, kidney and liver tissue samples were taken from animals and fixed with formalin solution for histopathological examination. Following the two-day fixation of the tissues; Histological tissue monitoring including tap water, graded alcohols (50, 70, 80, 90, 100%), xylol (xylol 1 and xylol 2) and paraffin (paraffin 1 and paraffin 2) were performed. The prepared paraffin blocks were cut into 5 µm sections in the microtome. Tissues were stained with Hematoxylin-Eosin (HE) and evaluated under light microscope.

Analysis of the Data

IBM SPSS Statistics 22.0 (IBM Inc., ILL, USA) software was used for statistical analysis of the data. Normal distribution of the data was evaluated by histogram, q-q graphs and Shapiro-Wilk test. The variance homogeneity was tested by Levene test. One way ANOVA and Kruskal Wallis test were used in intergroup comparisons. Tukey and Dunn-Bonferroni tests were applied for multiple comparisons. The data were evaluated by using the R 3.2.3 program. Data were presented as means±standard deviation of the means and median (25%-75% percentiles) where appropriate. Significance level was $p<0.05$.

Results

Biochemical Findings

Compared to that of the healthy control group, tumor development increased kidney and liver MDA levels slightly but not significantly. Paclitaxel treatment significantly reduced the increased MDA levels in kidney and liver ($p<0.001$). Paclitaxel had no effect on testis MDA but brain MDA level was reduced by EAT-cell injection and Paclitaxel returned the brain MDA level to the level of the healthy control group ($p<0.001$). EAT-cell injection reduced catalase activity in kidney and liver ($p<0.001$) and Paclitaxel had no effect on catalase activities in these tissues. In EAT-cell-injected mice, testis and brain catalase activities were higher than that of the healthy control group that were returned to control levels by Paclitaxel treatment. Paclitaxel had no significant effect on decreased kidney and liver SOD activities whereas it significantly reduced the increased SOD activities in testis ($p<0.05$) and brain ($p<0.01$).

Histopathologic Findings

The kidney tissues of Group I, the connective tissue capsule appeared normal. Also kidney parenchyma, renal corpuscles, proximal and distal tubules, peritubular capillaries showed normal. In Group II, EAT cells were observed attached to the connective tissue capsule. When the kidney sections of this group were examined, invasive tumor cells were observed at different densities in the tissue capsule. The presence of tumor cells in tumor group was also detected in the kidney capsule of Group III, but the density was lower (Fig. 2).

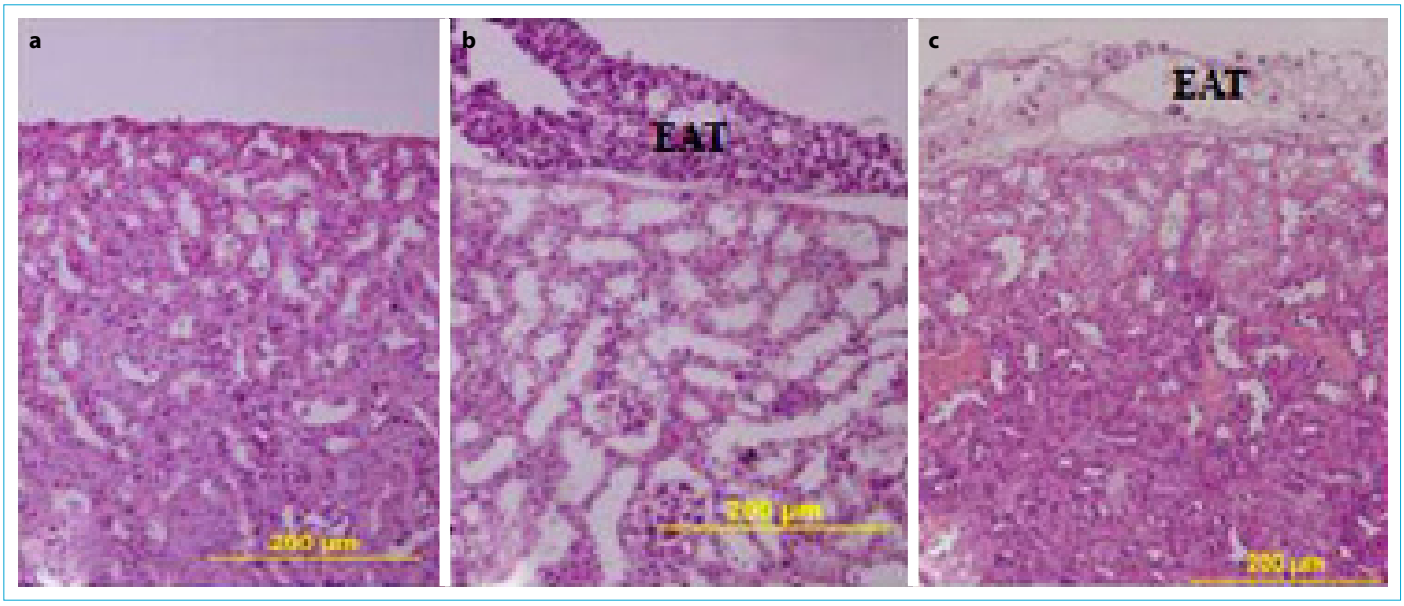

Figure 2. Histopathological findings of kidney tissue (H&E, 20X) **(a)** Healty control group **(b)** Tumor control group **(c)** Paclitaxel group.

In the liver tissues of Group I, normal parenchymal structure was observed. Liver cells progressing radially around the vena centralis in the lobules were normal. Liver sinusoids were observed to extend normally between the hepatocyte cords. In the portal areas, bile duct, hepatic artery and venous structures were visible in the connective tissue. In Group II, EAT cells were observed attached to the connective tissue forming the glisson capsule whereas in Group III EAT cells were observed attached to the capsule of liver tissue (Fig. 3). Paclitaxel had no significant effect on decreased kidney and liver SOD activities whereas it significantly reduced the increased SOD activities in testis ($p<0.05$) and brain ($p<0.01$) (Tablo 1).

Discussion

Cancer cells demonstrate alterations in oxidative metab-

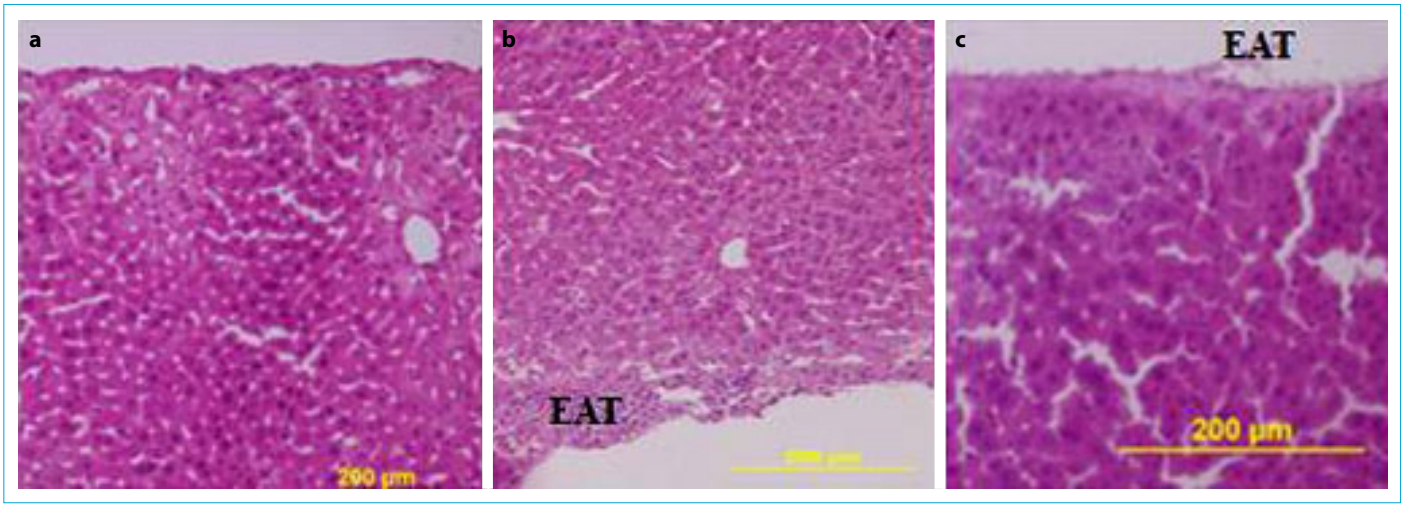

Figure 3. Histopathological findings of liver tissue (H&E, 20X) **(a)** Healty control group **(b)** Tumor control group **(c)** Paclitaxel group .

Table 1. Effects of paclitaxel on tissue malondialdehyde level and antioxidant enzymes in mice bearing ehrlich solid tumor

Organs	n	Healthy Control	n	Cancer Control	n	10 mg Paclitaxel	p
MDA							
Kidney	6	0.87^{ac} (0.83-0.89)	7	0.94^{bc} (0.91-0.96)	7	0.60^{a} (0.42-0.62)	0.000
Liver	7	12.02^{ac} (11.69-12.47)	7	15.93^{bc} (14.54-16.77)	7	10.90^{a} (9.89-11.40)	0.000
Testis	6	0.79 (0.69-0.93)	6	0.97 (0.89-24.24)	6	0.94 (0.69-21.24)	0.146
Brain	9	8.20^{a} (7.80-8.42)	9	6.23^{b} (5.85-6.45)	7	8.20^{a} (7.90-9.10)	0.000
Catalase							
Kidney	7	29.26±2.53^{a}	6	23.97±2.92^{b}	7	22.07±2.13^{b}	0.000
Liver	7	47.96±3.10^{a}	8	41.76±5.96^{b}	7	33.89±1.93^{c}	0.000
Testis	6	12.95±0.64^{b}	6	15.97±0.39^{a}	6	12.17±0.91^{b}	0.000
Brain	6	25.53±1.32^{b}	5	32.64±1.65^{a}	7	26.64±1.32^{b}	0.000
SOD							
Kidney	6	5.45^{b} (5.38-5.68)	7	3.70^{a} (3.50-3.90)	7	3.60^{a} (2.90-4.2)	0.002
Liver	7	6.50^{b} (6.40-6.90)	7	4.50^{a} (4.30-4.50)	7	4.70^{a} (3.50-4.90)	0.001
Testis	6	2.45^{ab} (2.40-2.95)	6	2.75^{b} (2.70-3.33)	10	2.40^{a} (2.10-2.63)	0.020
Brain	6	4.10^{ac} (3.71-4.53)	6	4.40^{bc} (3.98-4.83)	10	3.25^{a} (2.86-3.63)	0.006

olism characterized by the increased production of ROS compared to normal cells[23] and it is speculated that tumorigenic signaling increases expression of antioxidant proteins to balance the high ROS production to maintain redox homeostasis.[16, 17] It was reported that oxidative stress, chronic inflammation and cancer are closely related.[28] Ehrlich ascites carcinoma, a spontaneous murine mammary adenocarcinoma, is adapted to ascites formed by serial intraperitoneal passages.[6] Ehrlich ascites tumor cells rapidly proliferate in almost all mouse species because of the lack of H-2 histocompatibility antigens.[4] Ehrlich ascites tumor cells cause morphological and metabolic changes including alterations in oxidant and antioxidant status in the animals.[5] Previous studies have shown that the oxidative stress, especially the lipid peroxidation, increases in cancer cases.[14, 15, 18, 20, 21, 29] Therefore, in the present study, Ehrlich solid tumor model was preferred in order to investigate the effect of paclitaxel on lipid peroxidation and antioxidant status in the tissues of solid tumor-bearing mice.

Taxol has been used effectively in the treatment of various cancers including ovarian and breast cancer, lung cancer, melanoma, head and neck cancer, bladder cancer and other cancer types.[7–9]

Oxidative stress is defined as an imbalance between ROS and the anti-oxidant capacity of the cell.[13] Patmavathi et al.[7] have shown the increases in the level of lipid peroxidation in the breast and liver of breast cancer bearing rats. Didziapetriene et al.[15] detected elevated MDA level in ovarian cancer. In the present study, the MDA levels in the kidney and liver were increased by the tumor development in the EAT-cell-injected mice. The elevated kidney and liver MDA levels were reversed with Paclitaxel treatment and the result was lower than that of the healthy control group. However, Paclitaxel had no significant effect on testis MDA level. On the other hand, brain MDA level was lower than that of the healthy control group mice but it returned to the level of controls after paclitaxel treatment.

In cancer-bearing animals, significant decreases were reported in the SOD and CAT activities inthe breast and liver of breast cancer bearing rats.[7] Didziapetriene et al.[15] reported lower CAT activity in ovarian cancer patients. Similarly, in the present study, kidney and liver SOD and CAT activities were decreased by the cancer development but in contrast to the findings of Patmavathi et al.,[7] paclitaxel had no effect on the activities of these antioxidants. In testis and brain, the activities of SOD and CAT were higher in cancer group than both control and paclitaxel treated cancer-bearing animals. Catalase is a tetrameric protein that consists of four similar subunits containing heme group. It is excessively expressed in some tissues to protect cells against excess ROS formation. It has an oxidase activity as well as it is involved in ROS generation.[10, 30] Thus, higher CAT levels in cancer group may be attributed to the modification of CAT levels in cancer cells resistant to some chemotherapeutics or hydrogen peroxide.[30]

In the study of Salem et al.[31] EAT cells were inoculated into CD-1 mice subcutaneously to form solid tumor and then treated with intraperitoneal injection with venom (0.22 mg/kg) every other day. A. amoreuxi venom treatment decreased MDA level while increased GSH in liver kidney and serum. In our study Paclitaxel decreases the lipid peroxidation in kidney and liver. In addition, histopathological evaluations of liver and kidney tissues also support these results. In the study of Cosan et al.,[24] Paclitaxel treatment returned the altered MDA level and SOD and CAT activities to control levels and paclitaxel restored the damaged kidney and liver structure. Campos et al.[22] determined decreases in catalase activity and metahemoglobin levels after paclitaxel infusion in rats. Panis et al.[19] detected high oxidative stress status characterized by elevated lipid peroxidation and reduced CAT activity in advanced breast cancer and these authors found that paclitaxel enhanced lipid peroxidation due to systemic oxidative stress and red blood cell oxidative injury with anemia development.

Conclusion

The results of this study have shown that Paclitaxel alleviates the lipid peroxidation in kidney and liver but has no effects on antioxidant status in these tissues whereas it significantly reduced the increased SOD activities in testis and brain of Ehrlich solid tumor-bearing mice.

Disclosures

Ethics Committee Approval: The study was held at DEKAM with the permission of Erciyes University Experimental Animals Local Ethics Committee, Approval No. 15/03 and dated 14.01.2015.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Authorship Contributions: Concept – M.N., E.K., S.Ö.; Design – M.N., E.K., S.Ö.; Supervision – M.N., E.K., S.Ö.; Materials – E.K., M.N., D.C.; Data collection &/or processing – E.K., M.N., T.E.; Analysis and/or interpretation – M.N., E.K., S.Ö.; Literature search – M.N., E.K., S.Ö.; Writing – M.N., E.K., S.Ö., N.İ., D.C., T.E.; Critical review – M.N., E.K., S.Ö., N.İ., D.C., T.E.

References

1. T.C. Sağlık Bakanlığı (2015) Turkiye Kanser Kontrol Programı. T.C. Sağlık Bakanlığı Yayın No: 1. Ankara. http://kanser.gov.tr/Dosya/NCCP_2013-2018.pdf. Accessed 30 May 2017.
2. T.C. Sağlık Bakanlığı, TürkiyeHalk Sağlığı Kurumu (2016) Türkiye kanser istatistikleri,Ankara. http://kanser.gov.tr/Dosya/

ca_istatistik/ANA_rapor_2013v01_2.pdf. Accessed May 30 2017.; Cancer J Clin 2017; 67:7-30.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2017;67:7–30. [CrossRef]
4. Kumar RS, Rajkapoor B, Perumal P, Dhanasekaran T, Jose MA, Jothimanivannan C. Antitumor activity of ProsopisglandulosaTorr on Ehrlich ascites carcinoma (EAC) tumor bearing mice. Iranian J Pharmaceut Res 2011;10:505–10.
5. Kabel AM. Effects of combination between methotrexate and histone deacetylase inhibitors on transplantable tumor model. Am J Med Stud 2014;2:12–8.
6. Jaganathan SK, Mondhe D, Wani ZA, Pal HC, Mandal M. Effect of honey and eugenol on Ehrlich ascites and solid carcinoma. J Biomed Biotechnol Accessed 22 August 2017.
7. Padmavathi R, Senthilnathan P, Chodon D, Sakthisekaran D. Therapeutic effect of paclitaxel and propolis on lipid peroxidation and antioxidant system in 7,12 dimethyl benz(a)anthracene-induced breast cancer in female Sprague Dawley rats. Life Sciences 2006;78:2820–5. [CrossRef]
8. Vennila R, Thirunavukkarasu S V, Muthumary J. In-vivo studies on anticancer activity of taxol isolated from an endophytic Fungus pestalotiopsispaucisetasacc. VM1.Asian Journal of Pharmaceutical and Clinical Research 2012;4:30–4.
9. Wei Y, Ma L, Zhang L, XuX. Noncovalent interaction-assisted drug delivery system with highly efficient uptake and release of paclitaxel for anticancer therapy. Int J Nanomedicine 2017;12:7039–51. [CrossRef]
10. Wang YF, Chen CYu, Chung YSF, Chiou H, Ren LoH. Involvement of oxidative stress and caspase activation in paclitaxel-induced apoptosis of primary effusion lymphoma cells. Cancer Chemother Pharmacol 2004;54:322–30. [CrossRef]
11. Zang X, Wang G, Cai Q, Zheng X, Zhang J, et al. A Promising Microtubule Inhibitor Deoxypodophyllotoxin Exhibits Better Efficacy to Multidrug-Resistant Breast Cancer than Paclitaxel via Avoiding Efflux Transport. Drug Metab Dispos 2018;46:542–51.
12. Mohamed M. Abdel-Daim, Khaled Abo-EL-Sooud , Lotfi Aleya, Simona G. Bungu, Agnieszka Najda, and Rohit Saluja. Alleviation of Drugs and Chemicals Toxicity: Biomedical Value of Antioxidants Hindawi Oxidative Medicine and Cellular Longevity 2018;2.
13. Loft S, Poulsen HE. Cancer risk and oxidative DNA damage in man. J Mol Med 1996;74:297–312. [CrossRef]
14. Abdel-Salam O M E, Youness ER, Hafez H F. The antioxidant status of the plasma in patients with breast cancer undergoing chemotherapy. Open Journal of Molecular and Integrative Physiology 2011;29–35. [CrossRef]
15. Didžiapetrienė J, Bublevič J, Smailytė G, Kazbarienė B, Stukas R. Significance of blood serum catalase activity and malondialdehyde level for survival prognosis of ovarian cancer patients. Medicina 2014;50:204–8. [CrossRef]
16. Sullivan LB, Chandel NS. Mitochondrial reactive oxygen species and cancer. Cancer Metabolism 2014;2:1–17. [CrossRef]
17. Glasauer A, Chandel NS. Targeting antioxidants for cancer therapy. Biochem Pharmacol 2014;92:90–101. [CrossRef]
18. Bakan E, Tays S, Polat MF, Dalga S, Umudum Z, Bakan N, et al. Nitric oxide levels and lipid peroxidation in plasma of patients with gastric cancer. JPn J Clin Oncol 2002;162–6. [CrossRef]
19. Panis C, Herrera AC SA, VictorinoV J, Campos FC, Freitas LF, De RossiT, et al. Oxidative stress and hematological profiles of advanced breast cancer patients subjected to paclitaxel or doxorubicin chemotherapy. Breast Cancer Res Treat 2012;133: 89–97.
20. El-DeebM M K, El-SheredyH G, MohammedA F. The Role of Serum Trace Elements and Oxidative Stress in Egyptian Breast Cancer Patients. Advances in Breast Cancer Research 2016;5:37–47.
21. Radenkovic S, Milosevic Z, Konjevic G, Karadzic K, Rovcanin B, Buta M, et al. Lactate dehydrogenase, Catalase, and Superoxide dismutase in tumor tissue of breast cancer patients in respect to mammographic findings. Cell Biochem Biophys 2013;66:287–95. [CrossRef]
22. Campos FC, Victorino VJ, Martins-Pinge MC, Cecchini AL, Panis C, Cecchini R. Systemic toxicity induced by paclitaxel in vivo is associated with the solvent cremophor EL through oxidative stress-driven mechanisms. Food ChemToxicol 2014;68:78–86.
23. Hadzic T, Aykin-Burns N, Zhu Y, Coleman MC, Leick K, Jacobson GM, et al. Paclitaxel combined with inhibitors of glucose and hydroperoxide metabolism enhances breast cancer cell killing via H 2-mediated oxidative stress. FreeRadic Biol Med 2010;15:48:1024–33. [CrossRef]
24. Cosan D, Basaran A, Degirmenci I, Gunes HV, Aral E. The effect of paclitaxel on rats following benzo(a)pyrene treatment. Saudi Med J 2008;29:657–61.
25. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem 1979;95:351–8. [CrossRef]
26. Sun Y, Oberley LW, Elwell JH, Sierra-Rivera E. Antioxidant enzyme activities in normal and transformed mouse liver cells. Int J Cancer 1989;44:1028–33. [CrossRef]
27. Aebi H. Catalase. In: Burgmeyer HU, editor. Methods of Enzymatic Analysis. New York: Academic Press Publisher 1983;273.
28. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How they are linked? Free Radic Boil Med 2010;49:1603–16. [CrossRef]
29. Kasapović J, Pejić S, Todorović A, Stojiljković v, Pajović SB. Antioxidant status and lipid peroxidation in the blood of breast cancer patients of different ages. Cell Biochem Funct 2008;26:723–30. [CrossRef]
30. Glorieux C, Dejeans N, Sid B, Beck R, Calderon P B, Verrax J. Catalase overexpression in mammary cancer cells leads to a less aggressive phenotype and an altered response to chemotherapy. Biochemical Pharmacology 2011;82:1384–90. [CrossRef]
31. Salem ML, Shoukry NM, Teleb WK, Abdel-Daim MM and Abdel-Rahman MA. In vitro and in vivo antitumor effects of the Egyptian scorpion Androctonus amoreuxi venom in an Ehrlich ascites tumor model. Springer Plus 2016;5:570. [CrossRef]