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Research Article

Investigation of the Effects of Lycopene Against Cisplatin-Induced Renal Damage in Rats: A Histopathological Study

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Abstract

Aim: This study aimed to investigate the protective effect of lycopene (LP) on kidney damage induced by cisplatin (CPT), which is used as a potent agent in chemotherapy, in rats.

Material and Method: A total of 35 female Wistar albino rats between 220-250 grams which were 2-4 months old were included in the study. The rats were divided into 5 equal groups as control (Cont) group, CPT group, CPT+LP group, LP group and Dimethyl sulfoxide (DMSO) (solvent) group. Cont group did not receive any treatment during the 7-day long experiment. Rats in the CPT group were administered a single dose of 7 mg/kg CPT intraperitoneally on the first day of the experiment. CPT+LP group was administered 5 mg/kg of LP dissolved in DMSO intraperitoneally every day for 7 days after CPT was administered at the mentioned dose and duration. LP and DMSO groups were intraperitoneally administered 5 mg/kg of LP dissolved in DMSO and 1 ml/kg 0.1% DMSO, respectively during the experiment. At the end of the experiment, kidney tissues taken from the rats were evaluated histopathologically.

Results: When the histopathological analyses were evaluated, it was found that glomerular shrinkage, tubular vacuolisation, desquamous epithelium and interstitial hemorrhage were statistically more intense in the CPT group when compared with the Cont, DMSO and LP groups. In the CPT+LP group, cellular organization in the renal tissue was found to be close to normal when compared with the CPT group and it was found that apart from other parameters, especially glomerular atrophy was minimised by LP ($p<0.01$).

Conclusion: In conclusion, it was shown that LP administration alleviated nephrotoxicity, which is one of the primary adverse effects of CPT in rats.

Keywords: Cisplatin, lycopene, nephrotoxicity, histopathology, rat

INTRODUCTION

As a chemotherapeutic agent in cancer treatment, cisplatin (CPT) is often administered intravenously as first-line chemotherapy for tumours of testis, breast, ovary, bladder, lung and various malignancies. In this context, after being absorbed by the cancer cell, CPT may show cytotoxic effect leading to inhibition of Deoxyribo Nucleic Acid (DNA) synthesis by interacting with cellular macromolecules (1). Although CPT is one of the widely used and potent chemotherapeutic drugs, its use may cause side effects such as nephrotoxicity in normal tissues and organs, especially in kidneys (2). This is the most important side effect limiting CPT use. Studies have shown that the pathogenesis of CPT induced renal damage is caused by decreased activity of antioxidant enzymes and increased reactive oxygen species in renal tissue (3,4). When the nephrotoxic effect of CPT was analysed molecularly and cellularly, it was found that it resulted in the damage and death of renal tubular cells (2). Renal proximal tubules, especially epithelial tubular cells of the S-3 segment, are the main sites where the toxic effects of CPT are seen (5). In addition, the inflammatory response caused by CPT damages the plexus in the kidney and causes ischemic damage, resulting in decreased glomerular filtration (2).

Lycopene (LP) is a carotenoid pigment found in red and orange fruit and vegetables (6). It has a high-capacity antioxidant effect due to its hydrophobic structure and the conjugated double bond it contains. While LP shows

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a strong antioxidant property in in vitro environments, in in vivo environments it has multi-targeted activities such as inducing apoptosis, decreasing DNA damage, preventing oxidative stress and decreasing metastasis (7,8). A large number of diseases are characterized by oxidative stress and chronic inflammation. In this context, studies are frequently planned with antioxidants to alleviate the side effects of CPT. LP can be used as a molecule that has synergic effects on cancer cells and that minimizes the undesirable effects mediated by CPT. LP, which is an important agent in oxidative damage and tissue healing due to its strong antioxidant activity, has been reported to reduce renal damage in a large number of renal damage models, to have dose-dependent beneficial effects and to maintain metabolic homeostasis in the kidney (9-11).

In the light of all this information, CPT is still used as an effective chemotherapeutic agent in various cancer types despite the nephrotoxicity it causes. In this context, the aim of the present study is to investigate the efficacy of LP, which was shown to have anti-apoptotic and antioxidant effects in previous studies, against CPT-induced kidney damage at histopathological level in the light of available information in the literature.

MATERIAL AND METHOD

Experimental Design

Experimental procedures of the study were carried out at Bolu Abant İzzet Baysal University Experimental Animals Application and Research Centre after obtaining the 02.08.2023 dated and 2023/22 numbered decision from Bolu Abant İzzet Baysal University Animal Research Local Ethics Committee. In this context, 35 female Wistar albino rats, each weighing 220-250 gram and 2-4 months old, obtained from the relevant centre were used in the study. The animals were kept at the centre in an environment with a constant temperature (24±2°C) and humidity (55±15%) in a 12-hour light-dark cycle. The rats were allowed access to ad libitum standard rat feed and water during the experiment. A power analysis test was conducted using Minitab software version 16 to determine the requisite number of animals in all groups. In this context, the subjects were randomly allocated to 5 groups, with 7 rats in each group:

Control (Cont) group: This group was not administered any treatment.

CPT group: Single dose 7 mg/kg CPT (12) was administered intraperitoneally on the first day of the experiment

CPT+LP group: Single dose 7 mg/kg CPT was administered intraperitoneally on the first day of the experiment. Following this, 5 mg/kg of LP (13). dissolved in dimethyl sulfoxide (DMSO) was administered intraperitoneally every day for 7 days.

LP group: 5 mg/kg of LP dissolved in DMSO was administered intraperitoneally every day for 7 days.

DMSO (Solvent) group: 1 ml/kg 0.1% DMSO was administered intraperitoneally during the 7-day long experiment.

Tissue Sampling

At the end of the 7-day long experiment, the kidney tissue was removed under 90 mg/kg ketamine (Ketalar®, Pfizer, İstanbul) and 10 mg/kg xylazine (Citanest®, AstraZeneca, İstanbul) anaesthesia and the animals were sacrificed. Kidney tissues taken for histopathological analyses were fixed in 10% buffered neutral formalin for two weeks.

Preparation of Tissue Samples and Histopathologic Analysis

Following the completion of two weeks fixation period, the kidney tissues were labelled appropriately and kept overnight in running water and formalin was removed from the tissue. The tissues kept in running water were dehydrated first through alcohol series (70%, 80%, 96%, 96%, 100%, 100%). Afterwards, the tissues made transparent with xylene were infiltrated with paraplast. The tissues taken from the hot paraffin were embedded in L-iron filled with paraffin and labelled. Thus, the tissue tracking process was completed. Using a rotary microtome (Leica RM2125RT) with 1/50 sampling in compliance with the systematic random sampling criteria, 3 µm thick sections were extracted from the paraffin embedded sections for light microscopic examinations. Sections from each group were later stored in an oven set to 58°C for the entire night in order to remove the paraplast for staining. Next, the sections were stained with Haematoxylin-Eosin for histological examination. Kidney tissues were evaluated histopathologically in terms of glomerular shrinkage, tubular vacuolization, desquamated epithelium and interstitial haemorrhage by using Nikon Eclipse 80i light photomicroscope with camera attachment. In this context, 10 different areas were examined in each section at X20 magnification and scored semi quantitatively from 0 to 3. According to this scoring, absence of pathology was scored as 0, the presence of mild pathology was scored as 1, the presence of moderate pathology was scored as 2 and the presence of severe pathology was scored as 3 (14). Quantitative results were obtained by making comparisons among groups. The same histologist assessed each parameter by randomly picking tissue samples from each group and without knowing which tissue sample belonged to which group (blind evaluation).

Statistical Analysis

Statistical analyses were performed with SPSS version 21.0 analysis program. Shapiro-Wilk test was used to evaluate whether the data of the subjects conformed to the assumption of normal distribution, and in the comparison of continuous variables, the data conforming to normal distribution were evaluated with One-Way ANOVA and Post-hoc Bonferroni tests. $P<0.05$ indicated statistically significant difference.

RESULTS

When the kidney sections stained with Hematoxylin-Eosin were examined histopathologically in terms of glomerular shrinkage, tubular vacuolization, interstitial hemorrhage and desquamous epithelium, it was observed that the interstitial tissue density surrounding the renal glomeruli, tubules and veins in Cont, DMSO and LP groups had normal morphology. In the CPT group, shrunken glomeruli were observed in places in the cortical labyrinth of the related tissue. Bowman's interval of the renal corpuscles whose glomeruli were degenerated in this way was wider compared to the Cont group. In addition, tubular dilatation and interstitial hemorrhage were found to be intense in this group. In the CPT+LP group, renal bodies had more normal morphology, tubule cell damage was lower, and tubule epithelial cell loss was significantly improved when compared with the CPT group (Figure 1). In this context, when the groups were evaluated semi-quantitatively, no statistical difference was found between the Cont, DMSO and LP groups ($p>0.05$). When a statistical difference of $p<0.01$ was found between Cont and CPT groups in terms of glomerular shrinkage, tubular vacuolization and desquamous epithelium, this difference was found to be at $p<0.05$ in the evaluation of interstitial haemorrhage. When CPT and CPT+LP groups were compared statistically, difference was found between groups in terms of tubular vacuolization, desquamous epithelium and interstitial hemorrhage ($p<0.05$). This difference was at $p<0.01$ in the parameter in which glomerular shrinkage was examined (Figure 2-5).

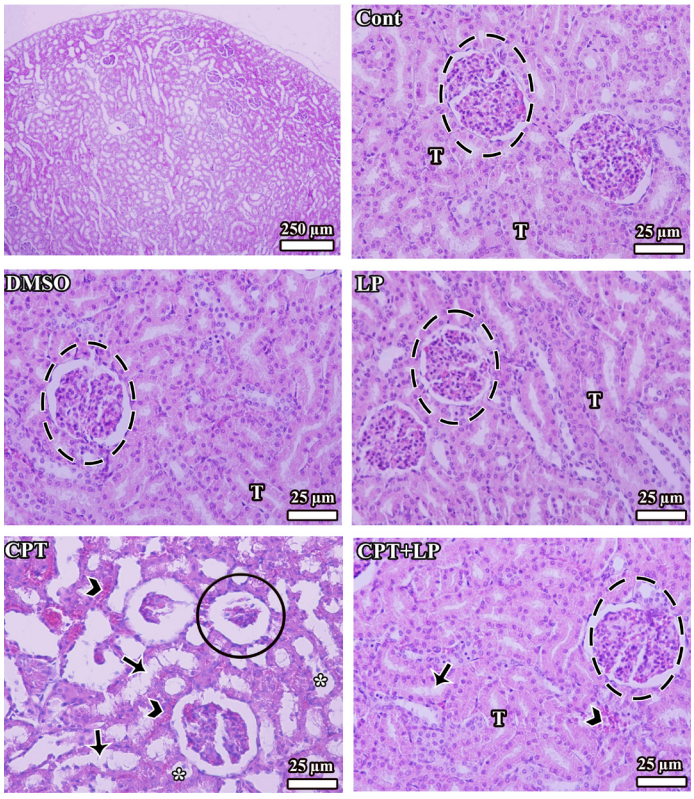

Figure 1. Light microscopic images obtained from the kidney of rats in all groups. The first image points out the panoramic view of the kidney (x5). **Arrow:** tubular vacuolation; **Arrowhead:** interstitial haemorrhage; **Star:** desquamous epithelium; **Circle:** glomerular shrinkage; **T:** healthy tubule; **Dashed circle:** healthy glomerulus;. Hematoxylin-Eosin staining. X20

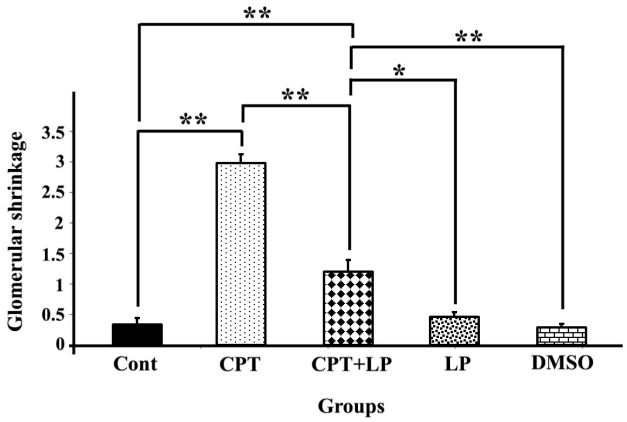

Figure 2. Semi-quantitative evaluation of glomerular shrinkage parameter in all groups. Differences at the level of $p<0.05$ were shown with "*" while differences at the level of $p<0.01$were pointed out by "**"

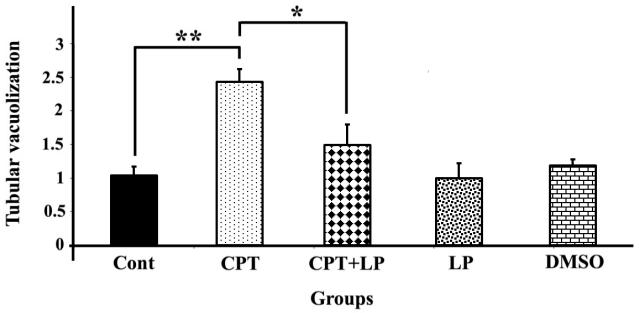

Figure 3. Semi-quantitative evaluation of tubular vacuolization parameter in all groups. Differences at the level of $p<0.05$ were shown with "*" while differences at the level of $p<0.01$were indicated by "**"

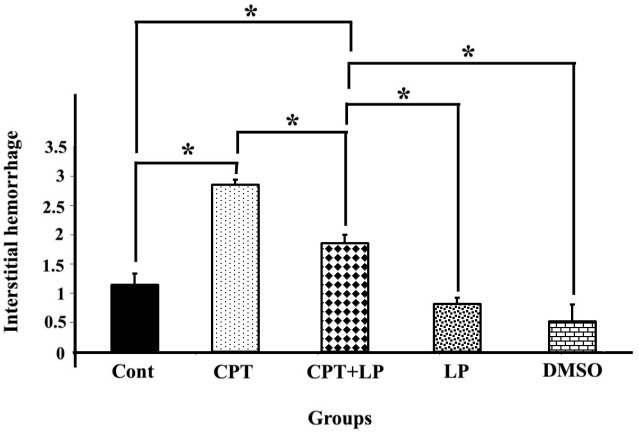

Figure 4. Semi-quantitative evaluation of interstitial hemorrhage parameter in all groups. Differences at the level of $p<0.05$ were shown with "*"

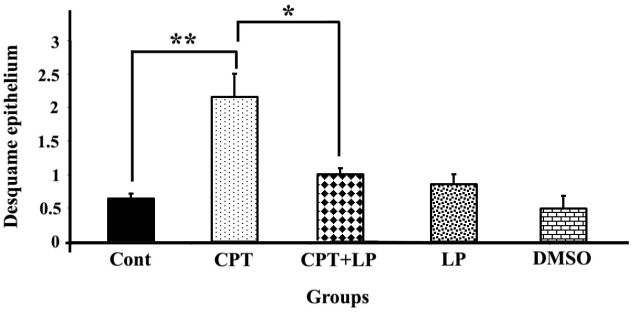

Figure 5. Semi-quantitative evaluation of desquame epithelium parameter in all groups. Differences at the level of $p<0.05$ were shown with "*" while differences at the level of $p<0.01$were displayed by "**"

DISCUSSION

Most of the chemotherapeutic drugs used in cancer treatment work by generating free radicals and reactive oxygen species (15). In this context, CPT is a chemotherapeutic agent used effectively in various cancer treatments that induce cell death by binding to DNA. This agent can show its antitumor mechanism in many ways, the most important of which is creating DNA damage. It may also cause cellular damage through stress on endoplasmic reticulum and mitochondria and activation of apoptotic pathway. According to the data obtained from the studies conducted, exposure to CPT has been shown to cause nephrotoxicity by causing damage to the proximal tubule S3 segment in the kidneys of mice, rats and humans (16). The result reported in a large number of studies that oxidative stress may cause nephrotoxicity was also found in our study as mediated by CPT. In clinical use, CPT nephrotoxicity is characterized by elevated serum creatinine, decreased serum potassium and magnesium levels, and low glomerular filtration rate days after treatment with CPT. There are also studies which show that it reduces renal filtration permanently in the long term (2). While nephrotoxicity was observed in 42% of the patients, it was found that CPT treatment was not completed in 7% due to renal toxicity (17). This is one of the primary problems leading to dose limitation in the use of CPT. CPT exposure causes the production of reactive oxygen species including hydroxyl radicals, oxidation of protein, lipid and nucleic acids and eventually damage to tubule epithelium cell membrane (18). In this case, inflammation may cause high nephrotoxicity potential through reactive oxygen species (ROS)-mediated endoplasmic reticulum (ER) stress and autophagy (19). Atrophic glomerular structure was observed in CPT-treated rats in histological examination of the kidney tissue in our study. We believe that the reason for this damage may be the ischemic effect caused by inflammation.

LP, which is a carotenoid, has many biological activities. These are stopping the growth of cancer cells by regulation of cell cycle proteins, regulating the immune function, and preventing oxidative DNA damage (15). LP is known to contribute to cell survival against oxidative damage by strengthening the antioxidant system like many antioxidant substances (20). In our study, it was found that 5 mg/kg LP reduced the CPT-mediated nephrotoxicity in the renal tubular cells. Open polyene chain in the structure of LP plays an effective role in neutralizing superoxide anions and free radicals. In this context, we think that in our study LP reversed the histopathological deterioration in the CPT+LP group by reducing oxidative stress and inflammation. Previous studies have reported that LP minimized cell swelling and organelle deformation and prevented cytoplasmic division and atrophy in renal cells (21). In our study, it was found that when compared with the CPT group, atrophy of glomeruli and deterioration in tubular structure decreased in the CPT+LP group. A study by Salari et al. showed that in lipopolysaccharide-induced renal injury, LP treatment improved NF-kB gene expression, TNFα, IL6, TLR4 levels. In other words, LP showed anti-inflammatory effect by attenuating TLR4 and NF-kB mediated inflammation and reduced nephrotoxicity by contributing to the repair of intracellular antioxidant mechanism through regulation of Nrf2 and HO-1 (20). In the present study, which evaluated whether the CPT-induced nephrotoxicity in rats can be prevented by using LP, our results showed that LP showed protective effects on tubular vacuolization, interstitial hemorrhage, glomerular atrophy, and epithelial changes that occur due to CPT. In a study conducted by Deng et al., it was shown that CPT caused acute kidney injury in many different ways such as CHOP-mediated endoplasmic reticulum stress, renal tubular damage by triggering inflammation and oxidative stress with ROS and TNF-a and IL6 mediated cytokines, direct apoptosis by caspase-3 and caspase-9 activation and mitochondrial dysfunction (16). In the light of literature, we believe that a large number of mechanisms such as endoplasmic reticulum stress are involved in the observed damage and LP provides protection by reducing reticulum stress. In this context, there is a need for molecular studies to elucidate the mechanism underlying the protective effect.

In a study conducted by Li et al., it was reported that the kidneys shrunk in the renal damage induced by using di (2-ethylhexyl) phthalate (DEHP) and that the kidney size returned to normal after using LP. In addition, histological examinations showed that the degradation of the brush edges, dilatation and damage in the tubular structure decreased after treatment (21). A study conducted by Doğukan et al. reported that LP treatment reduced lipid peroxidation against the nephrotoxic effect caused by CPT administered to mice (22). In addition, a study conducted by Pektaş et al. examined renal markers through blood samples in ischemia-reperfusion-induced renal damage, and it was shown that pathological biomarkers including malondialdehyde (MDA), glutathione and catalase were higher in the control group when compared with the LP administered group (23). In a study conducted by Saylan et al., it was shown that LP decreased tubular dilatation, tubular epithelial degeneration, glomerular shrinkage and desquamous epithelium amount significantly in ischemia-reperfusion induced renal damage (14). Another study conducted by Gori et al. showed that LP treatment minimised renal inflammatory changes due to adenine histopathologically, physiologically and biochemically (24). In this context, it was shown in our study that LP treatment reversed the histopathological deterioration of CPT-induced renal damage. In other words, it was found that LP protected renal tissue significantly against complications caused by CPT. In the light of these researches, by adding our results, we believe that LP has a protective effect in the nephrotoxic effect of CPT and with the increase in clinical research, CPT can be added in the diets of patients who receive chemotherapy and used as a protective factor.

CONCLUSION

Based on the histopathological examinations of the present study, it was found that LP use minimised the degree of damage in the rats which were administered CPT injection. It was shown that LP, which is a string antioxidant, prevented the nephrotoxicity caused by CPT by alleviating the destructive effects of oxidative stress in renal tissue, especially in tubule and glomerular structures. In this context, there is a need for further clinical research, especially at the molecular level, for the use of LP as an agent that reduces the side effects of LP in chemotherapy regimens. This way, it is certain that more comprehensive information using different animals, different laboratories, different periods of time and different methods will help to further improve clinical studies in the field.

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Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *Ethical approval was taken from the local Ethics Committee of Bolu Abant İzzet Baysal University with the decision number 2023/22 dated 02.08.2023.*

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