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The Effects of *Prunus Laurocerasus* Fruit Extract on Oxidative and Endoplasmic Reticulum Stress Responses in Doxorubicin-induced Cardiac Damage

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ABSTRACT

Objective: In this study, the effects of *Prunus laurocerasus* fruit extract (PLE), which is known for its high levels of phenolic compounds and antioxidant efficiency, on doxorubicin (DXR)-induced cardiotoxicity were examined.

Methods: Male Sprague-Dawley rats were randomly assigned to the Control, DXR, PLE_{500}+DXR, and PLE_{1000}+DXR groups (n=6). PLE was orally administered to the animals in the PLE_{500}+DXR (500 mg/kg) and PLE_{1000}+DXR (1000 mg/kg) groups for 2 weeks. DXR was injected (15 mg/kg, intraperitoneally) 2 days before sacrification in the DXR, PLE_{500}+DXR, and PLE_{1000}+DXR groups. At the end of the study period, serum troponin I levels, myocardial superoxide dismutase (SOD) and catalase (CAT) activities, malondialdehyde (MDA), glutathione (GSH), glucose-regulated protein (GRP)78, and pro-caspase 12 levels were measured.

Results: In the DXR group, serum troponin I concentration significantly increased ($p<0.001$), however PLE treatment significantly reduced this DXR-induced increment ($p<0.001$ and $p<0.05$ in the PLE_{500}+DXR and PLE_{1000}+DXR groups, respectively). DXR-induced increase in myocardial MDA ($p<0.001$) significantly reduced in the PLE_{500}+DXR ($p<0.001$) and PLE_{1000}+DXR ($p<0.001$) groups. However, DXR-induced changes, such as GSH depletion ($p<0.001$), reduced CAT ($p<0.001$) and SOD ($p<0.001$) activities, increased GRP78 ($p<0.01$) and decreased pro-caspase 12 ($p<0.001$) levels, were not significantly affected by PLE treatment.

Conclusion: The present results indicate that pretreatment with PLE reduced, but not completely prevented, cardiac damage induced by DXR. While a reduction in oxidative stress appears to play a role in the partial protective effect of PLE treatment, endoplasmic reticulum stress appears to have no role. Further research is necessary to understand the mechanisms of action underlying PLE treatment.

Keywords: MDA, GSH, CAT, SOD, GRP78, pro-caspase 12, troponin

INTRODUCTION

Doxorubicin (DXR) belongs to the anthracycline group of chemotherapy drugs and is widely used for treating various cancer types, including sarcoma, lymphoma, and breast cancer. Nonetheless, its substantial efficacy is frequently overshadowed by cardiotoxic side effects, which often constrain the clinical application of DXR (1-3). Different molecular mechanisms have been suggested to underlie the development of DXR-induced cardiotoxicity, including topoisomerase II inhibition, oxidative stress, mitochondrial dysfunction, disturbances in calcium balance, and cell death (4). Among these, oxidative stress is a notable mechanism of DXR-induced cardiotoxicity. DXR increases the generation of reactive oxygen species (ROS) and weakens enzymatic and non-enzymatic antioxidant defense systems (5). Contemporary studies have demonstrated the involvement of endoplasmic reticulum (ER) stress in DXR-induced cardiotoxicity (6). ER stress is a condition arising from disruptions in ER functions due to various stressors, including adenosine triphosphate deficiency, oxidative stress, drugs, or toxins, and if it persists for a prolonged period, it can lead to cell death (7). In DXR-induced cardiotoxicity, the upregulation of ER stress proteins, including glucose-regulated protein (GRP)78, as well as caspase-12 activation have been reported previously (8,9).

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To reduce the cardiotoxic effects of DXR, various strategies have been discussed, including combination therapies with different bioactive compounds (10). Phenolic compounds, including rutin, caffeic acid, chlorogenic acid, vanillic acid, quercetin, naringenin, and resvarotrol, have been reported to exhibit protective effects by mitigating damage mechanisms, including oxidative stress, ER stress, or apoptosis, in DXR-induced cardiotoxicity (10-16). *Prunus laurocerasus* (*P. laurocerasus*) (synonym *Laurocerasus officinalis*), a perennial plant rich in bioactive compounds, is primarily found on the Black Sea coast of Türkiye and throughout southeastern Europe and southwestern Asia (17,18). In experimental studies using *P. laurocerasus* fruit, leaf, or seed, the protective effects of extracts have been reported in conditions such as kidney and liver damage induced by paracetamol, gastric damage stimulated by indomethacin, and diabetes (17,19-23). In most cases, treatment with the extract resulted in a reduction of oxidative stress, leading to alleviation of tissue damage. Although it has the potential to be protective against DXR-induced cardiotoxicity because of its bioactive components, the possible protective effect of *P. laurocerasus* against the systemic side effects of DXR has not been investigated until now. The objective of this research was to evaluate the impact of *P. laurocerasus* fruit extract (PLE) on DXR-induced cardiotoxicity through two important mechanisms in its pathophysiology: oxidative stress and ER stress responses.

METHODS

Extraction of *P. laurocerasus* Fruits

Freshly collected *P. laurocerasus* fruits were first dried and then ground into a powder. The ground fruits were mixed with 80% ethanol (1:5), and the mixture was agitated for 2 days at room temperature in a shaking water bath. The mixture was filtered through the filter paper at the end of the second day, and the fruit extract was obtained by evaporating the solvent using an evaporator at 50 °C. The concentrated extracts were diluted with tap water and administered to the treatment groups as described below.

Animals and Their Grouping

In this study, 24 male Sprague-Dawley rats weighing between 280 and 320 g were used. The Ordu University Animal Experiments Local Ethics Committee approved all the experimental procedures (decision no: 12, date: 22.10.2020). The 24 rats were randomly separated into 4 groups, namely Control, DXR, PLE_{500}+DXR, and PLE_{1000}+DXR, with 6 rats in each group.

Control group (n=6): For 2 weeks, the animals received drinking water via intragastric gavage (ig).

DXR group (n=6): The rats were administered drinking water (ig) for 2 weeks, and DXR (15 mg/kg, single dose) was injected intraperitoneally (IP) 2 days before the end of the experimental period (24).

PLE_{500}+DXR group (n=6): The animals received a daily administration of PLE (500 mg/kg, ig) for 2 weeks, and DXR (15 mg/kg, IP) was administered on the 13th day of the experimental period.

PLE_{1000}+DXR group (n=6): For a duration of 2 weeks, the rats orally received a daily administration of PLE (1000 mg/kg, ig), and DXR (15 mg/kg, IP) was injected on the 13th day of the study.

On the 15th day of the study, the rats were anesthetized with ketamine and xylazine (80 mg/kg: 10 mg/kg, IP). Blood samples were collected from the abdominal aorta and allowed to coagulate at ambient temperature. Subsequently, serum samples were obtained by centrifugation at 1000 g for 20 min. Heart tissue and serum samples were kept in a 80 °C deep freezer until these parameters were analyzed:

Serum troponin I: The level of cardiac troponin I in the serum samples was measured using a commercial enzyme-linked immunosorbent assay kit (Elabscience, E-EL-R1253, China). The analysis was performed in accordance with the guidelines provided by the manufacturer, and the outcomes were evaluated by comparing the optical density of the samples against the standard curve.

Malondialdehyde (MDA): Myocardial MDA levels were determined using Buege and Aust's (25) thiobarbituric acid reactive substance formation method. The pink color formed by the reaction of MDA with thiobarbituric acid was detected at 535 nm using a spectrophotometer (25).

Glutathione (GSH): GSH levels in cardiac homogenates were measured by the method of Aykaç et al. (26). The yellow color formed by the interaction of GSH and 5,5-dithio-bis (2-nitrobenzoic acid) was detected using a spectrophotometer at 412 nm.

Catalase (CAT) activity: CAT activity in cardiac tissue was assessed by measuring absorbance at 240 nm, reflecting the rate of hydrogen peroxide (H_2O_2) decomposition catalyzed by CAT per unit of time (27).

Superoxide dismutase (SOD) activity: SOD activity in cardiac tissue was measured by determining the red color created by superoxide radicals, which are formed using xanthine and xanthine oxidase by reducing nitroblue tetrazolium at 505 nm (28).

GRP78: GRP78 levels were measured using commercial ELISA kits (Bioassay Technology Laboratory BT-E1255Ra, China) in cardiac tissue homogenates. The assay protocol was performed in accordance with the manufacturer's guidelines. The results were computed using a standard curve and conveyed as ng/mg of protein.

Pro-caspase 12: Myocardial pro-caspase 12 concentrations were assayed using a commercial ELISA kit (Bioassay Technology Laboratory BT-E2111Ra, China) according to the manufacturer's instructions. The pro-caspase 12 concentration in tissue homogenates was determined by contrasting the optical density of the samples with the standard curve, and the findings were expressed in relation to the total protein content.

Statistical Analysis

The findings are presented as mean ± standard deviation. Normality and homogeneity of the data were assessed using the Kolmogorov-Smirnov and Levene's tests, respectively. Normally distributed and homogeneous data were then tested by One-Way analysis of variance, followed by the Tukey test as a post hoc analysis. Significance was assigned to values with $p<0.05$

RESULTS

Serum troponin I: The serum troponin I level was 806.75±52.72 pg/mL in the control group. This value was significantly higher in the DXR (1813.68±142.36 pg/mL, $p<0.001$), PLE_{500}+DXR (1554.34±174.63 pg/mL, $p<0.001$) and PLE_{1000}+DXR (1514.03±141.74 pg/mL, $p<0.001$) groups. Compared with the DXR group, PLE_{500}+DXR ($p<0.05$) and PLE_{1000}+DXR ($p<0.01$) groups had higher levels of troponin I. No statistical difference was observed between the two extract treatment groups (Figure 1).

Oxidative Stress Parameters

In the control group, the MDA level was measured as 188.28±45.85 nmol/g wet tissue (wt). Increased concentrations of MDA were observed in the DXR (527.67±64.68 nmol/g wt, $p<0.001$), PLE_{500}+DXR (343.245±47.99 nmol/g wt, $p<0.001$) and PLE_{1000}+DXR (368.71±72.26 nmol/g wt, $p<0.001$) groups. In the PLE_{500}+DXR and PLE_{1000}+DXR groups, MDA levels were significantly lower than those in the DXR group ($p<0.001$ and $p<0.001$, respectively) (Figure 2A).

GSH levels were significantly lower in the DXR (1.13±0.26 µmol/g wt, $p<0.001$), PLE_{500}+DXR (1.42±0.32 µmol/g wt, $p<0.001$) and PLE_{1000}+DXR (1.25±0.34 µmol/g wt, $p<0.001$) groups than in the control values (3.82±0.59 µmol/g wt). Treatment with two different doses of PLE did not significantly change cardiac GSH levels, and the results were not different from the DXR group or each other (Figure 2B).

Cardiac CAT activity was 3.7±0.36 µmol/H_2O_2/min/mg wt in the control group. The value significantly reduced to 1.412±0.41 µmol/H_2O_2/min/mg wt in the DXR group ($p<0.001$). CAT activities were significantly lower in the PLE_{500}+DXR (1.79±0.38 µmol/H_2O_2/min/mg wt) and PLE_{1000}+DXR (1.62±0.47 µmol/H_2O_2/min/mg wt) groups compared with the control ($p<0.001$ and $p<0.001$, respectively), and the values were not significantly different from the DXR group or each other (Figure 2C).

SOD activity was measured as 4.24±0.53 U/mg wt in the control group and was significantly reduced in the DXR (1.37±0.50 U/mg wt, $p<0.001$), PLE_{500}+DXR (1.64±0.57 U/mg wt, $p<0.001$) and PLE_{1000}+DXR (1.82±0.539 /mg wt, $p<0.001$) groups. Compared with the DXR group, no significant alterations were noted in the PLE_{500}+DXR and PLE_{1000}+DXR groups (Figure 2D).

ER Stress Parameters

The GRP78 level was 0.59±0.07 ng/mg prot in the control group and significantly increased to 0.79±0.08 ng/mg prot in the DXR group ($p<0.01$). Although the GRP78 levels were lower in the PLE_{500}+DXR (0.68±0.13 ng/mg prot) and PLE_{1000}+DXR (0.64±0.11 ng/mg prot) groups, the results were not significantly different from the control or DXR groups (Figure 3A).

The pro-caspase 12 level in the DXR-injected group (10.14±1.57 ng/mg prot) was found to be significantly lower ($p<0.01$), than that in the control group (16.32±3.43 ng/mg prot). In the PLE_{500}+DXR and PLE_{1000}+DXR groups, pro-caspase 12 levels did not significantly change (12.91±1.82 and 13.19±2.93 ng/mg prot, respectively) (Figure 3B).

DISCUSSION

Cancer remains a major global health challenge, with a growing number of individuals being diagnosed due to rising life expectancy and population growth. Therefore, research is ongoing to reduce the cardiotoxic side effects of DXR, a widely used anticancer drug. This study investigated the effectiveness of PLE in reducing the cardiotoxic side effects of DXR.

Myocardial damage induced by DXR can be monitored using various circulating biomarkers, including cardiac troponins. The cardiac-specific troponin proteins (troponin I, troponin T) are located in the myocardium, enabling their use as specific biomarkers to identify alterations in cardiac muscle. Because troponin I is accepted as a sensitive and specific indicator of DXR-induced myocardial injury, its serum concentrations were evaluated in the present study (29,30). Increased troponin I levels in the DXR group were considered an indicator of cardiac damage. Oxidative stress is a conspicuous mechanism in the pathophysiology of DXR-induced cardiotoxicity (5,31). Elevated ROS levels lead to modifications in the functional and structural components of the cell, resulting in myocardial damage and functional loss. Previous studies have reported that a decrease in cardiac antioxidant enzymes such as CAT, SOD, and GSH peroxidase and a reduction in the level of the non-enzymatic antioxidant molecule GSH are important factors in the development of oxidative damage of the myocardium during DXR treatment (5,31,32). In the current study,

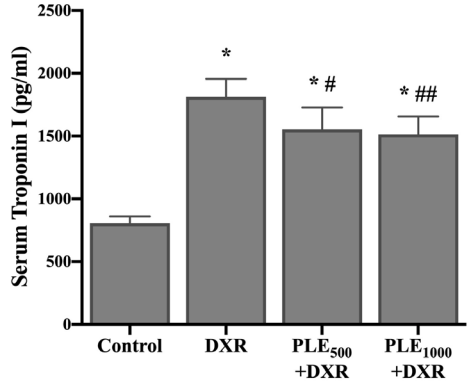

Figure 1. Circulating troponin I concentrations in the control, DXR, PLE_{500}+DXR and PLE_{1000}+DXR groups (n=6). The results were presented as the mean ± standard deviation. Comparing to the control group *$p<0.001$, comparing to the DXR group #$p<0.05$, ##$p<0.01$.
PLE: Prunus laurocerasus fruit extract, DXR: doxorubicin

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the increase in lipid peroxidation, along with GSH depletion and decreased SOD and CAT activities, suggested the presence of DXR-induced cardiac oxidative stress.

The *P. laurocerasus* fruit used in this study is rich in phenolic compounds such as chlorogenic, caffeic, gallic, vanillic, benzoic, and coumaric acids, rutin, and quercetin. This high phenolic content largely contributes to the pharmaceutical significance of the plant (33,34). In studies using different experimental damage models, it has been shown that pretreatment with *P. laurocerasus* extracts successfully reduces injury-related oxidative stress in stomach, kidney, and liver tissues (17-22). Not only fruit extract but also seed and leaf extracts of *P. laurocerasus* have been used in previous studies. For example, Uslu and Uslu (23) demonstrated a significant improvement in oxidative stress parameters (MDA, GSH peroxidase, GSH) in diabetic rats treated with leaf, fruit, or seed extracts of *P. laurocerasus* (21 days, 500 mg/kg) and reported that the effectiveness of these different extracts was at the similar level. To date, it has not been shown whether *P. laurocerasus* extracts affect cardiac oxidative stress in any injury model. Our study is the first to demonstrate that treatment with fruit extracts of *P. laurocerasus* can reduce oxidative stress in cardiac tissue. According to the present results, lipid peroxidation induced by DXR significantly decreased in the extract treatment groups; however, it did not return to control values. Similar changes observed in serum troponin levels indicate that the treatment could

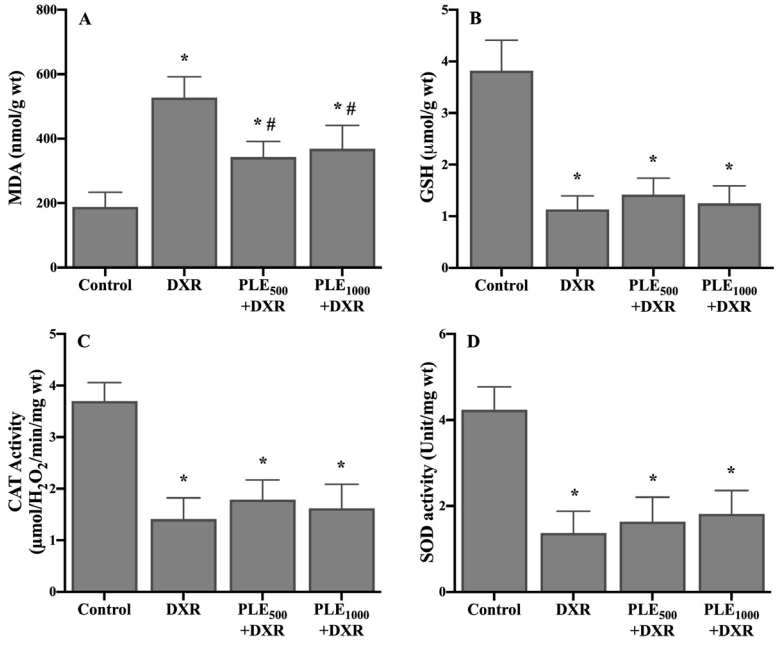

Figure 2. Oxidative stress parameters measured in myocardial tissue of the control, DXR, PLE_{500}+DXR and PLE_{1000}+DXR groups (n=6). Myocardial MDA levels (A), GSH levels (B), CAT activity (C) and SOD activity (D). The results were presented as the mean ± standard deviation. Comparing to the control group *p<0.001, comparing to the DXR group #p<0.001.
PLE: Prunus laurocerasus fruit extract, DXR: doxorubicin, CAT: catalase, GSH: glutathione, MDA: malondialdehyde, SOD: superoxide dismutase

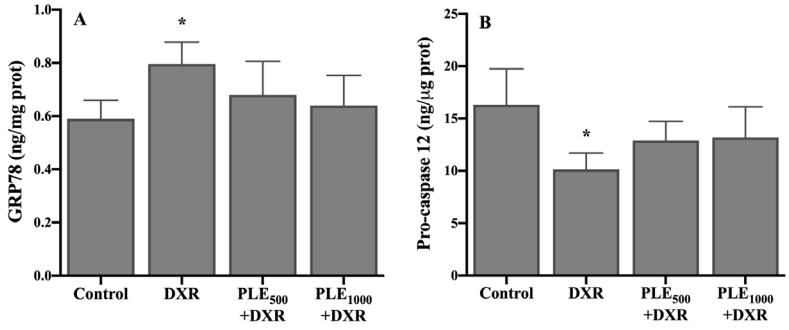

Figure 3. ER stress parameters measured in myocardial tissue of the control, DXR, PLE_{500}+DXR and PLE_{1000}+DXR groups (n=6). Myocardial GRP78 levels (A), pro-caspase 12 levels (B). Comparing to the control group *p<0.01.
PLE: Prunus laurocerasus fruit extract, DXR: doxorubicin, GRP78: glucose-regulated protein78

not completely prevent oxidative damage of the myocardium but was successful in reducing it. Decreased lipid peroxidation after *P. laurocerasus* treatment appeared to be related to the free radical scavenging properties of the extract because there was no improvement in endogenous GSH levels or antioxidant enzyme activities (CAT, SOD). This finding contradicts previous studies demonstrating elevated GSH levels and increased SOD and CAT activities in renal, gastric, and hepatic tissues following *P. laurocerasus* treatment (17-22), indicating that the efficacy of *P. laurocerasus* might vary depending on the tissue, as increasing the dose of the extract did not alter its efficiency for the heart.

The ER plays a crucial role in eukaryotic cells, being responsible for tasks such as the synthesis, folding, and secretion of proteins and maintaining calcium homeostasis. ER stress is a cellular response aimed at restoring ER functions and generally involves a slowing down of protein synthesis, accelerated proteasomal degradation of unfolded or misfolded proteins, and increased synthesis of ER chaperone proteins involved in the protein folding process, such as GRP78 (7). In the current study, the increased GRP78 level in the DXR group indicated the presence of cardiac ER stress, which is consistent with previous studies demonstrating the role of ER stress in DXR-induced cardiotoxicity (8,9,35). Although restoration of cellular homeostasis is aimed, severe or prolonged ER stress triggers cell death through apoptotic signaling pathways, namely caspase-12, c-JUN NH2-terminal kinase, and C/EBP homologous protein pathways. In the present study, a significant decrease in pro-caspase 12 levels was interpreted as an increase in caspase 12 activation, a result that is consistent with previous literature findings indicating the role of ER stress-mediated apoptosis in DXR-induced cardiotoxicity (8,9,35). While the effect of PLE on oxidative stress has been previously studied for different tissues, excluding the heart, its effect on ER stress in the heart was examined for the first time in this study. Our results showed a trend for GRP78 and pro-caspase 12 levels to return to the control levels, but these changes caused by extract pretreatment were not statistically significant in the DXR group. Although individual bioactive components within *P. laurocerasus* have been reported to reduce DXR-induced ER stress (10-16), it appears that their levels within the extract may not be sufficient to produce the same response even at higher doses. Because oxidative stress is one of the ER stress triggering factors, reduced oxidative stress would be expected to be accompanied by decreased ER stress in the extract-treated groups. However, it should be noted that oxidative stress was not completely prevented in the extract groups. Ongoing oxidative stress may play a significant role in the persistence of both ER stress and cardiac damage.

Study Limitations

One of the most significant shortcomings of this study is that cardiac damage was assessed only through serum troponin I measurement without histopathological evaluation. Demonstrating the histological evidence of both DOX-induced damage and partial recovery after treatment could have supported the current findings.

CONCLUSION

In this study, the effects of PLE on DOX-induced cardiotoxicity were investigated for the first time. Although histopathological evaluation was not conducted, which is a limitation of the current study, the results indicated that pretreatment with PLE partially prevented myocardial damage in DXR-induced cardiotoxicity. We suggested that PLE treatment decreased cardiac lipid peroxidation, possibly due to its endogenous radical scavenging property, without causing any changes in the tissue levels of enzymatic (SOD and CAT) or non-enzymatic antioxidants (GSH). While a reduction in oxidative stress appears to play a role in the partial protection of PLE treatment, it seems that the ER stress response plays no role. The incomplete prevention of DXR-induced cardiac damage does not appear to be related to dose insufficiency; however, future studies with longer treatment durations can be planned.

Ethics Committee Approval: The Ordu University Animal Experiments Local Ethics Committee approved all the experimental procedures (decision no: 12, date: 22.10.2020).

Informed Consent: Animal experiment study.

Author Contributions: Surgical and Medical Practices - S.C., E.K., G.H.; Concept - S.C.; Design - S.C.; Data Collection and/or Processing - S.C., E.K., G.H., E.G.G.P.; Analysis and/or Interpretation - S.C., E.K., G.H., E.G.G.P.; Literature Search - S.C., E.K.; Writing - S.C.

Conflict of Interest: The authors have no conflict of interest to declare.

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