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The Olive Constituent Oleuropein Prevents the Doxorubicin-induced Heart Failure in Anesthetized Rats by Nitro-oxidative Stress Suppression and by Reversing Cardiac Remodeling.

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INTRODUCTION

Doxorubicin (DXR) is an anthracycline antibiotic generally used in the treatment of solid tumors, but its use is limited by a dose-dependent cardiomyopathy and heart failure. The pathogenesis of DXR-induced heart failure is complex and the role of iNOS, nitrosative and oxidative stress is not completely understood. Oleuropein (OLEU) is a natural phenolic antioxidant, which is present in elevated concentration in olives, olive oil and olive tree leaves conferring protection to the heart. The aim of the present study was to evaluate a possible protective role of OLEU in DXR-induced heart failure and to investigate a possible mechanism of action.

METHODS

Ninety rats were randomly divided into 6 groups and treated as follows: *Control* group with no treatment, *OLEU-1* and *OLEU-2* groups, treated with 70 and 140 mg/Kg^{-1} of OLEU respectively, given intraperitoneally (i.p.), for 14 consecutive days, *DXR* group treated with i.p. injection of 18mg/kg^{-1} of DXR, divided into 6 equal doses and given over a period of 2 weeks, *OLEU-1-DXR* and *OLEU-2-DXR* groups, rats treated with OLEU and DXR for 14 days as previously described. At the end of the injection protocols the rats were anesthetized and subjected transthoracic echocardiography examination (Vivid-i, GE Healthcare with a 12MHz probe). Then the rats were sacrificed and the hearts were rapidly excised for histological evaluation and for tissue assessment of malondialdehyde (MDA) and protein carbonyl concentration (PCs) as an index of oxidative stress, nitrotyrosine (NT) as indicator of *nitrosative* stress, for interleukin-6 (IL-6) and Big endothelin-1 (Big ET-1) which are important indicators of cardiac remodeling and apoptosis. Finally, cardiac tissue sample was used for qualitative and quantitative evaluation of inducible synthesis of nitric oxide (iNOS), as a marker of inflammation, both by immunohistochemistry method and Western-Blot.

RESULTS

Eighty two rats completed the study. The mortality in the *DXR* group was 18.7% by end of the injection protocol. Normal morphology of the cardiac tissue was seen in the *Control* group and in groups *OLEU-1* and *OLEU-2*. Myocardium exhibited morphological changes in *DXR* group only including edema, chronic inflammation and de-

generation of myocardial cells such as vacuolization. In the *OLEU-1-DXR* and *OLEU-2-DXR* groups mild hypertrophy without edema, inflammation and myocardial degeneration was observed. DXR induced a small decrease in wall thickness, a decrease in left ventricular (LV) mass, a decrease in fractional shortening (an index of systolic function), an increase in end-systolic LV diameter, and a trend towards adverse cardiac remodeling. Combined *OLEU-DXR* and *OLEU* alone groups did not cause any change and the animals did not differ from the normal *Control*. A statistically significant elevation in the levels of MDA, NT, PCs, IL-6 and Big ET-1 was observed in the DXR group whereas a significant reduction of the above mediators was observed in the control and in groups treated with OLEU. A significant expression of iNOS was detected in the cardiomyocytes in the DXR group compared to the control and to the groups treated with OLEU.

CONCLUSION

The present study shows that the olive constituent OLEU successfully treats the DXR-induced heart failure by reducing oxidative and nitrosative stress and reversing cardiac remodeling and apoptosis. DXR-induced heart failure produced a significant induction in iNOS and nitrotyrosine formation in the myocardium. Combined OLEU-DXR treatment may improve the therapeutic outcome and additional research should be conducted to prove if it could be used for clinical cardioprotection against DXR-induced toxicity,