BERGAMOT POLYPHENOLS PROTECT AGAINST DOXORUBICIN-INDUCED CARDIOMYOPATHY REDUCING ROS PRODUCTION AND PROMOTING MYOCYTE SURVIVAL

1)Carresi C. 2)Musolino V. 3)Gliozzi M. 4)Giancotta C. 5)Scarano F. 6)Oppedisano F. 7)Paone S. 8)Palma E. 9)Muscoli C. 10)Mollace V.

Magna Graecia University of Catanzaro, IRC-FSH

Background: Doxorubicin (DOXO) is one of the most widely used antineoplastic drugs. Despite its highly beneficial effects against several neoplasias, the clinical use of DOXO has the serious drawback of cardiotoxicity, which over time causes a cardiomyopathy that leads to congestive heart failure. The molecular pathogenesis of anthracycline cardiotoxicity remains highly controversial, although the oxidative stress-based hypothesis involving intramyocardial production of reactive oxygen species (ROS) has obtained great interest. In this regard, dietary polyphenols, in particular flavonoids, play a cardiovascular protecting role due to their pleiotropic anti-oxidative and anti-inflammatory effects.

Purpose: Thus, we have investigated whether a rich mixture of flavonoids extracted from Bergamot (Citrus Bergamia Risso et Poiteau), the bergamot-derived polyphenolic fraction (BPF), could attenuate DOXO-induced cardiomyopathy in vivo.

Results: Here we show that BPF was able to prevent DOXO-induced LV impairment and myocardial strain dysfunction. Indeed, echocardiographic assessment demonstrated that BPF administration in DOXO+BPF group significantly reduced LV end-systolic diameter (LVESd), LV end-diastolic diameter (LVEDd), improving both ejection fraction (EF) and fractional shortening (FS) compared to DOXO-treated rats. BPF was also able to prevent time-to-Peak (TPk) delay of cardiac strain and strain rate and dyssynchrony of radial motion in short axis when compared to DOXO group.

Histological analysis of DOXO+BPF-treated rats revealed a significant reduction of myocyte apoptosis, accompanied by a decrease in reactive myocyte hypertrophy and myocardial fibrosis compared to DOXO-treated rats. Moreover, cardiomyocytes isolated from DOXO-treated rats showed a significant increase in Beclin-1 levels which were associated with a strikingly increase in LC3II/LC3I ratio and p62 levels compared to control rats. Importantly, all the pro- autophagic markers evaluated were significantly decreased by BPF co-treatment, compared to DOXO-treated rats.

Finally, we found that BPF significantly prevents 8-OHdG (marker of oxidative damage of DNA) nuclear accumulation in cardiac tissue and counteracts the increase in lipid peroxidation, tyrosine nitration of cardiomyocytes isolated from DOXO-treated rats.

Conclusion: BPF reduces DOXO-induced cardiotoxicity by decreasing ROS production and myocyte apoptosis that lead to a significant improvement of cardiac function. These data suggest that BPF may be used as a promising cardioprotective agent in patients undergoing anthracycline chemotherapy.