Potential Protective Effect of Orlistat: A Formulation of Nanocrystals Targeting Inflammation, Oxidative Stress, and Apoptosis in an Experimental Model of Doxorubicin-Induced Cardiotoxicity

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Abstract:

Background: Doxorubicin (DOX) is a widely used chemotherapeutic agent; nevertheless, cardiotoxicity limits its effectiveness. Orlistat (Orli) is an irreversible lipase enzyme inhibitor with poor solubility and bioavailability. Furthermore, Orli has a favorable impact on the decrease in cardiometabolic risk variables. Thus, this study aimed to investigate the novel use of Orlistat Nanocrystals (Orli-Nanocrystals) to mitigate DOX-induced cardiotoxicity and to identify probable pathways behind the cardioprotective effects.

Methods: The pharmacokinetic parameters—area under % dose/g heart time curve (AUC0→4h), Drug targeting index (DTI), and relative targeting efficiency (RTE)—were calculated. Furthermore, experimental design mice were categorized into six groups: a (1) Normal control group, (2) Orli-Free group, (3) Orli-Nanocrystals group, (4) DOX group, (5) Orli-Free-DOX group, and (6) Orli-Nanocrystals-DOX group. All treatments were intraperitoneally injected once daily for 14 days with a single dose of DOX (15 mg/kg) on the 12th day for 4, 5, and 6 groups.

Results: The pharmacokinetic parameters (Cmax, AUC) following oral administration of Orli-Nanocrystals presented a significant difference (higher values) in comparison to Orli due to the enhanced extent of the absorption of nanocrystals and, subsequently, their distribution to the heart. The study results indicated that DOX caused significant cardiotoxicity, as revealed by a remarkable rise in cardiac function biomarkers like LDH and CK-MB, which involve enzyme activities. Additionally, cardiac MDA content also increased; however, glutathione peroxidase, catalase, and superoxide dismutase activities were decreased. In the same context, DOX was found to have a remarkable downregulation in Nrf2, HO-1, Sirt-1, and Bcl2, while the upregulation of NF-κB, TNF-α, and BAX gene and protein expression occurred. Pretreatment with Orli-Nanocrystals displayed the most notable recovery of the altered immunohistochemical, histological, and biochemical characteristics as compared to the Orli-Free group.

Conclusions: This work is the first investigation into the potential use of antioxidant, anti-inflammatory, and anti-apoptotic characteristics of Orli-Nanocrystals to protect against DOX-induced cardiotoxicity in vivo.

Keywords:

Cardioprotective, Orlistat nanocrystals, Oxidative stress, Inflammation, Apoptosis.