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Entitled

THE EFFECT OF β-CARYOPHYLLENE ON DOXORUBICIN-INDUCED CARDIOTOXICITY

by

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Abstract

Doxorubicin is an effective and widely used chemotherapeutic drug. However, its clinical use is limited due to cardiotoxicity which it causes that appears in the form of dilated cardiomyopathy. Many efforts have been devoted to developing/discovering agents which can counter DOX-induced cardiotoxicity. The present study was undertaken to evaluate the cardioprotective potential of β-Caryophyllene (BCP), a dietary phytocannabinoid, in a rat model of DOX-induced acute and chronic cardiotoxicity. BCP is widely found in various herbs and spices and is a full agonist of the cannabinoid receptor type 2 (CB_2) and exhibits potent anti-inflammatory effects. In the present study, rats challenged with DOX showed cardiotoxicity as evidenced by increased serum levels of creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH) as well as reduced levels of the antioxidants superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) concomitant with increased lipid peroxidation. A significant rise in the levels of pro-inflammatory cytokines as well as inflammatory mediators, namely cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) was also observed in DOX-challenged rats. Furthermore, histopathological observations showed severe muscle degradation in DOX-challenged rats. However, BCP reversed all the changes found in acute and chronic DOX-induced cardiotoxicity as evidenced by improved antioxidants activities/levels, reduced inflammation, reduced cardiomyocyte injury and structural salvaging of heart tissue. Additionally, in the chronic model of DOX-cardiotoxicity, we also investigated the CB_2 receptor dependent mechanism of cardioprotection elicited by BCP using AM630, a CB_2 receptor antagonist. Pretreatment with AM630 abrogated the beneficial effects of BCP. This demonstrates that BCP exhibits cardioprotective effects by attenuating oxidative stress and inflammation and the underlying mechanism of this protection is the activation of CB_2 receptors. This study, for the first time, demonstrates the cardioprotective effect of BCP in DOX-induced cardiotoxicity and also suggests that BCP could be a promising agent for cardioprotection against DCM.

Keywords: Doxorubicin, β-Caryophyllene, cannabinoid receptor type 2, CB_2, dilated cardiomyopathy, oxidative stress, inflammation.