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β-Caryophyllene, a natural bicyclic sesquiterpene attenuates doxorubicin-induced chronic cardiotoxicity via activation of myocardial cannabinoid type-2 (CB_2) receptors in rats.

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Abstract

The cannabinoid type 2 receptor (CB_2) has recently emerged as an important therapeutic target for cancer as well as cardiovascular diseases. The CB_2 receptor downregulation has been reported in solid tumors and cardiovascular diseases, therefore the CB_2 receptor activation has been considered as a viable strategy for chemotherapy as well as cardioprotection. Doxorubicin (DOX) is an important drug that continues to be the mainstay of chemotherapy in solid tumors, leukemia, and lymphoma. However, the use of DOX is often limited due to its lethal cardiotoxicity. Considering the role of CB_2 receptors in cardiovascular diseases and cancer, the activation of CB_2 receptors may protect against DOX-induced chronic cardiotoxicity in rats. In the present study, we investigated the cardioprotective effect of a selective CB_2 receptor agonist; β-Caryophyllene (BCP), a natural bicyclic sesquiterpene, against DOX-induced chronic cardiotoxicity in rats. AM630, a CB_2 receptor antagonist was administered as a pharmacological challenge prior to BCP treatment to demonstrate CB_2 receptor mediated cardioprotective mechanism of BCP. DOX (2.5 mg/kg) was injected intraperitoneally once a week for five weeks to induce chronic cardiotoxicity in rats. BCP was also injected into rats six days a week for a total duration of five weeks. DOX induced a significant decline in cardiac function and oxidative stress evidenced by the depletion of antioxidant enzymes, glutathione, and increased lipid peroxidation. DOX also triggered activation of nuclear factor kappa B (NF-κB) and increased the levels of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) and expression of the inflammatory mediators (iNOS and COX-2) in the heart. Furthermore, DOX also upregulated the expression of pro-apoptotic markers such as Bax, p53, cleaved PARP, active caspase-3 and downregulated anti-apoptotic marker Bcl-2 in the myocardium. BCP treatment exerted significant cardioprotective effect by salvaging the heart tissues, improving cardiac function, mitigating oxidative stress, inflammation, and apoptosis. The histological and ultrastructural

studies also appear in line with our findings of biochemical and molecular parameters. The CB_2 receptor-mediated cardioprotective mechanism was further confirmed by the abrogation of the beneficial effects of BCP with prior administration of the CB_2 receptor antagonist; AM630. Our study revealed the novel mechanism of BCP in cardioprotection against DOX-induced chronic cardiotoxicity by the activation of CB_2 receptors.

KEYWORDS: AM630; Cannabinoid 2 receptor; Cardiotoxicity; Doxorubicin; β-Caryophyllene

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