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Article

Nerolidol Attenuates Oxidative Stress, Inflammation, and Apoptosis by Modulating Nrf2/MAPK Signaling Pathways in Doxorubicin-Induced Acute Cardiotoxicity in Rats

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Abstract: The clinical usage of doxorubicin (DOX), a potent anthracycline antineoplastic drug, is often limited by its cardiotoxic effects. Thus, for improving usage of DOX, the aim of this study was to assess the cardioprotective effects of nerolidol (NERO) in a rat model of DOX-induced acute cardiotoxicity and examine underlying molecular mechanisms that contribute to these effects. To induce acute cardiotoxicity male albino Wistar rats were injected with single dose intraperitoneal DOX (12.5 mg/kg). The rats were treated with NERO (50 mg/kg, orally) for five days. DOX-injected rats showed elevated levels of cardiac marker enzymes and enhanced oxidative stress markers along with altered Nrf2/Keap1/HO-1 signaling pathways. DOX administration also induced the activation of NF-κB/MAPK signaling and increased the levels and expression of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) as well as expression of inflammatory mediators (iNOS and COX-2) in the heart. DOX also triggered DNA damage and apoptotic cell death in the myocardium. Additionally, histological studies revealed structural alterations of the myocardium. NERO treatment exhibited protection against the deleterious results of DOX on myocardium, as evidenced by the restoration of altered biochemical parameters, mitigated oxidative stress, inflammation, and apoptosis. The findings of the present study demonstrate that NERO provides cardioprotective effects against DOX-induced acute cardiotoxicity attributed to its potent antioxidant, anti-inflammatory, and antiapoptotic activities through modulating cellular signaling pathways.

Keywords: acute cardiotoxicity; cardioprotective; doxorubicin; inflammation; nerolidol; oxidative stress; sesquiterpene

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1. Introduction

Chemotherapeutic agents have significantly improved the likelihood of survival among cancer patients [1]. Of the numerous chemotherapeutic agents, doxorubicin (DOX) also known as Adriamycin belongs to anthracycline class of cytotoxic antibiotic, which is extensively used in the treatment of multiple types of malignancies sarcoma, carcinoma, lymphoma and leukemia [2]. However, the clinical use of DOX is often limited due to its severe adverse effects, including neurological disturbances, bone marrow aplasia and cardiotoxicity [3]. The appearance of acute cardiotoxicity necessitated the need for effective agents to mitigate DOX-induced acute cardiotoxicity [4].

To reduce the occurrence of acute cardiotoxicity induced by DOX, numerous protective strategies have been developed. This includes the development of improved dosage forms of DOX itself, as well as the development of agents that mitigate oxidative stress, inflammation, and apoptosis. This leads to biochemical, molecular, structural and histological

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