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Nerolidol, a Sesquiterpene from the Essential Oils of Aromatic Plants, Attenuates Doxorubicin-Induced Chronic Cardiotoxicity in Rats

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ABSTRACT: The clinical usage of doxorubicin (DOX), a potent anthracycline antineoplastic drug, is limited due to its cardiotoxicity. The aim of this study was to assess the possible cardioprotective effects of nerolidol (NERO) in a rat model of DOX-induced chronic cardiotoxicity and the underlying molecular mechanisms. DOX (2.5 mg/kg) was injected intraperitoneally once in a week for 5 weeks to induce chronic cardiotoxicity in male albino Wistar rats. The rats were treated with NERO (50 mg/kg, orally) 6 days a week for a duration of 5 weeks. DOX-injected rats showed a significant decline in cardiac function, elevated levels of serum cardiac marker enzymes, and enhanced oxidative stress markers along with altered PI3K/Akt and NrF2/Keap1/HO-1 signaling pathways. DOX also triggered the activation of NF-κB/MAPK signaling and increased the levels/expression of proinflammatory cytokines (TNF-α, IL-6, and IL-1β) and expression of inflammatory mediators (iNOS and COX-2) in the heart. DOX activated NLRP3 inflammasome-mediated pyroptotic cell death along with fibrosis, mitochondrial dysfunction, DNA damage, and apoptosis in the myocardium. Additionally, histological studies, TUNEL staining, and myocardial lesions revealed structural alterations of the myocardium. NERO treatment showed considerable protective effects on the biochemical and molecular parameters studied. The findings demonstrate that NERO protects against DOX-induced chronic cardiotoxicity and the observed cardioprotective effects are attributed to its potent antioxidant and free radical scavenging properties.

KEYWORDS: *nerolidol, sesquiterpene, doxorubicin, myocardial fibrosis, apoptosis*

INTRODUCTION

Doxorubicin (DOX), a quinone-containing anthracycline antibiotic, is a frequently used antineoplastic agent and remains an inevitable drug in most chemotherapeutic regimens to treat different types of cancer including lymphoma, leukemia, and sarcoma.[1] Despite its extensive use and potential clinical usefulness, long-term treatment with DOX is associated with higher incidences of cumulative cardiotoxicity manifesting as heart failure.[2] Cardiotoxicity may arise following acute treatment with a high dose of DOX that is characterized by tachyarrhythmias and acute heart failure, whereas chronic toxicity or heart failure may appear in patients decades after treatment with last doses of DOX, which results in progressive myocardial dysfunction followed by irreversible heart failure.[3] Even though numerous satisfactory efforts have been undertaken in the past few years to prevent DOX-induced cardiotoxicity, the occurrence of cardiotoxicity among cancer patients is rising and necessitates the search of cardioprotective agents. Thus, there is an immediate requirement to develop novel protective and therapeutic strategies against DOX-associated cardiovascular complications.

The exact pathogenesis of DOX-induced cardiotoxicity is yet unclear. However, the role of free radical-mediated oxidative stress encompassing lipid peroxidation, mitochondrial dysfunction, inflammation, and apoptosis was convincingly showed to be crucial in this clinical event.[4,5] Cardiomyocytes are more susceptible to reactive oxygen species (ROS)-mediated oxidative damage due to the prominence of aerobic metabolism and intense mitochondrial density with a lesser availability of antioxidant defense networks.[6] Subsequently, the generation of superoxide anions and hydroxyl radicals by DOX via NADPH-cytochrome P-450 enzyme triggers myocardial injury.[7] DOX has also been shown to trigger pro-inflammatory cytokine levels and myocardial inflammatory mediators.[8] Nuclear factor kappa-B (NF-κB) activation and mitogen-activated protein (MAPK) signaling were known to trigger apoptosis by activating pro-apoptotic events.[9] DOX was shown to induce apoptosis via c-Jun N-terminal kinases (JNKs) and MAP kinase signaling pathways.[10] In addition to this, NF-κB can inversely regulate the transcription and activities of nuclear factor erythroid 2-related factor 2 (NRF2). NRF2 is known to orchestrate redox defense through heme oxygenase-1 (HO-1) activation and endogenous antioxidant defense mechanisms.[7] In addition, the phosphoinositide 3-kinase (PI3K)-mediated signaling cascade is classically known to contribute to cardioprotective mechanisms and

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Abstract

The clinical usage of doxorubicin (DOX), a potent anthracycline antineoplastic drug, is limited due to its cardiotoxicity. The aim of this study was to assess the possible cardioprotective effects of nerolidol (NERO) in a rat model of DOX-induced chronic cardiotoxicity and the underlying molecular mechanisms. DOX (2.5 mg/kg) was injected intraperitoneally once in a week for 5 weeks to induce chronic cardiotoxicity in male albino Wistar rats. The rats were treated with NERO (50 mg/kg, orally) 6 days a week for a duration of 5 weeks. DOX-injected rats showed a significant decline in cardiac function, elevated levels of serum cardiac marker enzymes, and enhanced oxidative stress markers along with altered PI3K/Akt and Nrf2/Keap1/HO-1 signaling pathways. DOX also triggered the activation of NF-κB/MAPK signaling and increased the levels/expression of proinflammatory cytokines (TNF-α, IL-6, and IL-1β) and expression of inflammatory mediators (iNOS and COX-2) in the heart. DOX activated NLRP3 inflammasome-mediated pyroptotic cell death along with fibrosis, mitochondrial dysfunction, DNA damage, and apoptosis in the myocardium. Additionally, histological studies, TUNEL staining, and myocardial lesions revealed structural alterations of the myocardium. NERO treatment showed considerable protective effects on the biochemical and molecular parameters studied. The findings demonstrate that NERO protects against DOX-induced chronic cardiotoxicity and the observed cardioprotective effects are attributed to its potent antioxidant and free radical scavenging properties.

Keywords: apoptosis; doxorubicin; myocardial fibrosis; nerolidol; sesquiterpene.

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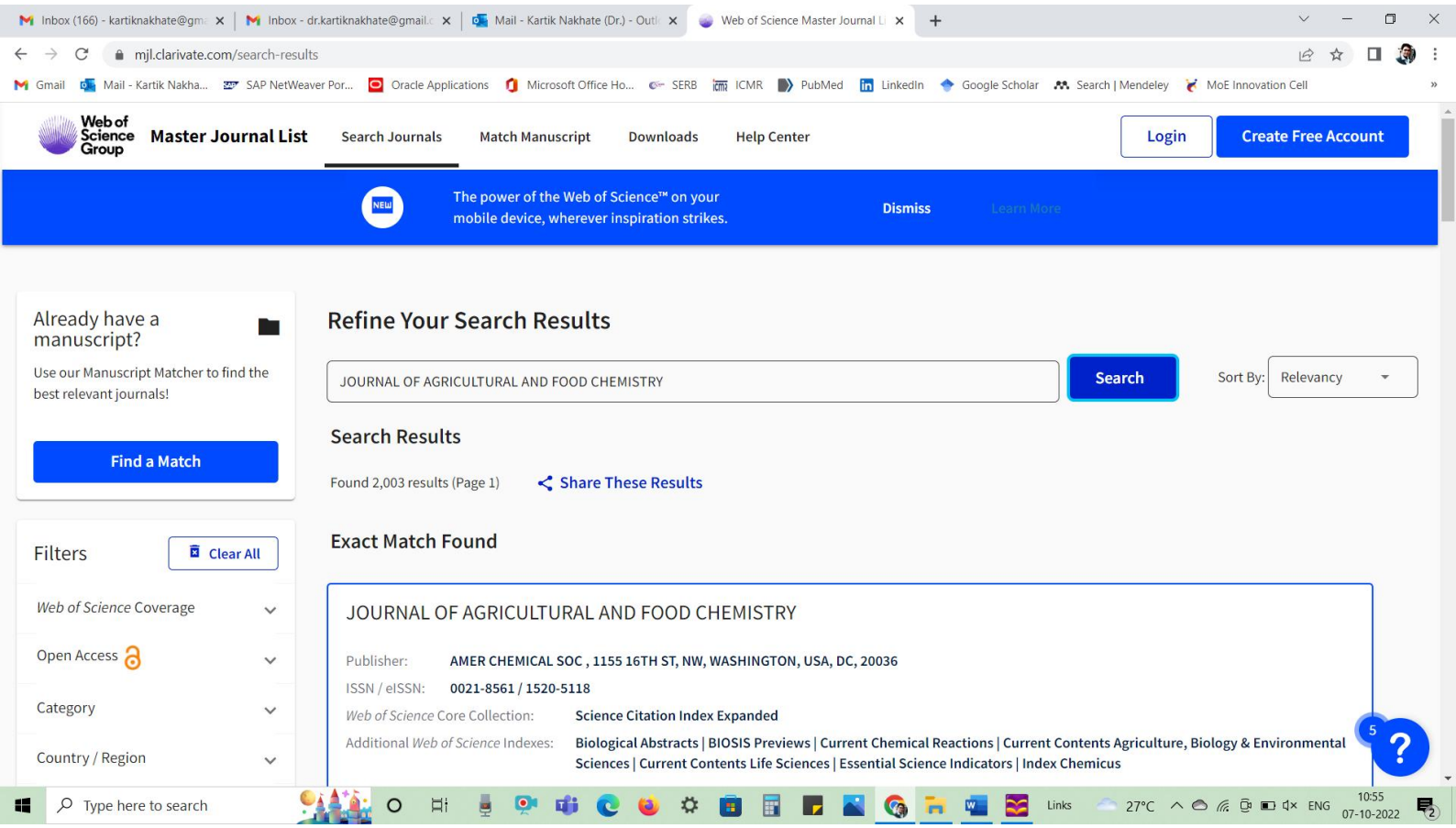
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