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Original Article

Potential Role of Selenium to Ameliorate Doxorubicin Induced Cardiotoxicity in Male Rats

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KEYWORDS

Cardiotoxicity
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ABSTRACT

Abstract: Selenium (SE) is well known for its immune boosting, antioxidant, and anti-tumor properties. Doxorubicin (DOXO), a commonly used chemotherapy drug, causes cardiac-damage by increasing the level of reactive oxygen species (ROS). Selenium (SE) is well known for its immune boosting, antioxidant, and anti-tumor properties. Doxorubicin (DOXO), a commonly used chemotherapy drug, causes cardiac-damage by increasing the level of reactive oxygen species (ROS). SE has been shown to improve heart development dysregulation, CMY structural damage, antioxidant enzyme (GSH, and SOD) activity, and caspase-3 (CASP3) levels in the cardiac tissue. Furthermore, SE could reduce the inflammation marker, ICAM-1 activity, and cardiotoxicity marker levels in the serum, cTn-1 serum levels. Finally, SE may protect against cardiotoxicity by inhibiting the oxidative induced by doxorubicin.

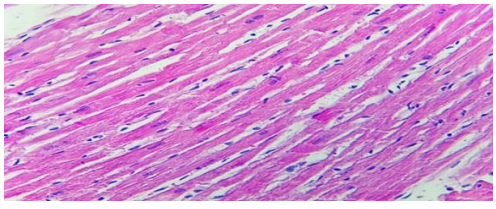
Objectives: The aim of the study is to investigate if selenium has protective role against the cardiotoxicity induced by DOXO in laboratory rats**.**

Method: A total of 32 male rats were used, and they were randomly divided into 4-groups (8 rats * in each group). The rats in the control group started drinking distilled water for the experiment period. Rats in the doxorubicin group (the induced group) were given 2.5 MG/KG three times per wek, continue for 2-weeks. The second group was treated with SE only had SE administered at a dose of 1 mg/kg, continue for 2-weeks.

Results: Doxorubicin induced cardiotoxicity, as shown by a significant increase (~P < 0.001) in the levels of cTnI, ICAM-1, and caspase-3. At the same time, the levels of GSH and SOD when compared to the control group, were significantly reduced (P < 0.001) in the cardiac tissues of rats in the doxorubicin treated group. Histological changes and lesions were also caused by the Doxo. The administration of selenium was found to reduce cardiotoxicity, this can be proved by significant-decreases (p* < 0.001) in cardiac-TnI, ICAM-1, casp-3 and significant-increases (~P < 0.001) in SOD and GSH when compared to the DOXO group; and significant improvements (~P < 0.001) in the score for cardiomyopathy histopathological lesions.

Conclusion: At the drugs-doses used in this study, selenium protected the hearts of rats from DOXO-induced cardiotoxicity. This is may related to the interfered and may ameloirate oxidative stress, inflammation, and the apoptotic pathway.

GRAPHICAL ABSTRACT



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Introduction

Selenium is an essential trace-element that plays a vital role in a wide variety of biological processes due to its role as a cofactor in a SE-containing enzyme, most commonly as antioxidant enzymes [1]. After obtaining selenium from meals that contain trace amounts of it, the body will normally store some of it in human tissue, most of it in the skeletal muscles [2]. It may prevent the oxidative- modifcation of the lipids [3-5], or bodily fat. It is possible that this will minimize inflammation as well as the accumulation of platelets. Damage to the heart may occur either temporarily or permanently as a side effect of receiving some cancer therapies [6]. Doxorubicin, commonly used to treat leukemia, lymphoma, breast cancer, and other solid tumors, has been linked to cardiac toxicity [7]. Doxorubicin as HCL intercalates between DNA bases, preventing DNA replication and protein synthesis. Besides that, doxorubicin works by inhibiting topoisomerase-11, which leads to a more stable enzyme-DNA linked complex during DNA replication. This prevents nucleotide strand ligation from occurring after double-strand breaks [8, 9]. In addition, doxorubicin generates oxygen free radicals that oxidize cell membrane-lipids, contributing to the toxicity of Doxo [10]. The aim of the study is to investigate if selenium has protective role against the cardiotoxicity induced by DOXO in laboratory rats**.**

Materials and Methods

32-male rats, 3 month aged & weight (150-200 g) have been used. Thereafter, they were divided by random into four-groups with a total of eight rats in each group. The rats in the control group treated with distilled water. The doxorubicin-group (the induced group), 2.5 mg per kg were injected intraperitoneally 3-times a week for 2 weeks period for each rat. SE - group only given 1 mg per kg treated with SE continued for two weeks. Selenium with Doxo-group (induced pretreated), the group treated with Selenium was administered orally at a dose of 1 mg per kg, and induction with 2.5mg per kg OF Doxo (for 2 weeks, SE, commenced 3 days before Doxo injection). In the Doxo (induced) group, Doxo- was given the same way as in the other groups. After 48 hours had passed since the previous injection of Anticancer drug, the body weight of each animal was recorded. We used ketamine at a dose of 100 mg per kg and x-ylazine at a dosage of 10 mg per kg to anesthetize the animals. The blood was centrifuged and the serum was collected and freezed in deep freeze until to be tested, the parameters such as cardiac troponin I (CTn-I), inflammatory-parameters, and apoptotic-markers were studied by using Eliza-Kits. And The bottom half of the hearts were utilized to create tissue homogenates to quantify other oxidative-stress paramters, while the upper-half was used for histopathological analyses.

Results and Discussion

The result showed that Doxo-caused cardiotoxcty, which was shown by a-significant increase (~P< 0.001) in the levels of cTnI, ICAM-1, and caspase-3.Compared to the control group at the same time, the levels of GSH and SOD showed significant reduction (~P <0.001) in the cardiac-tissues of rats. in the doxorubicin group when compared to the control group, also showed changes in histological lesions were also caused by the drug (Table 1).

The administration of selenium was found to reduce cardiotoxicity, as evidenced by significant decreases (~p < 0.001) in CTn-1, ICAM-1, and cas-3; significant increases (P < 0.001) in SOD and GSH when compared to the DOXO group; and significant improvements (~P < 0.001) in the score of the CMYO lesions. Briefly, at the doses was used in this ^study, while the selenium protected the hearts of rats from DOXO-induced cardiotoxicity (Table 2). This is likely because it interfered with oxidative stress, the inflammatory response, and the apoptotic pathway.

Table 1: Effects in the cardiac troponin-1 (cTn-1) for 4 experiment-groups after two-weeks

Cardiac troponin-1	Group
8.458 ± 0.40	-Control
8.255 ± 0.32	-Selenium
16.81 ± 0.39***	-Doxorubicin
11.50 ± 0.38+++*	-SE+ DOXO

*-Data expressed as mean ± standard error mean for eight-rats in each group, ((+++P < 0.001)) groups VS. DOXO-group, ((***P < 0.001)) group VS. -control & SE-group, and ((*p <0.05)) group VS.- control & SE-group*

Table 2: Effects in the antioxidant enzymes GSH & SOD for 4- groups after 2weeks

Glutathione (GSH)	Superoxide dismutase (SOD)	Group
19.82 ± 0.724	228.3 ± 3.1	Control
19.9 ± 0.74	228.5 ± 4.3	Selenium
9.195 ± 0.65 * **	158.2± 9.6***	Doxorubicin
18.87 ± 0.68 + ++	212.9 ± 5.3 +++	SE+ DOXO

*- Data expressed as mean ± standard error mean for eight-rats in each group, ((+++P < 0.001)) groups VS. DOXO-group, ((***P < 0.001)) group VS. -control & SE-group*

Table 3: Effects in the Intercellular adhesion molecule-1 (ICAM-1) for 4 groups after 2 weeks

Group	ICAM-1
Control	74.55 ± 2.264
Selenium	74.11 ± 2.638
Doxorubicin	143.4 ± 5.614 ***
SE+ DOXO	86.64 ± 1.401 + ++

*- Data expressed as mean ± standard error mean for eight-rats in each group, ((+++P < 0.001)) groups VS. DOXO-group, ((***P < 0.001)) group VS. -control & SE-group*

Table 4: Effect in caspase-3(CASP3) for 4-experiment groups after 2 weeks

Group	CASP3
Control	0.05083 ± 0.00171
Selenium	0.05013 ± 0.00127
Doxorubicin	0.1021 ± 0.00275 ***
SE+ DOXO	0.0567 ± 0.00183 +++

*- Data expressed as mean ± standard error mean for eight-rats in each group, ((+++P < 0.001)) groups VS. DOXO-group, ((***P < 0.001)) group VS. -control & SE-group,*

The histopathologic examination evaluated the severity of cardiomyopathy (CMY) from 0 to 4:

- ✓ 0 reflects no CMY,
- ✓ +1 mild CMY,
- ✓ +2 moderate CMY,

and 3 or more represents severe CMY

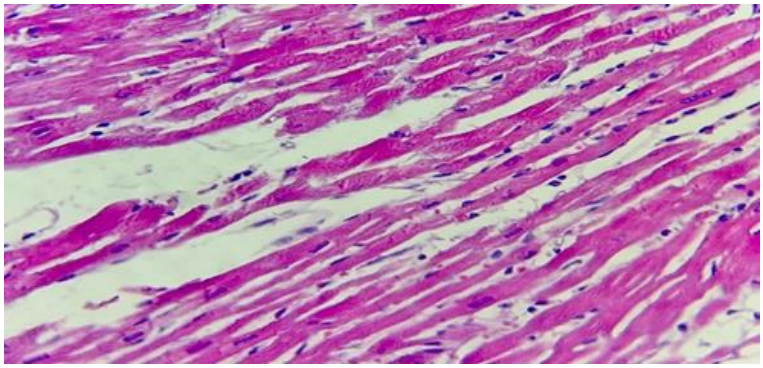

Figure 1: The structure of the muscle cells in the myocardium of control rats was normal, with score 0, normal histology H&E (*400)

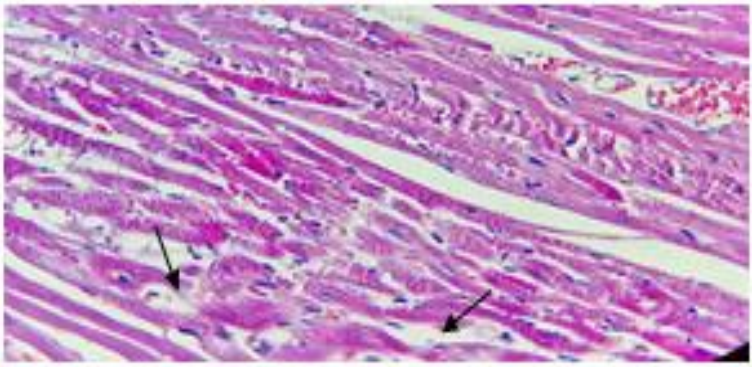

Figure 2: Doxorubicin group with score 4, the cardiotoxicity manifested by disorganization of myocardial fibers, represented by (↘) showed in H&E (100*)

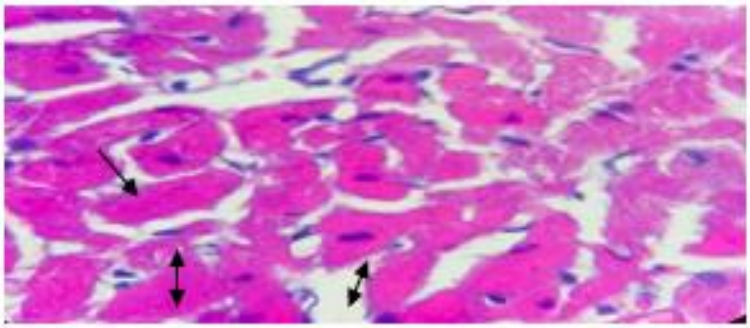

Figure 3: Doxorubicin group with score 4, the cardiotoxicity manifested by Cellular swelling, deep cytoplasmic eosinophilia, some with pyknotic nuclei, represented by (↔) and others with nuclear lysis (necrotic cell) in H&E (*400), represented as (↘)

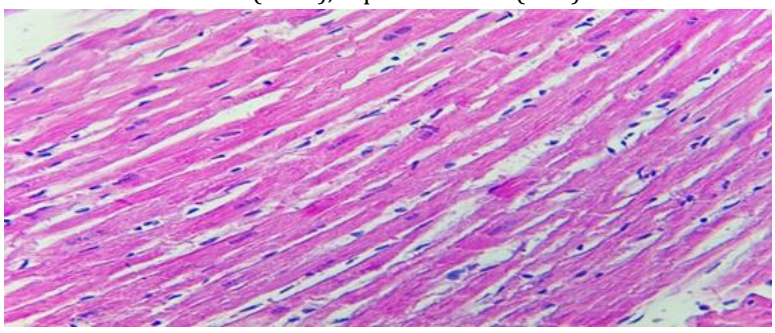

Figure 4: Selenium only-treated rats, have no damage, with score 0 in H&E (*400)

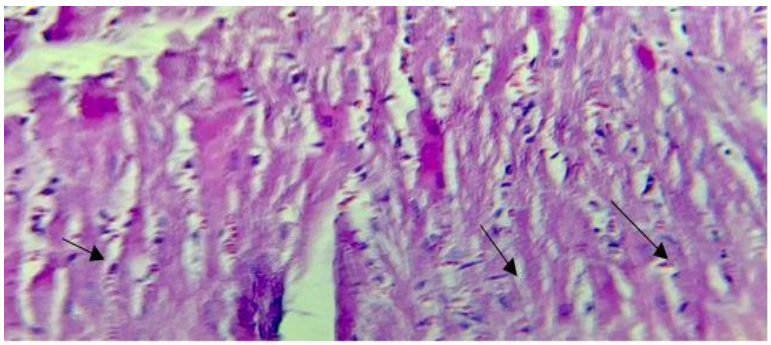

Figure 5: SE+DOXO-treated rat, with score 1, the damage shown with very little cellular swelling, represented as (↘) in H&E (*400)

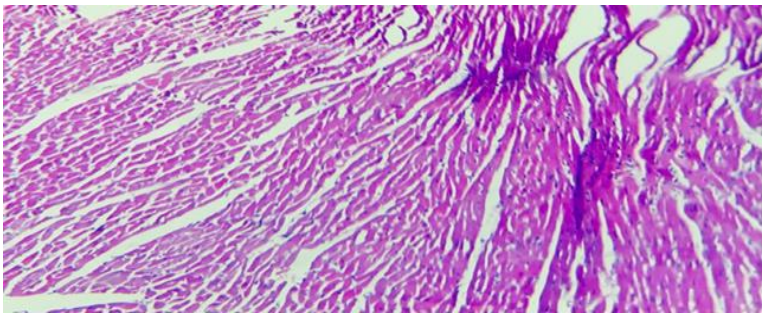

Figure 6: Other SE+DOXO-treated rat, with score 0, no damage in H&E (*100)

The present study showed a protective effect of selenium against the cardiotoxicity induced by anticancer drug. Several studies have examined serum selenium levels with cardiovascular disease [11-13]. SE fights against cancer and cardiovascular disease, controls inflammatory mediator levels, supports bone homeostasis, and prevents bone loss (Table 3) [14, 15]. Also, these studies show different mechanisms revealed the cardio protective-effects of SE by its antioxidant capabilities, capacity to inhibit inflammation, autophagy, and intrinsic and extrinsic apoptotic pathways (Table 4). According to the collected data, treatment with selenium for about two weeks was able to reduce the severity of cardiac damage caused by Doxo. This was shown by a lower level of cTn-1 in the selenium-doxorubicin treated group in comparison to the Doxo-group (Figures 1, 2, 3 and 4). These result in agreement with previous research has been done, as far as we are aware, examining the influence that selenium has on cardiac troponin [16-18]. In our study, it was shown that SE therapy significantly ameliorated the lipid peroxidation in the heart tissue, as indicated by the increasing SOD level, and maintained the antioxidant status, as expressed by GSH, in comparison to DOXO-induced and untreated rats. Recent studies have shown that many forms of SE reduce the toxicity of many parts of the body that are affected by other toxic drugs [19, 20]. That reflected, Se, in reality, works as an antioxidant, inhibiting the oxidation of lipids and lipoproteins in cell membranes. Other study, discovered ultrastructural alterations in animal heart tissue as a result of drugs treatment [21-30]. In our study SE treatment was proven to reduce the inflammatory response associated with DOXO-induced cardiotoxicity, as revealed by a significant decrease in cardiac ICAM-1 when compared to the DOXO group. The findings of this study is in agreement with recent studies by Shalihat *et al*., 2021 [31] and Gunes *et al*., 2017 [32], shows the protective benefits of selenium on cell survival found that selenium improves antioxidant-activity and inhibits inflammation-pathways.

According to the findings of the current study, the administration of SE for three days prior to treatment with DOXO and for a total of two weeks afterward protected the heart from DOXO-induced apoptosis [33]. This was shown by a significant reduction in the level of capase-3 in cardiac tissue when compared to the group that received only DOXO. In a study published by Wu *et al*., (2019) [34, 35], it was shown that the anti-apoptotic effects of SE have also been demonstrated in the cardio-myocytes of adult rats (Figures 5 and 6). This study found that the antiapoptotic-effects of selenium were associated with the attenuation of casp-3 activation and the prevention the DOXO-induced CMYO. Also, the histological findings showed that SE may has the ability to attenuate the lesions of cardiac tissue caused by DOXO, as evidenced by a significant improvement in CMYO-severity score as compared to the DOXO only group.

Conclusions: At the doses used in this study, selenium revealed the protection of the rats-hearts from DOXO-induced cardiotoxicity. This may relate to its interfered with oxidative stress, the inflammatory response, and the apoptotic pathway.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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