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Original Article

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

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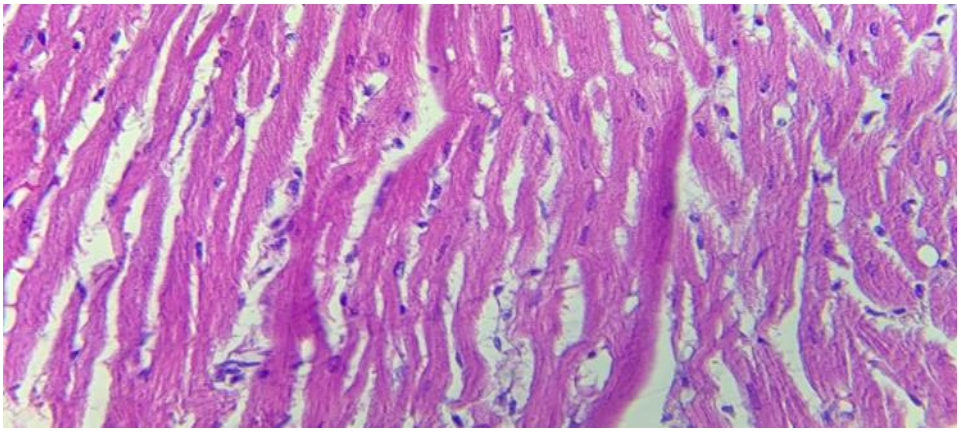
ABSTRACT

Empagliflozin (EMPA), a selective inhibitor of sodium-glucose cotranspoter2 (SGLT2), mainly regulates blood glucose levels. Many different mechanisms illustrated the significant impact on HD with CVs-outcomes that were unexpected. Specialists have speculated that it could be unrelated to lowering BG levels. The study aims to investigate if empagliflozin has promised a protective effect against the cardiotoxicity induced by doxorubicin in laboratory rats. Male Sprague- Dawley-type rats that did not yet have diabetes were randomly allocated to one of four different groups**.** The control group was given physiological DW (2 mL), the second group was given EMPA, which was given by oral route at a dose of 10 mg per kg, and the DOXO-group was given cumulatively 15 mg/kg of body weight DOXO, given by IP route at a dose of 2.5 mg per kg. The DOXO and EMPA were administered to the EMPA+DOXO group. Doxorubicin caused cardiotoxicity, which was shown by a significant increase (P< 0.001) in the levels of cTn-1, ICAM-1, and caspase-3. At the same time, the levels of GSH and SOD were significantly reduced- (P <0.001) in the cardiac tissues of rats in the doxorubicin-treated group compared to the control group. The drug also caused Histological changes and lesions. The administration of empagliflozin was found to reduce cardiotoxicity; this can be proved by significant decreases (p~< 0.001) in cTn-1, ICAM-1, and caspase 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 of CMYO and lesions. In the dosages used in this study, empagliflozin protected the hearts of rats from DOXO-induced cardiotoxicity. This may be related to the interfered^ and ameliorated oxidative stress, the inflammatory response, and the apoptotic pathway.

GRAPHICAL ABSTRACT



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Introduction

Empagliflozin (EMPA), a selective inhibitor of the sodium-glucose co-transporter 2, is especially effective at regulating blood-sugar levels [1]. Compared to conventional optimum therapy, this has significantly decreased HBA1c levels and weight and blood pressure [2]. It prevents the kidney's glucose transporters from taking up glucose again [3]. EMPA has been shown to reduce the risk of adverse cardiac events and death from cardiovascular disease in people with and without diabetes, making these drugs a viable option for people suffering from chronic heart failure [4]. Cardiac dysfunction is a common and severe side effect of cancer chemotherapy that seriously impacts the prognosis and quality of life of tumor patients [5]. Cardiac damage is a potential short-term or long-term complication of various anticancer treatments.

DOXO, commonly used to treat leukemia, lymphoma, breast cancer, and other solid tumors, has been linked to cardiac toxicity [6]. Doxorubicin as HCL intercalates between DNA bases, preventing DNA replication and protein synthesis. Besides that, doxorubicin stops topoisomerase-2 from working, making the enzyme complex and DNA more stable during DNA replication. The drug effects on DNA and keeps nucleotide strands from joining after a double-strand break [7, 8]. In addition, by oxidizing cell membrane lipids, doxorubicin generates oxygen free radicals, which contribute to the toxicity of anthracycline antibiotics, such as cardiac and cutaneous vascular effects [9]. There is currently no one medicine with an actual cardioprotective effect on DOXO toxicity that is free of side effects, reduces the sensitivity to cancer treatment, and or increases –the incidence of cancers. As a result, we examined the effectiveness of empagliflozin in cardiotoxicity and explored the effects in the hearts of male rats. The study aims to investigate if empagliflozin has an effect on the cardiotoxicity induced by doxorubicin in laboratory rats.

Materials and Methods

Thirty-two male rats, 3month age and weight (150-200 G), were used, and they were randomly separated into four groups (8-rats in each group). Moreover, during the experiment, the rats in the control group were treated with distilled water. In the doxorubicin group (the induced group), 2.5 mg per kg was given three times a week for two weeks to each rat. EMPA-group was only given a dose of 10 mg/kg and treated with EMPA for two weeks. Selenium with Doxo group (induced pretreated) n= 8, the group treated with EMPA was administered orally at a dose of 10 mg/kg, and induction with 2.5 mg /kg Doxo IP (for 2 weeks, EMPA, commenced 3 days before Doxo-administration). Doxo (induced) group, Doxo was given the same way as in the other groups. After 48 hours had passed since the previous injection of the anticancer drug, the body weight of each animal was recorded, and all materials and their provider show in Table 1. We utilized ketamine at a dosage of 100 mg/kg and xylazine at a dose of 10 mg/kg for rat anesthetizing. Blood was collected directly from the left heart's left ventricle; the blood was centrifuged, and the serum was collected and frozen in deep freeze until tested. The parameters, such as cardiac troponin I (cTnI), inflammatory parameters, and apoptotic markers by ELISA-kits. Hearts were taken out; the bottom part was used to make tissue homogenate to measure oxidative stress parameters, while the top was used for histopathological assessments.

Results and Discussion

The result showed that Doxorubicin-caused cardiotoxicity, which was shown by a ~significant increase (~P< 0.001) in the levels of cTn-1, ICAM-1, and caspase-3. Compared to the control group, at the same time, the levels of GSH and SOD showed a significant reduction (~P <0.001) in –the- cardiac- tissues of rats in the doxorubicin group. The drug also caused Changes in histological lesions. The administration of EMPA was found to reduce cardiotoxicity, as evidenced by a significant decrease (p<0.001) in cTn-1, ICAM-1, and caspase-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 of CMYO and lesions near in appearance to control group (Figure 1).

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

Table 1: Reagents, chemicals, and pharmaceuticals, as well as the companies that provide them

Providers	Pharmaceutical and reagents
Jardiance (Ingelheim am Rhein, Germany)	Empagliflozin
Pfizer, Australia	Doxorubicin (Vial of 50mg/25mL Adriamycin as HCL)
Sunlong, China, SL1366Ra	Caspase 3 - kit
ABO, Switzerland	Triton –X-100
Alfasan, Holland	Xylazine
Sunlong, China	ICAM-1 Kit
Trittau. Germany	Ketamine
Sunlong, China, NO.:SL1341Ra	SOD Kit
Sunlong, China	GSH Kit
Pioneer, Iraq	Normal saline 0.9%
Sunlong, China, NO.:SL0713Ra	Cardiac troponin -1 Kit
Promega, USA	Cocktail of protease inhibitor

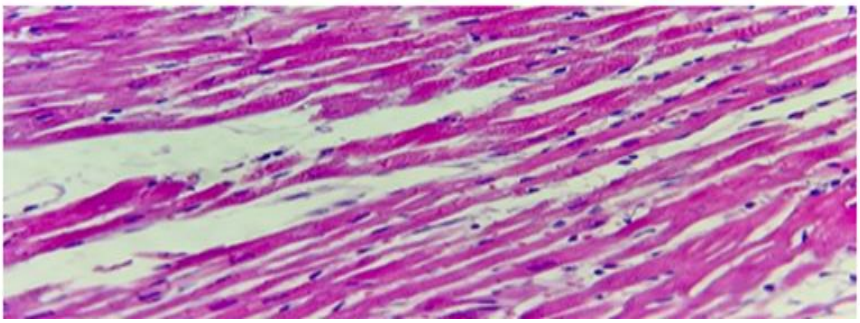

Figure 1: The structure of the muscle -cells in the myocardium of the control rats- was normal, with a score 0, and normal histology H&E (*400)

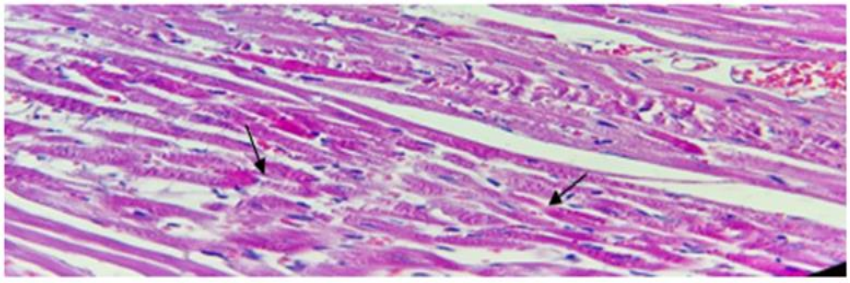

Figure 2: Doxorubicin group with score 4, the cardiotoxicity manifested by disorganization of myocardial fibers, represented by the arrow showed in H&E (100*)

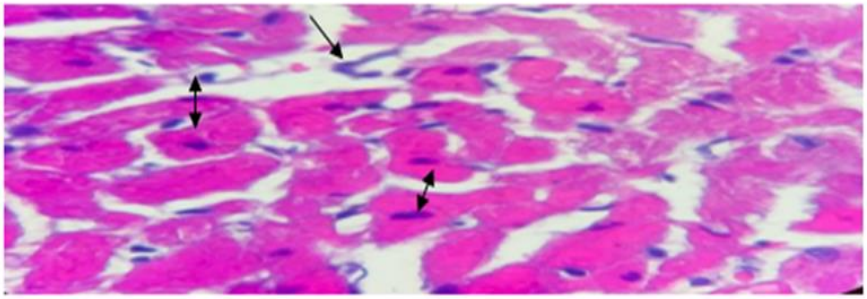

Figure 3: Doxorubicin group with a score of 4, the cardiotoxicity manifested by Cellular swelling, deep cytoplasmic eosinophilia, some with pyknotic nuclei, represented by the arrow and others with nuclear lysis (necrotic cell) in H&E (*400), represented as the arrow

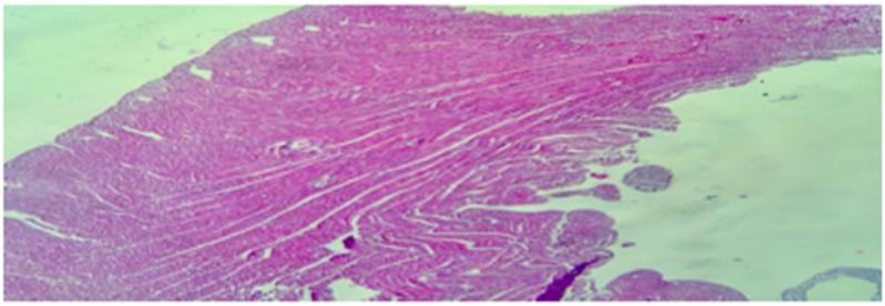

Figure 4*:* Treated group EMPA+DOXO, with score 1, histology manifested by normal organized myocardial fibers in H&E (*100)

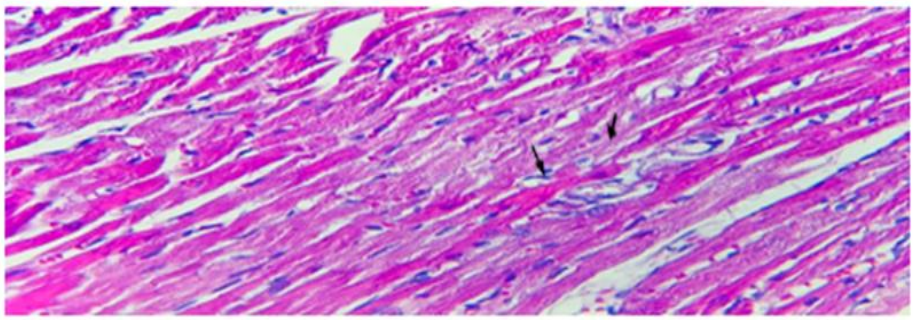

Figure 5*:* Treated group EMPA+DOXO, with score 1, histology manifested by mild cellular swelling, represented as the arrow H&E (*400)

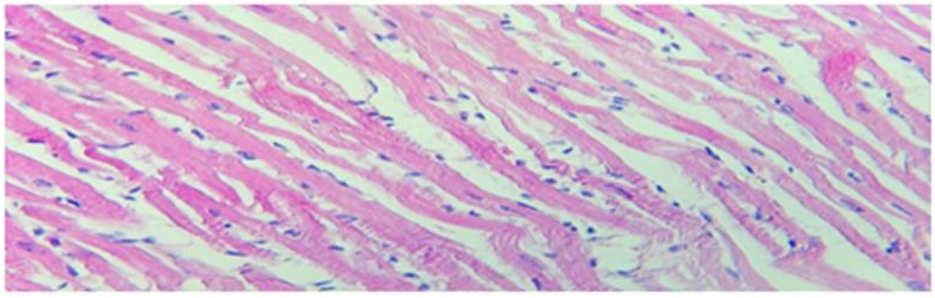

Figure 6: Other treated (EMPA+DOXO) group with normal cardiac muscle Histology, score 0 with no damage shown in H&E (*400)

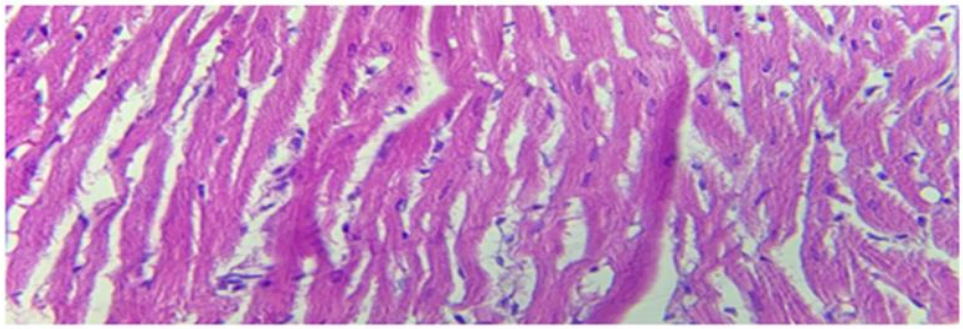

Figure 7: EMPA-only-treated rats, with a score 0, have no damage in H&E (*400)

The present study showed the protective effect of empagliflozin against the cardiotoxicity induced by the anticancer drug (doxo). Doxo- is booming in solid tumors and hematologic malignancy; however, cardiac damage and dysfunction development restrict its clinical usage [7]. Much research designed to explain DOXO's cardioprotective mode of action has focused on its anti-inflammatory qualities and their impact on the Na+ and Ca++ pathways in combination with anticancer drugs [10-12]. This makes our findings much more important since they show the immediate effect of the significant decrease in troponin-1 in Table 2**.** Similarly, another study by

Quagliariello *et al*., [13] showed the direct cardiac effects of SGLT2i by reducing ferroptosis, fibrosis, apoptosis, and inflammation in doxorubicin-treated animal models by involving NLRP3 and other-related pathways, which led to significant improvements in cardiac functions through improve ICAM-1 level as show in Table 3. Also, Empagliflozin's cardio-protective impact was AMPK activation-mediated energy repletion in the serum and heart tissue compared to the control group [14].

Table 2: Effect of Cardiac-Troponin I (cTn-1) in four- experimental groups after 2 weeks

Group	Cardiac troponin-1
Control	8.458 ± 0.40
Empagliflozin	8.199 ± 0.2945
Doxorubicin	16.81 ± 0.39***
EMPA+ DOXO	8.985 ± 0.5210 +++

-Values are M±SEM for eight rats in- each group

+++P < 0.001 groups. V.S. DOXO group

***P< 0.001 group VS. control & EMPA group

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

ICAM-1	Group
74.55 ± 2.264	Control
73.89 ± 3.218	Empagliflozin
143.4 ± 5.614 ***	Doxorubicin
80.79 ± 1.933 +++	EMPA+ DOXO

--Values are M ±SEM for eight rats in each group

+++ P < 0.001 groups. V.S. DOXO group

*** P< 0.001 group V.S. control & EMPA group

Recent studies revealed that empagliflozin's antioxidant capacity reduced oxidative stress indicators (MDA and NO) and restored antioxidant mechanisms (GSH and SOD) [15]. As well as this study shows the immediate effect of the significant increase in SOD and GSH percent in cardiac tissues from the Doxo-group treated with EMPA showed in Table 4. In addition to its effects on diabetes, empagliflozin has also been proven by many studies to possess a variety of anti-inflammatory activities [15-17]. On the other hand, empagliflozin has been shown to protect the heart against the damage that can be caused by doxorubicin due to ameliorated ion homeostasis, oxidative stress, and endothelial dysfunction [18]. Empagliflozin, on the other hand, was demonstrated to enhance cardiac function and cardiac remodeling after MI in another research. This was accomplished by attenuating oxidative stress, reducing cardiomyocyte apoptosis, and maintaining the integrity of mitochondrial membrane potential through activation of the AMPK signaling system (Figures 2, 3) [19-24]. This similarity in findings, as in our current finding showed that EMPA might inhibit the processes of cell apoptosis, as revealed by a significant decrease in caspase-3 levels in cardiac tissue cardiac tissue as compared to the DOXO alone group as in Table 5. Similar results were observed separately in diabetic mice by reducing oxidative stress and via AMPK's role in inhibiting the mitochondrial fission process [20, 21]. As a result, increased diastolic performance was associated with better glycemia and positive LV remodeling, such as decreased interstitial myocardial fibrosis and attenuation of cardiomyocyte-hypertrophy [22-28]. In agreement with the previous findings, we found EMPA may reduce myocardium changes in rats (male rats) with DOXO-induced CMYO- who were also given empagliflozin as showed in Figures 4, 5, and 6. However, our findings expand those findings to show a protective effect in non-diabetic persons, opening up promising new possibilities for the prevention and treatment of anthracycline-induced cardiotoxicity in patients

receiving anti-tumoral chemo-therapy, such as in breast-cancer patients (Figure 7) [29-34].

Table 4: Effects on the antioxidant enzyme activation (SOD) & Glutathione (GSH) level in four groups after 2 weeks

Glutathione (GSH)	Superoxide dismutase (SOD)	Group
19.82 ± 0.724	228.3 ± 3.1	Control
20.86 ± 1.119	228.3 ± 3.294	Empagliflozin
9.195 ± 0.65 ***	158.2± 9.6***	Doxorubicin
19.63 ± 0.766 +++	223.8 ± 3.390 +++	EMPA+ DOXO

--Values are M ±SEM for eight rats in each group
+++ P < 0.001 groups. V.S. DOXO group
***P< 0.001 group VS. control- & EMPA-group

Table 5: Effect on the - caspase-3(CASP3) in four-experimental groups after 2-weeks

Group	CASP3
Control	0.05083 ± 0.00171
Empagliflozin	0.04800 ± 0.00215
Doxorubicin	0.1021 ± 0.00275 ***
EMPA+ DOXO	0.05763 ± 0.00177 + ++

Values are Mean ± SEM for eight rats in each group
+++P < 0.001 groups VS. DOXO group
***P< 0.001 group V-S. control & EMPA -group

Conclusion

At the doses used in this study, empagliflozin revealed the protection of the rats' hearts from DOXO-induced cardiotoxicity. This may have been related to the alteration and ameliorating of the 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.

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