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Evaluate the effect of dapagliflozin in the prevention of doxorubicin-induced acute cardiotoxicity in rats

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Abstract

Cancer ranks second in frequency among non-communicable diseases after cardiovascular disorders. The increased life expectancy has made cancers more common, making it crucial to avoid side effects of the medications used to treat them. SGLT2i medications lower the risk of significant cardiovascular events and heart failure-related hospitalizations, as shown in clinical trials. Dapagliflozin is one such medication that is primarily regulated by blood glucose levels but may also impact cardiac disorders through other processes. This study will evaluate the potential protective effects of Dapagliflozin on DOX-induced cardiotoxicity in female rats, manifested by changes in biochemical parameters in tissue and serum samples, histopathological differences, and compare their changes. Twenty-four rats were divided into three weight-based groups. The first group received saline, the second group received doxorubicin, and the third group received dapagliflozin for three days before receiving doxorubicin for two weeks. Doxorubicin causes cardiotoxicity, as evidenced by increased caspase-3 and inflammatory markers. Dapagliflozin reduces cardiotoxicity by increasing SOD and GSH and decreasing caspase 3, as well as improving the CMYO score and lesions. Dapagliflozin successfully mitigated DOX-induced cardiotoxicity in rats at the concentrations utilized in this investigation. This phenomenon potentially pertains to inhibiting and safeguarding against oxidative stress, the pathway of apoptosis, and the inflammatory response.

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Introduction

With 17.9 million cases globally, cancer ranks second in terms of frequency among non-communicable diseases behind cardiovascular disorders. As a result of the increased life expectancy, cancers are more common, making it more crucial to avoid the side effects of the medications used to treat them. These four diseases, along with respiratory system disorders and diabetes, account for 80% of early deaths from non-communicable diseases. Cardiac toxicity is an emerging concern that is linked to the utilization of diverse classes of chemotherapeutic agents, which negatively impact prognosis and quality of life (WHO, 2022). We believe there are minimal additional interventions to safeguard the heart during the asymptomatic phase as opposed to when complications arise. As a result, additional reasonable research and development into cardioprotective adjuvants is crucial in this instance of limited clinical application (Liu *et al.*, 2020).

The adverse impact of various classes of chemotherapeutic agents on prognosis and quality of life has led to an increasing concern regarding cardiac toxicity (Pizzino *et al.*, 2014). Chemotherapy-induced cardiac dysfunction is a significant reason for patient mortality and morbidity (Yeh *et al.*, 2004; Ferlay *et al.*, 2013). Doxorubicin has a dual impact. It is effective in treating tumors, but its chronic use causes cardiomyopathy and heart failure; scientists are trying to find cardioprotective agents to combat doxorubicin-induced cardiotoxicity without compromising its efficacy (Liu *et al.*, 2020).

Thorough randomized clinical trials have shown that a selective inhibitor of sodium-glucose cotranspoter2 (SGLT2i) medications, whether taken by people with or without type 2 diabetes, lowers the risk of significant cardiovascular events and heart failure-related hospitalizations. The principal regulator of blood glucose is SGLT2 dapagliflozin (DAPA). However, experts estimate that numerous other processes may also have a substantial effect on cardiac disorders, which may not always be associated with a reduction in blood glucose levels (McMurray *et al.*, 2019).

Patients with type 2 diabetes mellitus (T2DM) are being treated with a novel class of pharmaceuticals (SGLT2i). These drugs induce glucosuria, natriuresis, and diuresis by impeding glucose reabsorption in the proximal tubule of the nephron (Scheen, 2020).

Dapagliflozin was the first SGLT2 inhibitor to be granted approval for the management of type 2 diabetes (T2D) (Hasan *et al.*, 2014). A relatively new class of medications is antihyperglycemic agents (AHAs) that obstruct sodium-glucose cotransporter-2 (SGLT2) for the treatment of type 2 diabetes (T2D). (Hsia *et al.*, 2017; Scheen, 2015). Unlike insulin, SGLT2 inhibitor compounds promote glucose excretion in the urine by inhibiting the proximal convoluted tubule-localized high-capacity glucose transporter SGLT2. This mechanism of action opposes insulin. Consequently, glucose levels decrease in the absence of insulin action (Hsia *et al.*, 2017; Wilding *et al.*, 2018). Complementing other classes of AHAs, this distinctive mechanism of action of SGLT2 inhibitors permits their combination therapy with other AHAs, such as insulin. Among these SGLT2 inhibitors, dapagliflozin (Forxiga®) has received approval for treating T2D in numerous countries, including the European Union and the United States (Plosker, 2014).

In order to increase the use of doxorubicin as a highly effective chemotherapeutic agent, it is crucial to investigate potential medications that can mitigate its severe cytotoxic effects. This study aimed to assess whether dapagliflozin could have cardioprotective effects in preventing cardiac impairment following DOX administration.

Materials and methods

Twenty-four female Sprague Dawley rats, aged 10-12 weeks and weight (150-200g) have been used. After that, they were divided according to their weight into three groups, each containing eight animals. The rats in the control group were administered 0.9% normal saline. For duration of two weeks, 2.5 mg per kg of doxorubicin (DOX) was administered intraperitoneally to each rat in the induced group at three injections per week (Abdulkareem Aljumaily *et al.*, 2021; Hekmat *et al.*, 2021).

The dapagliflozin with doxorubicin-group (induced pretreated), DAPA given by oral route in a dose of 1mg/kg for three days prior and continued for two weeks in addition to doxorubicin administered in the same manner in the (induced) group (Belen *et al.*, 2022). Dapagliflozin (Astra-Zeneca®) was dissolved in a normal saline solution (Lahnwong *et al.*, 2020). After 48 hours of doxorubicin's last dose, rats were sacrificed in all groups, and the body weight of each animal was recorded (Oliveira *et al.*, 2013).

Anesthetizing the animal with ketamine (90 mg/kg) and xylazine (20 mg/kg) was performed. The gathered serum was placed in deep freeze until the inflammatory parameters, which were analyzed with Eliza-Kits (BT LAB®), could be determined. For histopathological analyses and the quantification of apoptotic and oxidative stress parameters, heart tissue samples were utilized.

The histopathological study was according to the severity levels of cardiomyopathy scores method as in studies by Oner *et al.* (2019) and Abdulkareem *et al.* (2021). The histological appearance collected each number in the scoring method as follows:

0 = No significant occupied lesion (SOL)

1= Mild pathological changes

3= Severe Pathological changes

4= Highly severe pathological changes

5= Tissue damage (Point of no return)

Statistical analysis

The statistical analysis was performed using GraphPad Prism version 8.1. One-way ANOVA test followed by the Bonferroni post hoc test was used to compare the markers and histopathological changes in different groups.

Results and Discussion

Table 1 indicate a significant increase ($p<0.0001$) of the caspase-3 enzyme activity in both the DOX and DOX + DAPA groups relative to the control group, whereas the DOX + DAPA group exhibited statistically significant decreases ($p<0.0001$) in comparison to the DOX group. The DOX group exhibited a statistically significant reduction in SOD levels (Table 2) when compared to the control group.

Table 1. Effects of apoptotic marker caspase-3 for three groups after two weeks

Bonferroni's multiple comparison tests	Mean ± SEM
Control	0.7672 ± 0.03141****
DOX	1.690 ± 0.06614 ***
DOX + DAPA	1.138 ± 0.07773 ####

The data are expressed as the mean ± standard error mean for eight rats in each group, One Way ANOVA with Bonferroni post hoc test. ((****P < 0.0001)) group VS. control group and ((####P < 0.0001)) groups VS. DOX group. DOX: Doxorubicin, DAPA: Dapagliflozin.

Table 2. Effects of oxidative stress markers SOD & GSH for three groups after two weeks.

Bonferroni's multiple comparison tests	Mean ± SEM for SOD	Mean ± SEM for GSH
Control	2.662 ± 0.1374 *	176.3 ± 3.360 ****
DOX	1.562 ± 0.1008 ns	100.8 ± 2.598 ns
DOX + DAPA	3.470 ± 0.2247 ****	165.8 ±7.342####

The data are expressed as the mean ± standard error mean for eight rats in each group, One Way ANOVA with Bonferroni post hoc test. ((****P < 0.0001)) group VS. control group and ((####P < 0.0001)) groups VS. DOX group. DOX: Doxorubicin, DAPA: Dapagliflozin.

Table 3. Effects of Inflammatory Markers ICAM-1& TNFα for three groups after two weeks.

Bonferroni's multiple comparison tests	Mean ± SEM for ICAM-1	Mean ± SEM for TNFα
Control	1.621 ± 0.1917 ****	124.8 ± 4.168 ****
DOX	2.750 ± 0.07003 ***	176.4 ± 4.854 ****
DOX + DAPA	2.380 ± 0.1187 ns	169.9 ± 3.341 ns

The data are expressed as the mean ± standard error mean for eight rats in each group, One Way ANOVA with Bonferroni post hoc test. ((****P < 0.0001)) group VS. control group and ((####P < 0.0001)) groups VS. DOX group. DOX: Doxorubicin, DAPA: Dapagliflozin.

Table 4. The Histopathological lesion scores on the rat's cardiomyopathy according to study groups.

Groups	Scores		
	Control	DOX	DAPA
Cardiac muscle fiber hypotrophy	0	0	0
Hydropic degeneration	0	0	1
Blood Vessels Congestion (BVC)	0	3	0
Inflammation (Acute Myocarditis)	0	4	0
Thrombosis	0	4	0
Myocardial infarction (coagulative necrosis)	0	5	0

However, the DOX+DAPA group did not differ significantly from the control group. In contrast, the group treated with DOX+DAPA showed a significant increase ($p<0.0001$) in SOD level compared to the DOX group. The data in the same table indicate a significant decrease ($p<0.0001$) in GSH levels in the DOX-treated group compared to the control group. Also, the group DOX+DAPA showed significantly ($p<0.0001$) higher GSH levels than the DOX group, and the DOX+DAPA group did not differ significantly from the control group. The data in (Table 3) indicates a statistically significant increase ($P<0.0001$) in the level of heart ICAM-1 in the DOX and DOX+DAPA groups when compared to the control group. In contrast, the DOX+DAPA group exhibited no statistically significant disparities when compared to the DOX group. Also, the TNFα level significantly increased ($p<0.0001$) in the groups treated with DOX, DOX+DAPA compared to the control group, while there were no significant differences between DOX group and DOX+DAPA group. The histopathological study was according to the severity levels of cardiomyopathy scores method was shown in Table 4.

Histopathological study

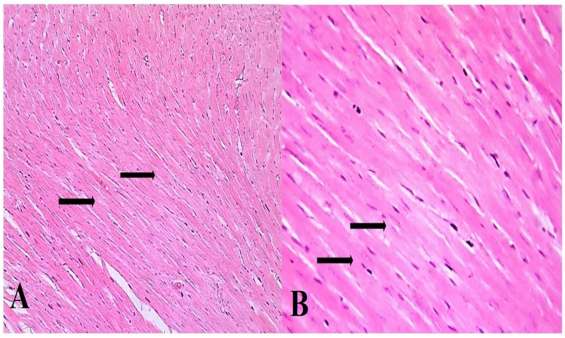

Fig. 1. The histological section with H&E stain of the rat's heart for the control group with magnification scale (A) 10X, (B) 40X.

The cardiac muscle fibers of the heart of a rat in the control group show normal texture and structure without significant occupied lesions (Fig. 1). In contrast, the doxorubicin-treated group had significant histopathological abnormalities, including severe damage in the muscle fibers as coagulative necrosis surrounded by a line of inflammatory cells. Also, due to cytoplasmic hydropic degenerative changes, several thrombi spots can be seen in the heart tissue as pinkish aggregation spots with pre-nuclear space as vacuoles (Fig. 2).

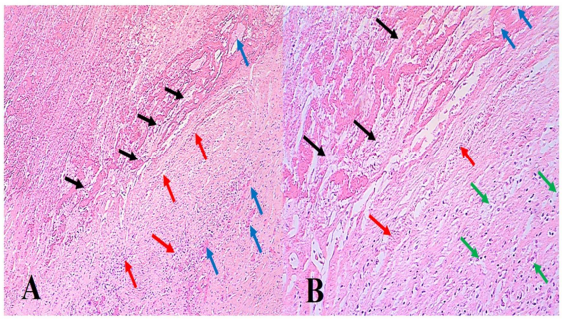

Fig. 2. The histological section with H&E stain of the rat's heart for the DOX group with magnification scale (A) 10X, (B) 40X.

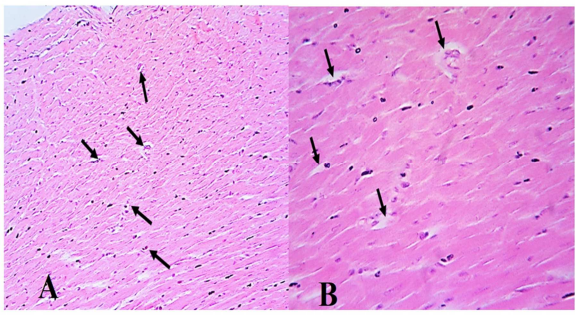

Fig. 3. The histological section with H&E stain of the rat's heart for the DAPA group with magnification scale (A) 10X, (B) 40X.

In addition, the myocardial lesions were significantly different from those of the control group. The Myocardial lesions were significantly reduced from 80% in the DOX group to 15% in the DAPA-treated group (Fig. 3).

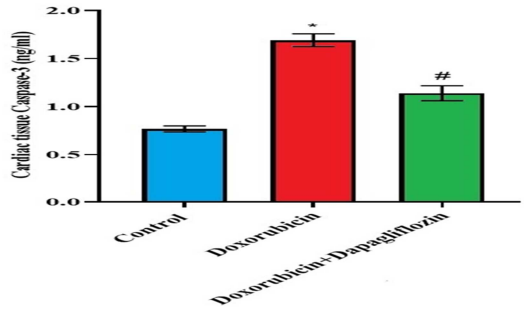

Fig. 4. Caspase-3 level in heart tissue of the experimental groups.

The current study (Fig. 4) indicates increased caspase-3 activity following doxorubicin treatment compared to the control group, which agreed with a recent study **(**Albakaa *et al.*, 2023**)**. The pathophysiology of doxorubicin-induced cardiotoxicity has been associated with apoptosis as the increase in caspase-3 activation in rats following doxorubicin treatment is consistent with reported recent studies (Mobaraki *et al.*, 2017; Nicol *et al.*, 2021). The increased caspase-3 level for the DOX + DAPA and DOX groups compared to the control group these findings agreed with the Chang study (Chang *et al.*, 2021); DOX treatment increased proapoptotic proteins, but dapagliflozin suppressed protein expression in rats. Dapagliflozin can help prevent cardiotoxicity in diabetic cancer patients (Chang *et al.*, 2021; Shibusawa *et al.*, 2019).

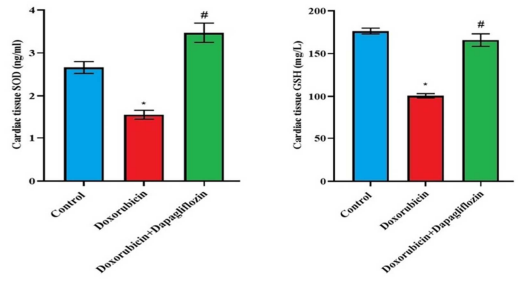

Fig. 5. Oxidative stress marker levels in the heart tissue of the experimental groups.

Two pathways have been implicated in apoptosis: the death receptor and the mitochondrial pathways. Mitochondria dysfunction induces the release of cytochrome C, which triggers caspase-9 and caspase-3, ultimately resulting in intranucleosomal DNA fragmentation and the concluding stages of apoptosis (Jiang and Wang, 2004; Wu *et al.*, 2002). Caspase-3 activation due to DOX leads to impaired mitochondrial function and apoptosis. SGLT2i may offer cardiac protection by reducing caspase-3 activity through renin-angiotensin system inhibition, anti-inflammatory and antioxidant effects, and reduced sympathetic overactivity (Bertero *et al.*, 2018; Lahnwong *et al.*, 2018).

In comparison to the control group, doxorubicin significantly increased lipid peroxidation levels in rats, as measured by a decrease in concentrations of GSH and SOD in cardiac tissue (Fig. 5).

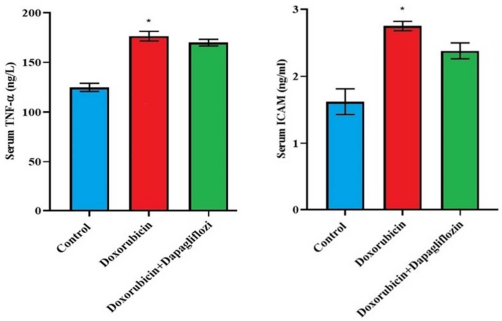

Fig. 6. Inflammatory Markers level in heart tissue of the experimental groups.

A recent study (Ko *et al.*, 2023) found that the DOX+DAPA group exhibited more favorable results in comparison to the DOX-only group, which refrained from utilizing alternative drug combinations. Due to many complex molecular mechanisms, doxorubicin induces carcinogenicity (Hassani *et al.*, 2021). An imbalance between the antioxidant defense system of the body and the production of reactive nitrogen species (RNS) and reactive oxygen species (ROS) results in oxidative stress. Cardiolipin, a phospholipid located in the mitochondrial membrane, employs its strong affinity for DOX to facilitate the dysfunction of mitochondria caused by oxidative stress (Aryal and Rao, 2016; Antonucci *et al.*, 2021). Expression of inflammatory cytokines could be directly induced by oxidative stress; this effect was substantially amplified following doxorubicin injection (Wang *et al.*, 2016). In accordance with the aforementioned results, pro-inflammatory cytokine levels (TNF-), VACM-1, and ICAM-1 were substantially elevated in rodents

induced with doxorubicin, whereas they were notably decreased in groups that received treatment (Ma *et al.*, 2017).

During cancer chemotherapy, doxorubicin has been shown to cause inflammation in the heart; it was revealed in these current investigations that doxorubicin administration raises ICAM-1, as demonstrated with Doxorubicin treatment significantly increased heart ICAM-1 level and TNFα level in rats compared to the control group; that agreed with the results of recent studies (Malek *et al.*, 2019; Alyasiry *et al.*, 2022). The upregulation of TNF- , ICAM-1, and caspase-3 in cardiac tissues indicates inflammation and apoptosis induced by DOX. The group receiving dapagliflozin treatment showed significant decreases in plasma concentrations of CTnT, pro-BNP, and TNFα compared to the DOX control group ($P<0.001$) (Belen *et al.*, 2022).

Recent research (Chen *et al.*, 2023; Reis-Mendes *et al.*, 2021) indicates that pretreatment with DAPA substantially reduced the proportion of myocardial infarction size and histopathological alterations. According to these results, Dapagliflozin may reduce the damage induced by myocardial ischemia/reperfusion and enhance cardiac function in rats. In non-diabetic rodents, dapagliflozin can ameliorate DOX-induced cardiac dysfunction and pathological changes. This result suggests that dapagliflozin may have the potential as a preventative measure against myocardial harm that may occur during cancer treatment (Belen *et al.*, 2022). Due to the critical involvement of inflammation in developing left ventricular dysfunction and heart failure, dapagliflozin demonstrates efficacy in DOX-induced cardiac dysfunction due to the significant decrease in TNF-α levels. This finding opposed our own (Fig. 6), as the DOX+DAPA group exhibited no significant difference from the DOX group. Unlike the majority of currently available glucose-lowering agents, SGLT2I reduces tissue inflammation. Atherosclerosis-associated inhibitory effects of SGLT2I on the expression of circulating inflammatory molecules, such as TNFα, MCP-1, PECAM-1, VCAM-1, ICAM-1, IL-1β, and IL-6, were observed in mouse models (Spigoni *et al.*, 2020; Dimitriadis *et al.*, 2019).

Conclusion

Dapagliflozin successfully mitigated DOX-induced cardiotoxicity in rats at the concentrations utilized in this investigation. This phenomenon potentially pertains to inhibiting and safeguarding against oxidative stress, the pathway of apoptosis, and the inflammatory response.

Recommendations

Our recommendations are as follows, in accordance with the findings of this study: Additional clinical investigations are suggested in this study to explore the potential of dapagliflozin to prevent cardiotoxicity induced by doxorubicin, examine the effects of dapagliflozin on echocardiographic and cardiac hemodynamic parameters in groups treated with doxorubicin, conduct western blot or immunohistochemical analysis of pro-apoptotic molecules (e.g., Bax) and antiapoptotic Bcl2 expression in cardiomyocytes to assess apoptosis in cardiomyocytes and conduct a longer-term study with a higher dapagliflozin dose.

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