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Effect of gemfibrozil on cardiotoxicity induced by doxorubicin in male experimental rats

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ABSTRACT

Cardiotoxicity is an adverse effect of the anticancer drug doxorubicin (DOX). Gemfibrozil (GEM) is a lipid-lowering drug with a number of biological properties such as anti-inflammatory and antioxidant activities. Therefore, we decided to investigate the effect of GEM on DOX-induced cardiotoxicity in rats. Twenty-eight adult male Wistar rats were divided into four experimental groups as follows: Group I received normal saline (2 ml/kg) orally for 14 days, group II received DOX (2.5 mg/kg; in six injections; accumulative dose: 15 mg/kg) intraperitonially for 14 days, group III received DOX + GEM (100 mg/kg) orally for 14 days concomitantly with DOX administration, and group IV received GEM orally for 14 days. Lipid panel, various biochemical biomarkers, and histological observations were evaluated in serum and heart samples. According to our results, DOX significantly increased the levels of lipid panel (triglycerides, total cholesterol, and low-density lipoproteins cholesterol) as well as markers of cardiac dysfunction (Aspartate aminotransferase, Creatine kinase-muscle/brain, Lactate dehydrogenase and Cardiac Troponin I). Moreover, DOX significantly increased malondialdehyde and nitric oxide levels in cardiac tissue. Furthermore, administration of DOX reduced the level of glutathione as well as the superoxide dismutase, catalase, and Glutathione peroxidase activities. DOX-treated rats showed significantly higher tumor necrosis factor-α and interleukin-1β. GEM administration significantly attenuated the lipid panel and biochemical biomarkers in DOX-treated rats. Our results were confirmed by histopathological evaluations of the heart. Based on our findings, GEM is a promising cardioprotective agent in patients treated with DOX through mitigative effects on biochemical markers and oxidative stress indices.

1. Introduction

The doxorubicin (DOX) is an anthracycline glycoside antibiotic and an anticancer drug that cause DNA intercalation as well as inhibit the DNA replication [1]. DOX has a wide spectrum of antineoplastic activity such as breast cancer, leukemia, and sarcoma [2]. One of the most common adverse effects of DOX is cardiotoxicity which is clinically manifested as congestive heart failure [3]. Although the exact mechanisms underlying cardiac toxicity induced by DOX are not completely understood several reports confirmed that DOX increases the inflammation and oxidative stress in the heart [4]. DOX induced-cardiotoxicity is a limiting factor for using the maximum allowable dose of DOX during anticancer treatment [5]. Therefore, using a compound or drug alongside the DOX is helpful to attenuate the DOX-induced cardiotoxicity [3]. It seems that antioxidant and anti-inflammatory compounds or drugs such as resveratrol, quercetin and nicorandil have protective effects on DOX-induced cardiotoxicity via preventing the oxidative damage as well as increasing the antioxidant capacity and reduced the inflammation processes [6–8].

Fibrates such as gemfibrozil (GEM) are agonists of peroxisome

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proliferator activated receptor- α (PPAR-α) which mainly reduce the triglyceride levels of plasma [9]. GEM is among the most widely prescribed drug for patients with hypertriglyceridemia and mixed dyslipidemia [10]. In addition to this well-established property, GEM exerts a wide range of pharmacological properties such as antioxidant and anti-inflammatory effects which may extend its clinical indications [11,12]. It is well established that GEM inhibits the production and releasing of inflammatory mediators including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) [11,13]. Also, it has shown that GEM decreased oxidative stress and inflammation in a model of diabetes-associated atherosclerosis [12]. It was demonstrated that fenofibrate (other fibrates which also a PPAR-α activator) has a cardioprotective effect in autoimmune myocarditis via reducing the inflammation [14].

In the current context, we assessed the ability of GEM to prevent cardiotoxicity induced by DOX, based on biochemical indices, oxidative stress parameters, and pathological alterations.

2. Materials and methods

2.1. Animals

Twenty-eight healthy adult male Wistar rats (200 ± 10 g) were used in this study. The rats were purchased from the animal house of Ahvaz Jundishapur University of Medical Sciences. Animals were housed with free access to water and food, a 12-h dark/light cycle (light from 8:00 to 20:00) with the temperature kept constant at 22 ± 2 °C [15]. The experimental procedures were conducted according to the Animal Ethics Committee Guidelines for the use of experimental animals (Ethic code: IR.AJUMS.REC.1396.41).

2.2. Drugs and experimental design

DOX (EBEDOXO®) was obtained from EBEWE Company (Austria) and GEM were purchased from Abidi Pharmaceutical Company (Iran).

After 2 weeks of acclimatization animals were aliquoted into four groups (n = 7).

Group I received normal saline (NS; 2 ml/kg) orally for 14 days.

Group II received DOX (2.5 mg/kg) intraperitoneally (i.p.) in six injections over a 2 weeks period (cumulative dose:15 mg/kg) [6].

Group III received GEM (100 mg/kg; orally) for 14 days concomitantly with DOX treatment (with the same dose in the aforementioned group) [16].

Group IV received GEM (with the same dose in the aforementioned group).

2.3. Sample collection

One day after the last administration, the rats were anesthetized with i.p. injection of ketamine (80 mg/kg) and xylazine (8 mg/kg). Then, the blood samples were collected from the left ventricle. The blood samples were centrifugated at 3000 rpm for 10 min to separate the serum and stored at −20 °C for lipid profile and biochemical analysis.

Then animals were decapitated, the heart tissues were isolated and washed with ice-cold saline quickly. Each heart was divided into two parts. One part was used for pathological study which fixed in 10% phosphate-buffered formalin. The second part was used for other biochemical study which minced and homogenized (1/10 w/v) with Tris−HCl buffer (100 mM, pH 7.4). Then, the homogenate was centrifuged (6000 rpm, 20 min, 4 °C) and the supernatant was collected and stored at −80 °C.

2.4. Serum analyses

Lipid panel and markers of cardiac dysfunction were measured in serum samples. Serum total cholesterol, triglycerides, high-density lipoproteins cholesterol (HDL-c) and low-density lipoproteins cholesterol (LDL-c) levels were determined by using a biochemical autoanalyzer (MINDRAY, PR China) with respective test kits (Technicon, Bayer S.A. Diagnostic). Aspartate aminotransferase (AST) activity was determined by the Reitman and Frankel method [17]. Creatine kinase-muscle/brain (CK-MB) activity was determined by the Bishop method [18]. Lactate dehydrogenase (LDH) activity was determined by the Whitaker method [19]. Cardiac Troponin I (cTnI) level was determined by an ELISA Kit specific for rats, following the manufacturer's protocol (MyBioSource, USA; Catalog number: MBS727624).

2.5. Biochemical analyses

The antioxidant enzyme, markers of oxidative stress and inflammatory cytokines were measured in supernatant samples. The total protein content was determined according to the method described by Bradford [20].

The catalase (CAT) activity was estimated by the Aebi et al. method [21]. The superoxide dismutase (SOD) activity was estimated by the Martin et al. method [22]. The glutathione (GSH) content was estimated by the Ellman et al. method [23]. Glutathione peroxidase (GPx) activity was estimated by a glutathione peroxidase kit specific for rats, according to the manufacturer's protocol (ZellBio GmbH, Germany).

Cardiac lipid peroxidation was estimated by the Buege and Aust method via measuring the malondialdehyde (MDA) levels [24]. Cardiac nitric oxide (NO) level was estimated by the Griess assay [25].

The concentrations of TNF-α and IL-1β in the cardiac tissue homogenate supernatant was measured by ELISA kit specific for rats, according to the manufacturer's protocol (IBL company; TNF-α catalog number: 27,194 and IL-1β catalog number: 27,193).

2.6. Histopathological evaluations

The heart samples were embedded in paraffin, sectioned (thickness: 5 μm) and stained with hematoxylin and eosin dyes (H&E) for light microscopic examinations. Six microscopy slides per animal were examined for assessment of histopathological changes such as nuclear pyknosis, inflammatory cell infiltration, myocardial disorganization, and myofibrillar loss.

2.7. Statistical analysis

GraphPad Prism software data analysis program version 6 was used for statistical analysis (GraphPad Software, USA). Data were analyzed by one-way analysis of variance (ANOVA) and presented as means ± standard deviation (SD). Individual differences were determined by Tukey's post hoc test. A value of less than 0.05 was considered statistically significant.

3. Results

3.1. Effects of DOX administration on serum, biochemical and histopathological alternations in rats

In our study, DOX cardiotoxicity was confirmed in several aspects. The DOX-treated rats showed significantly higher total cholesterol, triglyceride, and LDL-c and significantly lower HDL-c compared to the control group ($p < 0.001$ in all groups) (Table 1). The levels of cardiac dysfunction markers such as AST, LDH, CK−MB, and cTnI were markedly increased in the DOX-treated rats than their corresponding control ones ($p < 0.001$ in all groups) (Fig. 1). The NO and MDA levels of the heart were higher in the DOX group in comparison with the control animals ($p < 0.001$ in all groups) (Fig. 2). Rats receiving DOX also demonstrated a significant decrease in GSH level as well as the activity of GPx, SOD, and CAT than control group ($p < 0.001$ in all groups)

Table 1
Effect of gemfibrozil on lipid panel in doxorubicin-induced cardiotoxicity in rats.

	NS	DOX	DOX + GEM	GEM
Total cholesterol (mg/dL)	84.30 ± 6.30	146.6 ± 10.90***	127.6 ± 9.40##	81.70 ± 5.50
Triglyceride (mg/dL)	95.23 ± 7.52	285.7 ± 18.45***	173.6 ± 12.65###	84.12 ± 6.80
LDL-c (mg/dL)	17.53 ± 3.20	43.56 ± 5.95***	30.10 ± 4.40###	15.75 ± 2.50
HDL-c (mg/dL)	38.12 ± 4.31	21.65 ± 3.94***	29.10 ± 4.13#	43.55 ± 5.57

Values are mean ± SD (n = 7).
Data were analyzed by one-way ANOVA followed by Tukey's post hoc test for multiple comparisons.
*Significant change with respect to NS group (***p < 0.001).
#Significant change with respect to DOX group (#p < 0.05; ##p < 0.01 and ###p < 0.001).

(Fig. 3). DOX group had higher pro-inflammatory cytokines (TNF-α and IL-1β) contents in comparison with their control counterparts (p < 0.001 in all groups) (Fig. 4). Moreover, pathological examination revealed cardiomyocytes damage of DOX-treated rats such as myocardial disorganization, loss of myofibrillar, red blood cells (RBCs) congestion and infiltration of inflammatory cell (Fig. 5B).

3.2. Effects of GEM administration on serum, biochemical and histopathological alternations in DOX-treated rats

Our results indicated that administration of GEM with DOX mitigated the cardiac damage of DOX. Administration of GEM significantly reduced total cholesterol (p < 0.01), triglyceride (p < 0.001) and LDL-c (p < 0.001) and significantly increased HDL-c (p < 0.05) in comparison with the DOX group (Table 1). GEM attenuated the effect of DOX administration on markers of cardiac dysfunction (AST, LDH, CK−MB, and cTnI) (p < 0.05 for CK−MB; p < 0.01 for AST and cTnI; p < 0.001 for LDH) which reflecting the amelioration of cardiotoxicity in DOX-treated rats (Fig. 1). Moreover, GEM treatment (100 mg/kg for 14 days) significantly reduced the MDA and NO levels in cardiac tissue (p < 0.01 in all groups) (Fig. 2). Rats receiving GEM in combination with DOX also demonstrated a significant increase in GSH content as well as the activity of GPx than their corresponding control ones (p < 0.01 in all groups) (Fig. 3). GEM attenuated the effect of DOX treatment on inflammatory mediators (TNF-α and IL-1β) (p < 0.05 in all groups) levels than their DOX counterparts (Fig. 4). We observed a marked improvement in cardiac cells structure and nuclei as well as normal cytoplasm structure in rats receiving of GEM (Fig. 5C).

3.3. Effects of GEM administration on serum, biochemical and histopathological alternations in rats

GEM administration (100 mg/kg for 14 days) did not induce any serum, biochemical and histopathological changes in naïve rats compared to their control counterparts.

4. Discussion

DOX, an effective anticancer drug, has life-threatening side effects at a maximal therapeutic dose which may induce cardiac injury [2].

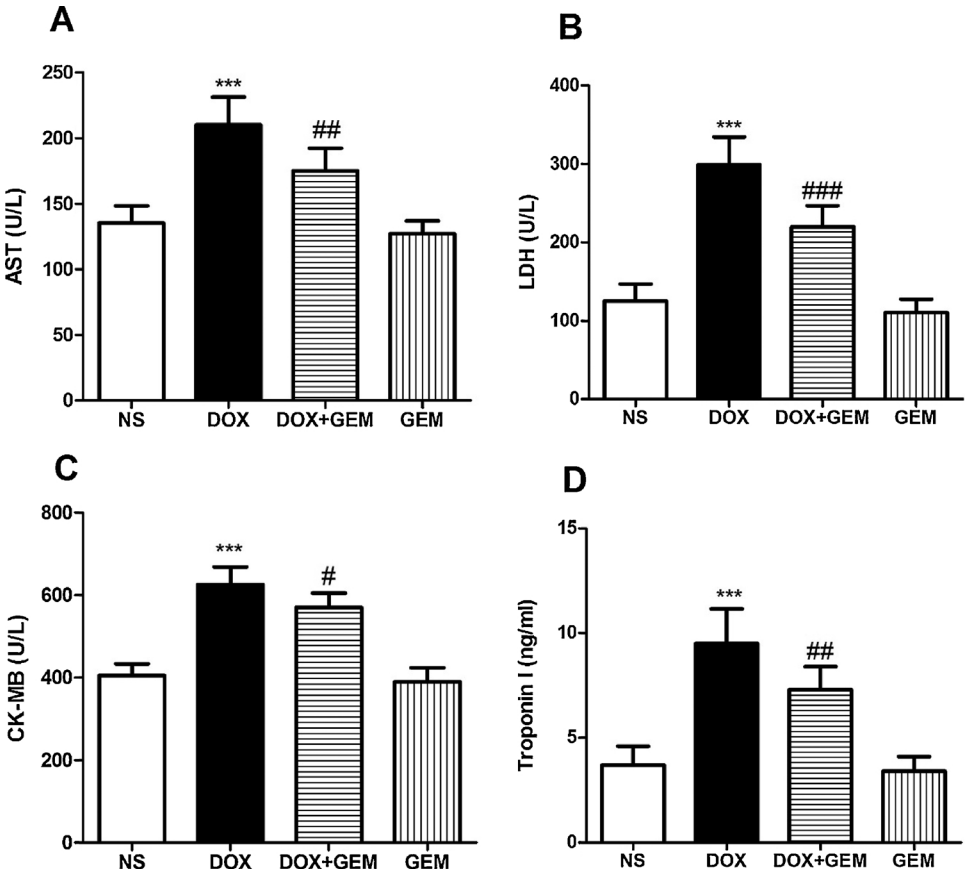

Fig. 1. Effect of gemfibrozil on markers of cardiac dysfunction in doxorubicin-induced cardiotoxicity in rats. Values are means ± SD (n = 7). Data were analyzed by one-way ANOVA followed by Tukey's post hoc test for multiple comparisons.
* Significant change with respect to NS group (***p < 0.001).
# Significant change with respect to DOX group (#p < 0.05; ##p < 0.01 and ###p < 0.001).

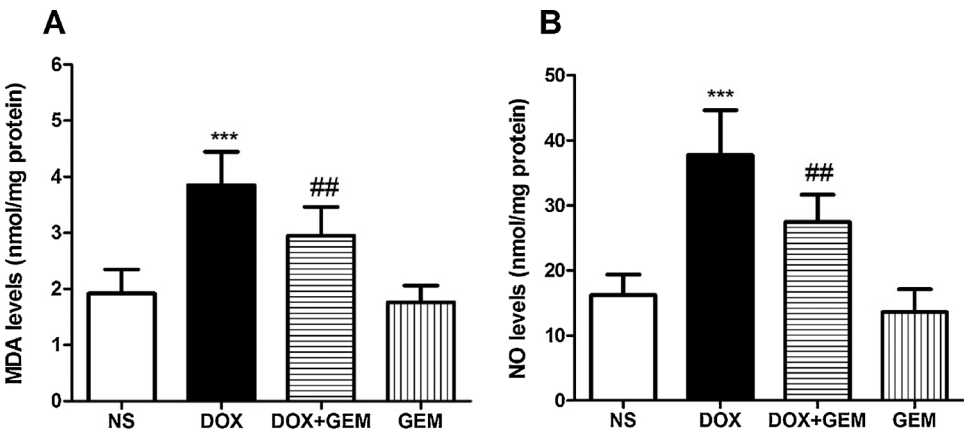

Fig. 2. Effect of gemfibrozil on markers of oxidative stress in doxorubicin-induced cardiotoxicity in rats. Values are means ± SD (n = 7). Data were analyzed by one-way ANOVA followed by Tukey's post hoc test for multiple comparisons.
* Significant change with respect to NS group (***p < 0.001).
# Significant change with respect to DOX group (##p < 0.01).

The main points arising from the current study were that DOX-induced inflammatory and oxidative injury in the cardiac tissue and GEM treatment attenuated cardiotoxicity induced by DOX through its profound antioxidant activity and anti-inflammatory properties.

It is well documented that DOX administration has deleterious effects on the lipid profile [5]. DOX-induced hyperlipidemia has deleterious effects for heart function and appears to contribute to DOX-induced cardiotoxicity [26]. On the other hand, it is well established that lipid-lowering drugs have protective effects against cardiotoxicity induced by DOX [27]. In our study, the cardiac injury by six doses of DOX (each dose: 2.5 mg/kg; cumulative dose: 15 mg/kg) was associated with significant increase in total cholesterol, triglyceride and LDL-c as well as decrease in HDL-c while GEM caused to significantly improve in these indies. Therefore, the cardioprotective effect of GEM in DOX-induced cardiotoxicity may be mediated by its lipid-lowering property.

Increasing the serum levels of AST, LDH, CK-MB, and cTnI have been indicated to cardiac tissue dysfunctions because these are normally located in the cytoplasm of cardiomyocytes and leakage occurs into the serum after cardiomyocytes damage [28]. Administration of DOX increases these cardiac markers in serum while co-administration of GEM with DOX attenuated these disturbances. It is worth mentioning that normalization serum levels of these markers by GEM indicating protection of cardiac cells [8]. The most acceptable mechanism for DOX-induced cardiotoxicity is oxidative stress [29]. These oxidative stress cause damage to cell membranes and cellular macromolecules such as lipids of the cardiomyocytes [1]. it is well established that GEM possesses potent antioxidant activity though dependent and/or independent pathways to PPAR α receptors [30]. Nikravesh et al., showed that GEM has protective effects against hepatotoxicity induced by acetaminophen via reducing the ROS formation [31].

DOX-induced cardiac injury by the generation of ROS and the protection of heart though augmentation of the cardiac antioxidant

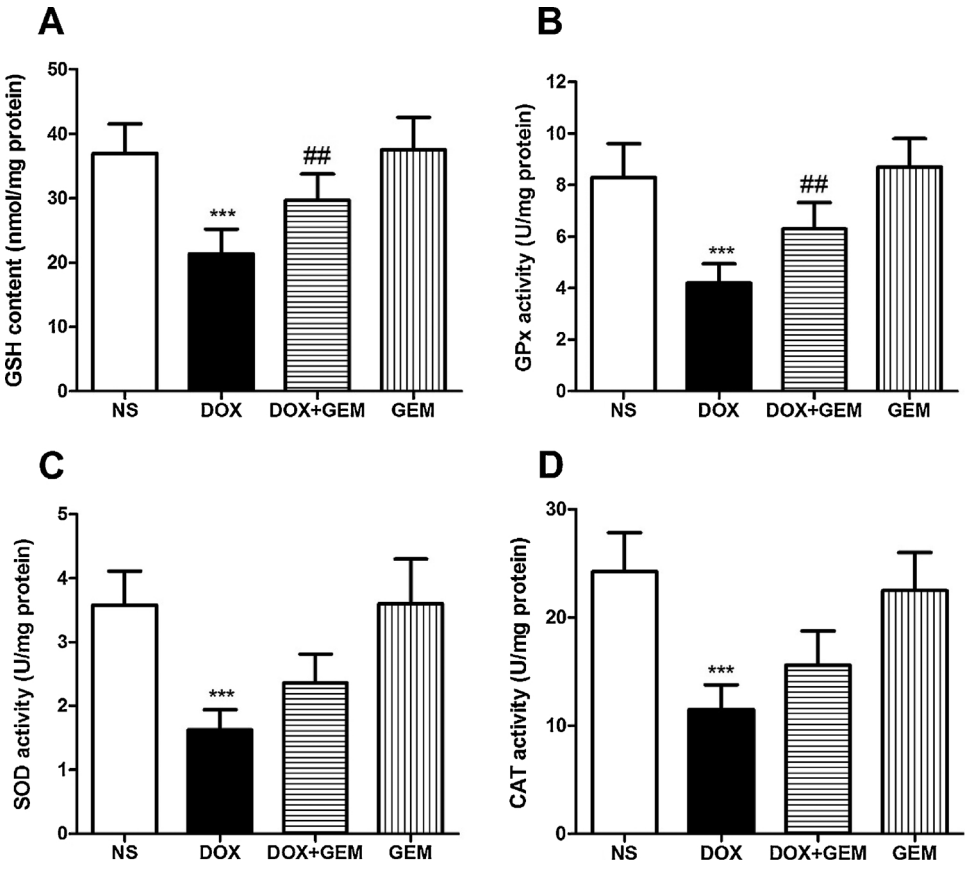

Fig. 3. Effect of gemfibrozil on antioxidant enzymes in doxorubicin-induced cardiotoxicity in rats. Values are means ± SD (n = 7). Data were analyzed by one-way ANOVA followed by Tukey's post hoc test for multiple comparisons.
* Significant change with respect to NS group (***p < 0.001).
# Significant change with respect to DOX group (##p < 0.01).

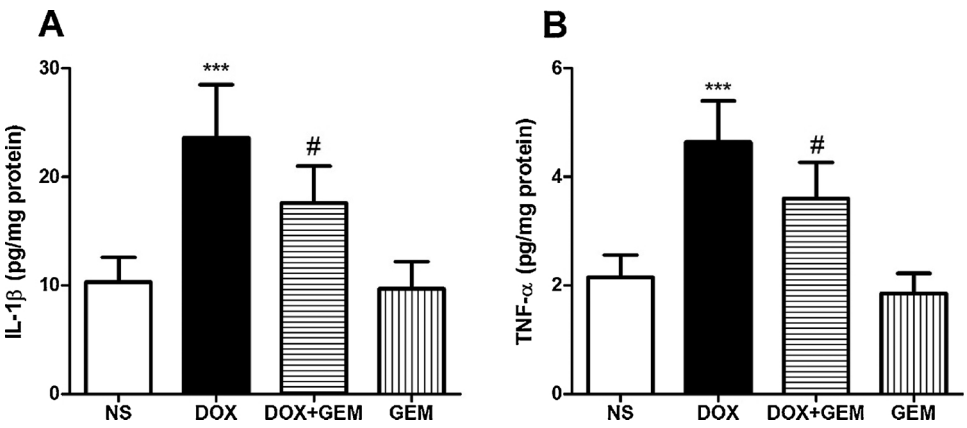

Fig. 4. Effect of gemfibrozil on inflammatory cytokines in doxorubicin-induced cardiotoxicity in rats. Values are means ± SD (n = 7). Data were analyzed by one-way ANOVA followed by Tukey's post hoc test for multiple comparisons.
* Significant change with respect to NS group (***p < 0.001).
# Significant change with respect to DOX group (#p < 0.05).

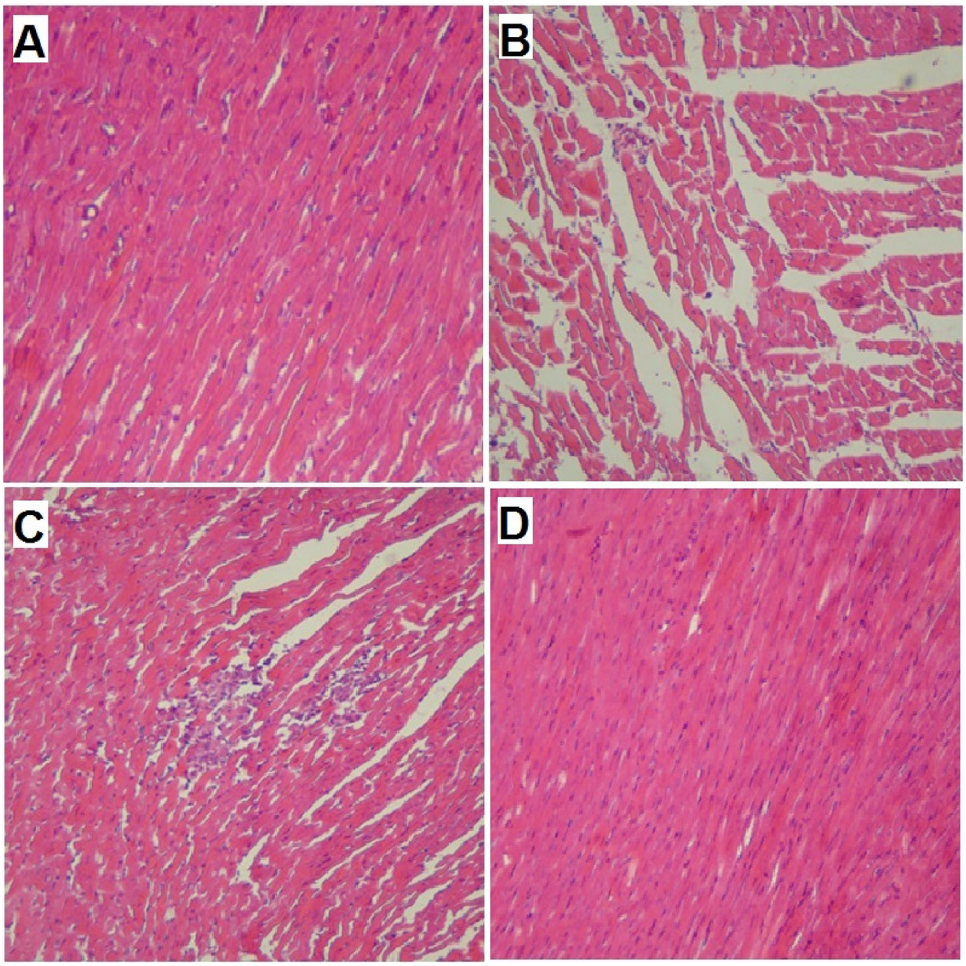

Fig. 5. The effect of normal saline, doxorubicin, doxorubicin + gemfibrozil and gemfibrozil administration on myocardium (stained with Hematoxylin & Eosin, magnification X 150). (A) normal saline-treated rats showing normal morphological appearance; (B) doxorubicin-treated rats showing massive inflammation, myofibrillar loss and congestion of red blood cells; (C) doxorubicin + gemfibrozil treated rat showing mild inflammation and myofibrillar loss and (D) gemfibrozil-treated rats showing normal morphological appearance.

defense system is critical in the protection against DOX-induced cardiac damage [6,7,26]. On the other hand, previous studies indicating that DOX administration is associated with reduction in enzymes involved in antioxidant defense including SOD, CAT, GPx and GSH [3,8,26]. Our results indicated that the activities of CAT, GPx and SOD as well as GSH level significantly reduced in cardiac tissue of rats exposed to DOX. Our results also showed that administration of GEM in combination with DOX increased the activity of GPx and the content of GSH. Previous studies showed that GEM increases the antioxidant capacity in different conditions such as acetaminophen-induced hepatotoxicity and cisplatin-induced nephrotoxicity [31,32]. Accordingly, it seems that GEM may possibly show its cardioprotective effects by increasing the antioxidant capacity.

DOX induces the production of NO and MDA in cardiac cells. These markers of oxidative stress cause mitochondrial dysfunction that may lead to organ damage [33,34]. On the other hand, GEM is known to decrease the production of MDA and NO in different conditions such as sepsis and diabetes [11,12]. Elevations in MDA and NO after DOX

administration were observed in the current study. In addition, a significant difference in the levels of MDA and NO were identified between the DOX and DOX + GEM group. Thus, GEM might induce cardioprotective effects through attenuation of DOX-induced oxidative injuries.

In addition to oxidative stress, the other mechanism that plays a critical role in the pathogenesis of DOX-induced cardiotoxicity is inflammation [3]. It is well documented that the overproduction of free radicals leads to increasing the production of inflammatory mediators and trigger the inflammatory processes in the heart [26,35]. Moreover, it is well established that GEM acts as an anti-inflammatory agent via inhibition of inflammatory cytokine production and releases [13,36]. In line with these previous reports, the results of our study demonstrated that GEM administration alongside with DOX attenuated the TNF-α and IL-1β levels in comparison with DOX-treated rats.

Marked oxidative stress results from DOX administration causes a degenerative change in cardiac tissue which can lead to cardiomyocytes damage such as necrosis [6]. GEM decreased the membrane peroxidation and disruption of cardiac cells and subsequently attenuated necrosis and tissue injuries. These findings are in line with the biochemical assessments. The cardioprotective effects of GEM have been shown only in heart transplantation. Benke et al., demonstrated that preconditioning with GEM attenuates the ischemia/reperfusion injury as well as preserves cardiac function after heart transplantation [37].

To conclude, our study showed that administration of GEM alongside the DOX reduced the cardiac levels of NO, MDA, TNF-α, and IL-1β as well as serum markers of cardiac injury such as AST, LDH, CK-MB, and cTnI. We also found that GEM increase in GSH content, as well as the activity of GPx in DOX-treated rats. These effects may explain the amelioration of cardiac injury in DOX-induced cardiotoxicity through improving the oxidative state and/or decreasing the inflammation. More studies are required to elaborate the exact mechanism of GEM. Finally, we suggest that further clinical trials with different lower doses of GEM conducted to reveal the beneficial effects of GEM in the clinic.

Conflict of interest

Authors declare no conflict of interest related to this study.

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