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The Potential Protective Role of Resveratrol in Doxorubicin-Induced Cardiac and Hepatic Toxicity in Male Adults Albino Rats

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Abstract

Introduction: Doxorubicin (Dox) is known to treat Acute myelocytic leukemia and various tumors but is associated with significant cardiac and liver toxicity. **Aim:**This study evaluated the toxic effects of Dox on these organs pathophysiologically, and the potential protective effects of resveratrol (Rs), which has anti-oxidative and anti-inflammatory properties. **Methodology:** Fifty male adult albino rats were divided into five groups for treatment, including control, saline, **Rs** alone, Dox alone (2mg/kg/IP/twice/weekly/for 5 weeks), and Rs pretreatment (20 mg/kg/day/orally/for 6 weeks) followed by Dox (2mg/kg/IP/twice/weekly/for 5 weeks). **Results:** The results showed severe pathological damage in the heart (including diffuse myomalacia, mild hyalinization, discontinuity of some fibers, loss of the normal striation,) and liver (including disrupted architecture, hepatocytes with lytic and coagulative necrosis, fibrosis, Langhans (giant cells invasion) of the Dox group compared with the first three groups. No significant physiological differences were observed among the control, saline, and **Rs** groups concerning cardiac and hepatic antioxidant levels of TAC/SOD/catalase/MDA/and caspase-3, as well as the cardiac markers (LDH/ CK-MB/AST/and troponin) and hepatic enzymes levels (ALT/AST/and TB). The findings suggest that resveratrol may help mitigate the toxicity of doxorubicin treatment. **Conclusions:** resveratrol can give hope to improve doxorubicin-related toxicity to a broader extent.

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Key words male adult rats, Doxorubicin, Resveratrol, ameliorative effect, Heart, Liver, sections, Physiological Parameters

Introduction

Doxorubicin is an effective chemotherapeutic agent that belongs to the anthracycline antibiotics group and it is widely used in the treatment of various cancers (Xiong et al., 2025). It accumulates in the stromal cells causing DNA breakdown (Rawat et al., 2021). After administration, about half of its dose is excreted in feces through biliary excretion affecting cancerous and non-cancerous cells (Moreira et al., 2014). The anticancer mechanism primarily focuses on targeting and intercalating the DNA of rapidly dividing tumor cells, which leads to a blockage in the G2 phase of the cell cycle (Renu et al., 2018). The main theory regarding its toxicity centers on the induction of oxidative stress and apoptosis (Matsumura, 2018).

Unfortunately, it causes dose-dependent cumulative irreversible and long-lasting cellular toxicity mainly for cardiac cells causing cardiomyopathy (Souza et al., 2021; Xiong et al., 2025), and hepatic cells causing necrosis (Prasanna et al., 2020; Wang et al., 2025).

Resveratrol is a natural polyphenol found in various plant-based foods, particularly in red grapes, tangerines, peaches, nuts like walnuts and peanuts, as well as berries such as blueberries, mulberries, bilberries, and cranberries (Xu et al., 2024). It is a potent antioxidant that enhances cell survival and decreases the production of reactive oxygen species (ROS) (Monahan et al., 2021; Alborzi et al., 2025; Alshehri et al., 2025). The most promising biomarkers are linked to the disease's underlying pathophysiological processes (Panda et al., 2022). Reactive oxygen species are produced by various sources, including mitochondria, xanthine oxidase, uncoupled nitric oxide synthases, and NADPH oxidase (Wang et al., 2018). The significant role of oxidative stress in cardiovascular disease has led to measuring ROS as a promising biomarker that reflects disease progression. Their short half-life allows them to be effectively measured within the circulation of complex biological systems using standard methods (Panda et al., 2022).

On the other hand, caspases are a family of protease enzymes whose functions are linked to the processes of apoptosis, necrosis, and inflammation. The human caspase family is divided into three main groups. A protein that is cleaved and thus activated

upon the initiation of apoptosis (Eskandari and Eaves, 2022).

Aim of the Work

This work aimed to investigate the potential protective role of resveratrol on rats treated with doxorubicin

Materials and Methods

A- Materials

1- Drugs and chemicals:

Doxorubicin "Dox" and Resveratrol "Rs" were purchased from a local pharmacy in Egypt as vials (each containing 10 mg in the form of powder, Pfizer-Egypt), and capsules (each containing 100 mg, a Squared Nutrition, USA), respectively. The chemicals, solvents, and reagents were of analytical and pure grade.

2- Animals and drugs administration:

Fifty male adult albino rats weighing 150-200 g were used in this study. The animals were purchased from the Unit of Biological and Experimental Animals, Theodor Bilharz Research Institute (TBRI), Nile Cornish, Embaba, Cairo, Egypt, and kept at the Research Studies and Training Centre on Vectors of Diseases, Faculty of Science, Ain Shams University. After the animals were purchased, they were allowed two weeks for accommodation and weighing to be separated into cages. Animals were allowed to adapt to the laboratory conditions for one week before commencing any experiment. The rats were provided with food and water ad libitum.

Rats were randomly divided into five equal groups; ten rats each as follows:

Group I: Negative control: rats were kept without any treatment. The experimental animals had access to tap water and a standard pellet diet ad libitum.

Group II: Saline group. In this group, the rats were administered saline as a positive control group of Dox-group (group no. 4), as the vials were dissolved in 5 ml 0.9% sodium chloride serving the administration of 5 rats IP.

Group III: Rats were orally treated with 20mg/kg/day resveratrol and dissolved tap water for 6 weeks (Singh, 2014). Resveratrol supplementary capsules (20 mg/kg) were evacuated and dissolved in tap water, mimicking the oral administration of humans, but for rats administrated using a gavage tube for 6 weeks, fed a standard pellet diet.

Group IV: Toxic group: doxorubicin group, rats were intraperitoneally injected with 2mg/kg twice weekly for 5 weeks prepared immediately before injection according to Berthiaume and Wallace, (2007), Abdu et al. (2019), and Timm et al., 2020. "According to Pfizer pharmaceutical insert instructions dilute Doxorubicin Hydrochloride is being prepared for injection in 0.9% Sodium Chloride Injection (which is used in this study), USP or 5% Dextrose Injection (which is not selected in this study), USP. Protect from light following preparation until completion of the administration. Use within 1 hour. If not used within 1 hour, discard the diluted product. Each vial (10 mg) was dissolved in 5 ml 0.9% sodium chloride and kept frozen until use but not more than one hour. Each ml (contained 2mg Dox / 5 rats weighed 200g/each).

Group V: (the combination group): The rats received resveratrol orally as a pre-treatment for 6 weeks and were then intraperitoneally given doxorubicin 2mg/kg for 5 weeks.

The animals were dissected 24 hrs after the end of the experiment, in which animals were anesthetized using diethyl ether. The blood samples were collected from the abdominal aorta, and sera were separated by centrifugation at 3,000 rpm at 4C for 20 min. The heart and liver specimens were dissected rapidly. The organs were further subdivided into two portions: the first portion exhibited the fixed specimens were placed in 10% formalin for histopathological study.

The second portion contained specimens immediately frozen and stored at -25C. The frozen tissues were homogenized in buffered saline and centrifuged at 10,000 rpm for 20 min. The supernatant was also collected and stored at -25C in a refrigerator for biochemical and antioxidant biomarkers.

Biochemical parameters:

Biochemical parameters were investigated to report cardiac and hepatic functions as follows:

1- Cardiac enzymes:

The following cardiac enzymes were assayed to follow up cardiac functions. Lactate Dehydrogenase (LDH) was assayed according to Buhl and Jackson (1978). Creatine Kinase-MB (CK-MB) was performed according to Ring (2019). Troponin I level was assessed using the method described by Giuliani et al. (1999).

2- Hepatic profile:

The hepatic function was determined through the following biomarkers: Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) were assayed using the colorimetric method of Reitman and Frakel (1957). Alkaline Phosphatase (ALP) was performed by the kinetic method of Rosalki et al. (1993). Total bilirubin was determined using the spectrophotometric method of Schellang and Wende (1960).

3- Oxidative stress parameters:

To assess the level of oxidative stress in cardiac and hepatic tissues, the following parameters were measured: Cardiac and hepatic MDA levels were measured by the spectrophotometric method using Mihara and Uchiyana (1978). SOD activity was measured according to Markland and Markland (1974). The TAC level was assayed according to Koracevic et al. (2001). Catalase activity was estimated by method of Goth (1991). Caspase activity quantification was calculated as per protocol outlined by Tietz (1986).

Ethical approval:

This study follows guidelines for the care and handling of experimental animals established by Research Ethical Committee belonging to the Higher Studies and Research Sector, Faculty of Science, Ain Shams University (ASU). For experimental design, animal accommodation, preventing contamination, animal way of handling, and getting rid of the wastes; the protocol was approved and accordingly given the code: ASU-SCI/ZOOL/2025/1/6.

Statistical analysis:

Statistical analyses were done using SPSS software, version 18. The results have been presented as the mean ± SD. The One-Way ANOVA was applied to compare more than two groups' differences. Where the ANOVA test showed significance, post hoc multiple comparisons were tested. $p < 0.05$ was regarded as significant.

Results

1- The biochemical Parameters:

A- Results of the heart:

The present experimental study was conducted on 5 groups of Wistar albino rats (n=10). As presented in Table 1 and Figure 1, no statistically significant differences were observed among I, II, and III groups concerning cardiac biomarkers, including LDH, CK-MB, AST, troponin, TAC, SOD, catalase, MDA, and caspase-3.

As demonstrated in Table 2 and Figure 2, cardiac biomarkers, including LDH, AST, Troponin, SOD, Catalase, MDA, and Caspase-3 were significantly increased ($P \leq 0.001$) in Group IV and Group V compared with Group I. On the other hand, other cardiac biomarkers, including CK-MB, and total antioxidants capacity (TAC) were significantly decreased ($P \leq 0.001$) in Group IV and Group V compared with Group I.

B- Results of the Liver:

As illustrated in Table 3 and Figure 3, the evaluation of hepatic function parameters revealed no significant differences among the same groups (I, II, and III groups) regarding ALT, AST, total bilirubin, TAC, catalase, MDA, SOD, and caspase-3.

As revealed in Table 4 and Figure 4, hepatic biomarkers, including ALT, AST, total bilirubin, MDA, and Caspase-3 were significantly increased ($P \leq 0.001$) in Group IV and Group V compared with Group I. On contrast, other hepatic biomarkers, including TAC, SOD, and catalase were significantly decreased ($P \leq 0.001$) in Group IV and Group V compared with Group I. Meanwhile, oral administration of resveratrol in Group V showed partially modulated cardiac and hepatic oxidative stress markers and antioxidant parameters.

2- The histopathological results:

A- Results of the heart:

The microscopical examination of the first, second, and third groups, representing the negative, saline, and resveratrol groups, respectively, shows normal myocardium with normal cardio myofibers striation and continuity with intact vasculature; of the heart sections of male adult albino rats stained with hematoxylin and eosin (Fig. A, B, and C). The fourth group; the doxorubicin-treated group, showed various pathological alterations ranging from vascular endotheliosis to diffuse myomalacia of cardiac fibers (Fig. D). In addition to interstitial extravasated erythrocytes with mild hyalinization of some cardiac fibers. Also, severe fibrosis of the vascular wall, with perivascular edema (Fig. E). In addition to diffuse vacuolation of some cardiac myofibers of mainly fatty degeneration (Fig. F). In Figure "G", the heart section showed severe vascular congestion and discontinuity of some fibers, with loss of the normal striation of others. The fifth group, also known as the combination group of the doxorubicin- and the resveratrol-treated group showed mild pathological alterations as interstitial inflammatory cells' infiltration and mild proliferation of Anitschkow cells (Fig. H). In addition to mild vascular congestion with focal normal myocardium, and intact fibers as shown in Fig. "I".

B- Results of the liver:

The liver sections of the male adult albino rats of the negative, saline, and resveratrol groups show normal tissue architecture, cellular details, and intact hepatic vasculature, as shown in Figures J, K, and L, respectively. While the doxorubicin-treated group showed severe hepatic alterations due to induced toxicity (Figures. M-Q). The microscopical examination showed hyperplasia of the biliary epithelium (Fig. M) with vascular congestion. Also, the sections exhibited severe congestion of the hepatic blood vessels (Fig. N). The hepatocytes' architecture was disrupted (Figs. M-Q). Most vacuolated hepatocytes were shown around the vanished cells and were characterized by several Langhans giant cells (Fig. O) that invaded the destroyed areas to scavenge the remnants of the hepatocytes. The hepatocytes showed lytic and coagulative necrotic, fibrosis, and vacuolated hepatocytes in addition to vacuolated the biliary epithelium (Figs. P & Q) with inflammatory cells infiltration (Figs. P & Q). The combination group of resveratrol- and doxorubicin-treated rats showed minimal inflammatory cellular infiltration with almost normal hepatic architecture (Figs. R & S), in addition to mild widened blood sinusoids (Fig. S).

Table (1): Comparison among groups I, II, and III; regarding cardiac LDH, CK-MB, AST, troponin level, TAC, SOD, catalase, MDA, and caspase-3.

Groups / Parameters	Group I No. = 10	Group II No. = 10	Group III No. = 10	Test value	P-value	Sig.
LDH	115.7 ± 5.4	112.9 ± 4.9	116.0 ±6.0	0.984•	0.387	NS
CK-MB	125.8 ± 2.8	124.9 ± 2.6	123.9 ± 2.5	1.300•	0.289	NS
AST	13.11 ± 1.01	13.5 ± 1.0	13.6 ± 1.02	0.657•	0.526	NS
Troponin (mg/ml)	0.04 ± 0.01	0.039 ± 0.01	0.041 ± 0.01	0.100•	0.905	NS
TAC	177.7 ± 50.2	175.0 ± 4.3	178.3 ± 51.1	0.018•	0.982	NS
SOD	50.0 ± 3.2	49.8 ± 3.1	48.91 ± 3.0	0.350•	0.708	NS
Catalase	29.09 ± 1.2	29.2 ± 1.3	28.9 ±1.1	0.159•	0.854	NS
MDA	10.2 ± 0.8	10.1 ± 0.7	9.9 ± 0.66	0.447•	0.644	NS
Capase-3	7.1 ± 0.5	7.3 ± 0.3	7.5 ± 0.6	1.714•	0.199	NS

Lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), aspartate aminotransferase (AST), total antioxidant capacity (TAC), superoxide dismutase (SOD), and malondialdehyde (MDA). Group I: negative control, Group II: saline group, Group III: resveratrol only. P-value > 0.05: Non-significant; •: One Way ANOVA test.

Table (2): Comparison among groups I, IV, and V; regarding cardiac LDH, CK-MB, AST, Troponin, TAC, SOD, catalase, MDA, and caspase-3.

Groups / Parameters	Group I No. = 10	Group IV No. = 10	Group V No. = 10	Test value	P-value	Sig.
LDH	11.5 ± 5.4	290 ± 9.9	119.9 ± 6.4	3516.529•	0.000	VHS
CK-MB	125.8 ± 2.81	12.65 ± 3.8	115.8 ± 4.2	2944.615•	0.000	VHS
AST	13.11 ± 1.01	90.9 ± 2.9	19.1 ± 0.9	5489.402•	0.000	VHS
Troponin (mg/ml)	0.04 ± 0.01	0.09 ± 0.02	0.05 ± 0.01	21.667•	0.000	VHS
TAC	155.3 ±22.5	67.3 ± 19.5	150.9 ± 20.0	57.335•	0.000	VHS
SOD	35.4± 0.8	89.9 ±0.90	36.9 ±0.7	14900.773•	0.000	VHS
Catalase	8.12 ± 4.27	25.1 ±0.69	10.1 ± 0.60	135.623•	0.000	VHS
MDA	38.1 ± 4.27	105.6 ± 10.51	45.2 ±5.6	257.878•	0.000	VHS
Caspase-3	6.9 ± 0.62	15.6 ± 2.1	7.5 ± 1.6	96.310•	0.000	VHS

Lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), aspartate aminotransferase (AST), total antioxidant capacity (TAC), superoxide dismutase (SOD), and malondialdehyde (MDA). Group I: negative control, Group IV: doxorubicin only, and Group V: resveratrol + doxorubicin. P-value < 0.001: very highly significant, •: One Way ANOVA test.

Table (3): Comparison among groups I, II, and III; regarding hepatic ALT, AST, TB, TAC, SOD, catalase, MDA, and caspase-3.

Groups / Parameters	Group I No. = 10	Group II No. = 10	Group III No. = 10	Test value	P-value	Sig.
ALT	26.9 ± 5.4	25.3 ± 3.1	28.2 ± 4.0	1.156•	0.330	NS
AST	66.6 ± 6.1	65.1 ± 8.8	62.9 ± 7.9	0.587•	0.563	NS
Total bilirubin	0.33 ± 0.09	0.35 ± 0.09	0.32 ± 0.08	0.310•	0.736	NS
TAC	155.3 ± 22.5	153.0 ± 2.0	154.1 ± 21	0.042•	0.959	NS
SOD	35.4 ± 0.08	33.5 ±0.6	34.3 ±0.5	3.289•	0.080	NS
Catalase	8.12 ± 0.53	8.0 ± 0.45	8.3 ± 4.2	0.000•	1.000	NS
MDA	38.1 ± 1.27	39.0 ± 1.3	37.7 ± 1.1	2.947•	0.070	NS
Caspase 3	7.1 ± 0.09	7.0 ± 0.7	7.3 ±0.8	0.615•	0.548	NS

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total antioxidant capacity (TAC), superoxide dismutase (SOD), and malondialdehyde (MDA). Group I: negative control, Group II: saline group, Group III: resveratrol only. P-value > 0.05: Non-significant; •: One Way ANOVA test

Table (4): Comparison among groups I, IV, and V; regarding hepatic ALT, AST, TB, TAC, SOD, catalase, MDA, and caspase-3.

Groups / Parameters	Group I No. = 10	Group IV No. = 10	Group V No. = 10	Test value	P-value	Sig.
ALT	26.9 ± 5.4	155.0 ± 7.8	30.9 ± 6.3	227.019•	0.000	VHS
AST	66.6 ± 6.0	190.3 ± 9	70.0 ± 6.6	927.545•	0.000	VHS
T. bilirubin	0.33 ± 0.09	1.2 ± 0.1	0.31 ± 0.01	425.659•	0.000	VHS
TAC	177.7 ± 0.50	157.0 ± 0.30	173 ± 0.303	181.627•	0.000	VHS
SOD	50.0 ± 3.2	18.0 ± 2.3	43.5 ± 1.0	519.208•	0.000	VHS
Catalase	29.09 ± 1.2	12.5 ± 0.90	2.5 ± 1.0	1665.010•	0.000	VHS
MDA	10.2 ± 0.8	80.5 ± 011.1	9.2 ± 0.5	403.980•	0.000	VHS
Caspase-3	7.1 ± 0.9	20.3 ± 1.2	9.5 ± 0.6	568.276•	0.000	VHS

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), total antioxidant capacity (TAC), superoxide dismutase (SOD), and malondialdehyde (MDA). Group I: negative control, Group IV : doxorubicin only, and Group V: resveratrol + doxorubicin. P-value < 0.001: very highly significant, •: One Way ANOVA test

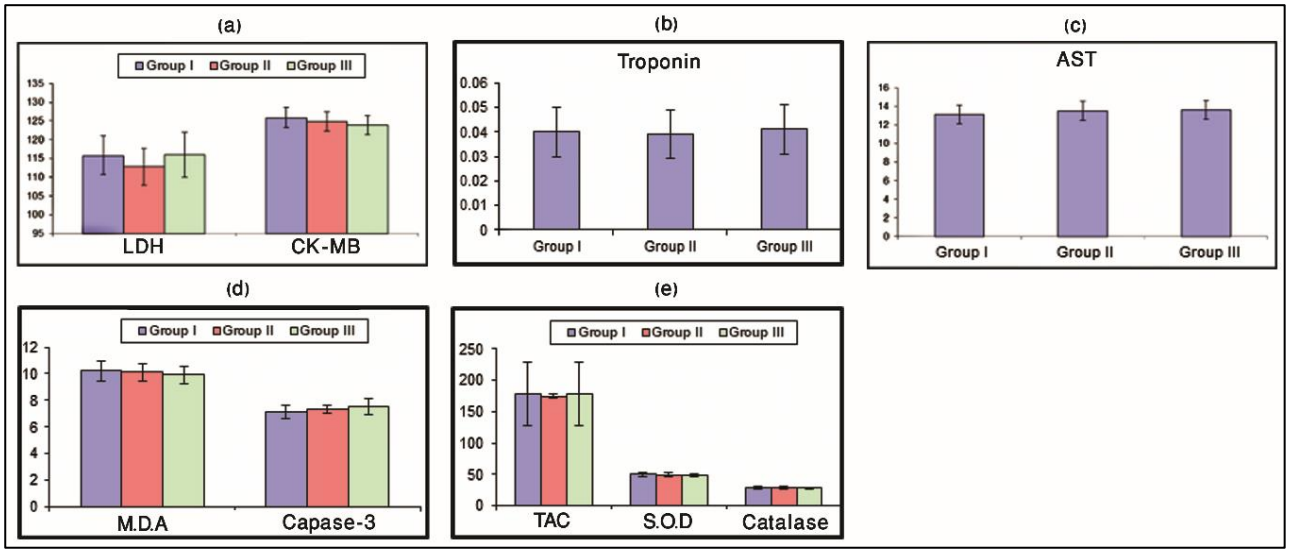


Figure (1): Comparison among groups I, II, and III; regarding cardiac LDH, & CK-MB (a), troponin (b), AST (c), MDA, & caspase-3 (d), and TAC, SOD, & catalase (e).

Lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), aspartate aminotransferase (AST), total antioxidant capacity (TAC), superoxide dismutase (SOD), and malondialdehyde (MDA). Group I: negative control, Group II: saline group, Group III: resveratrol only. P-value > 0.05: Non-significant; •: One Way ANOVA test.

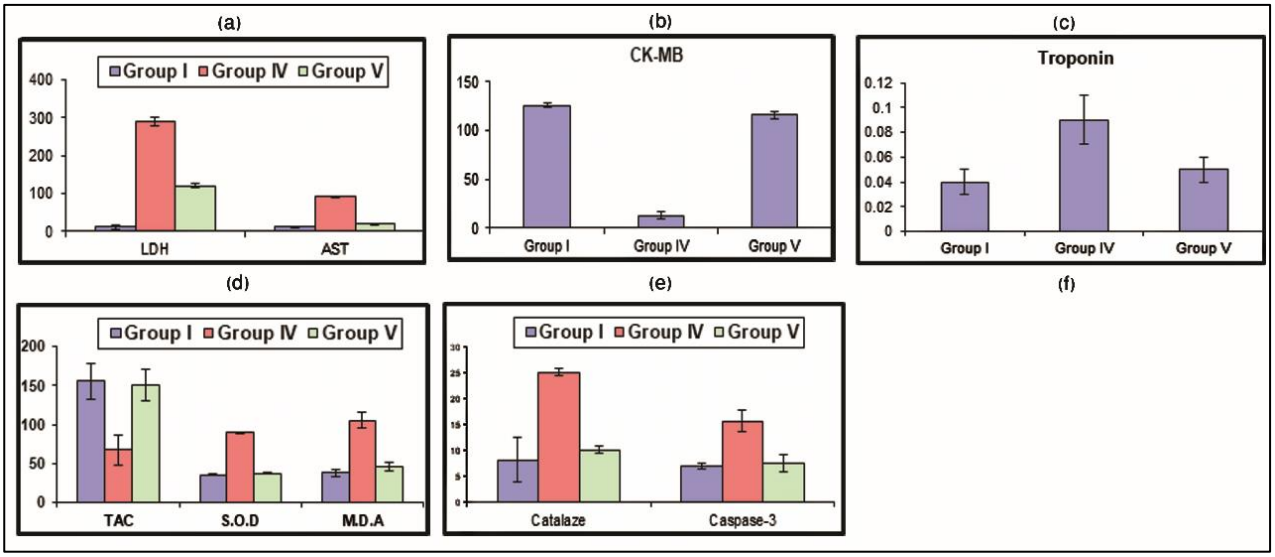


Figure (2): Comparison among groups I, IV, and V; regarding cardiac LDH, & AST (a) CK-MB (b), Troponin (c), TAC, SOD, & MDA (d), and catalase, & caspase-3 (e).

Lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), aspartate aminotransferase (AST), total antioxidant capacity (TAC), superoxide dismutase (SOD), and malondialdehyde (MDA). Group I: negative control, Group IV: doxorubicin only, and Group V: resveratrol + doxorubicin. P-value < 0.001: very highly significant, •: One Way ANOVA test.

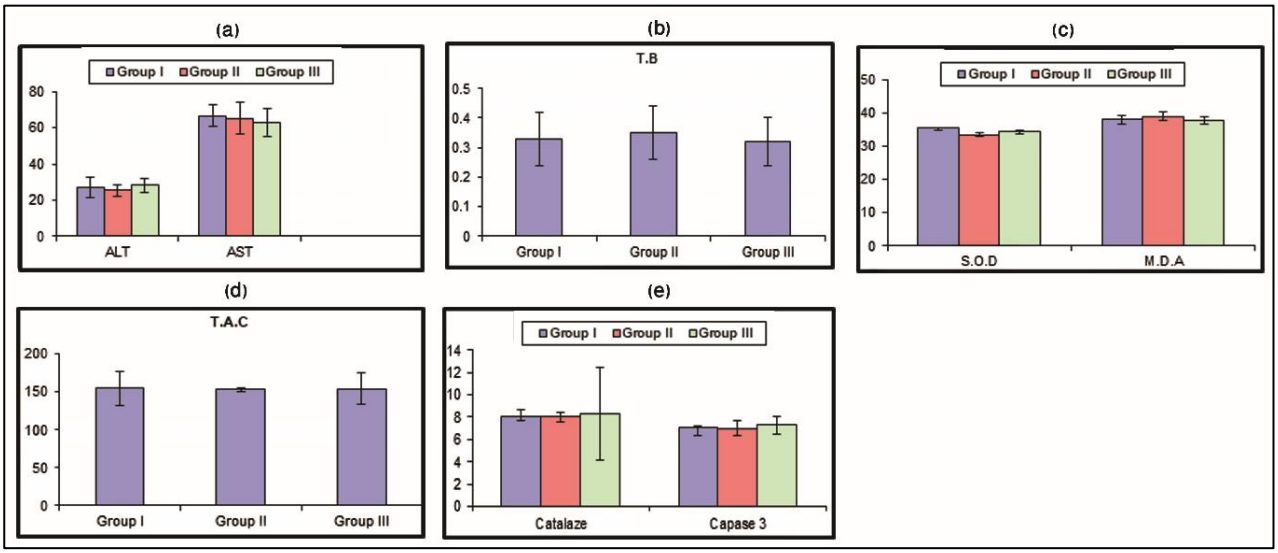


Figure (3): Comparison among groups I, II, and III; regarding hepatic ALT, & AST (a), total bilirubin (b), SOD, & MDA (c), TAC (d), and catalase, & caspase-3 (e).

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total antioxidant capacity (TAC), superoxide dismutase (SOD), and malondialdehyde (MDA). Group I: negative control, Group II: saline group, Group III: resveratrol only. P-value > 0.05: Non-significant; •: One Way ANOVA test.

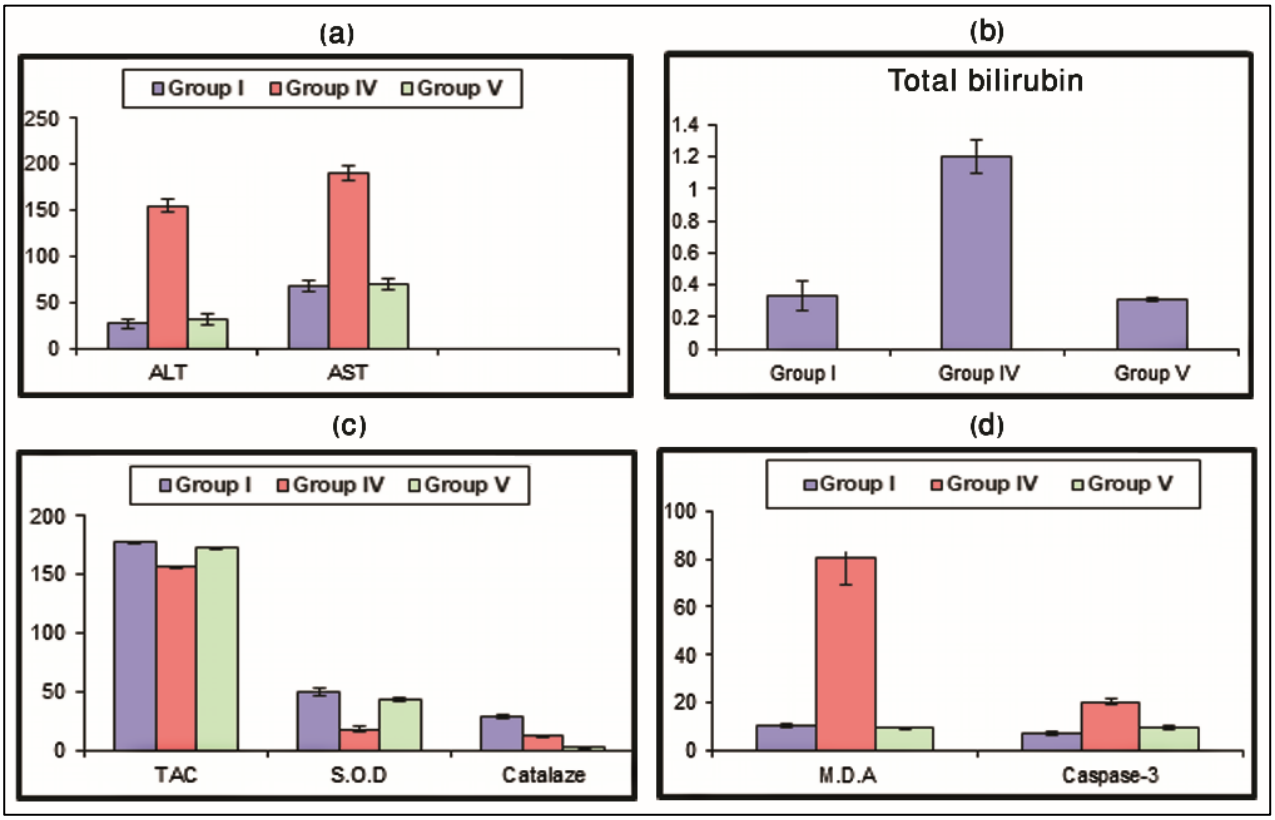
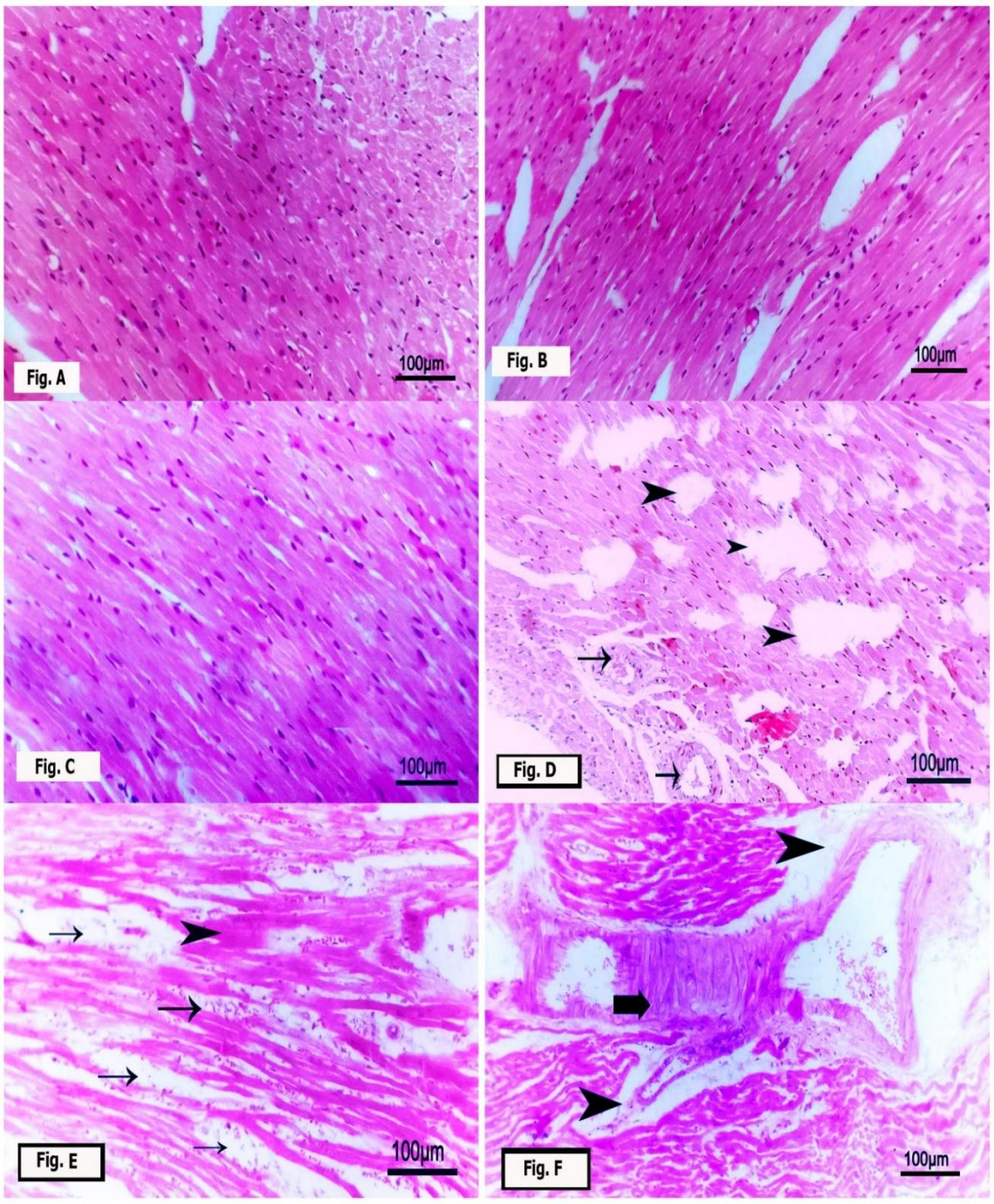


Figure (4): Comparison among groups I, IV, and V; regarding hepatic ALT & AST (a), total bilirubin (b), TAC, SOD, & catalase (c), and MDA, & caspase-3 (d).

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), total antioxidant capacity (TAC), superoxide dismutase (SOD), and malondialdehyde (MDA). Group I: negative control, Group IV: doxorubicin only, and Group V: resveratrol + doxorubicin. P-value < 0.001: very highly significant, •: One Way ANOVA test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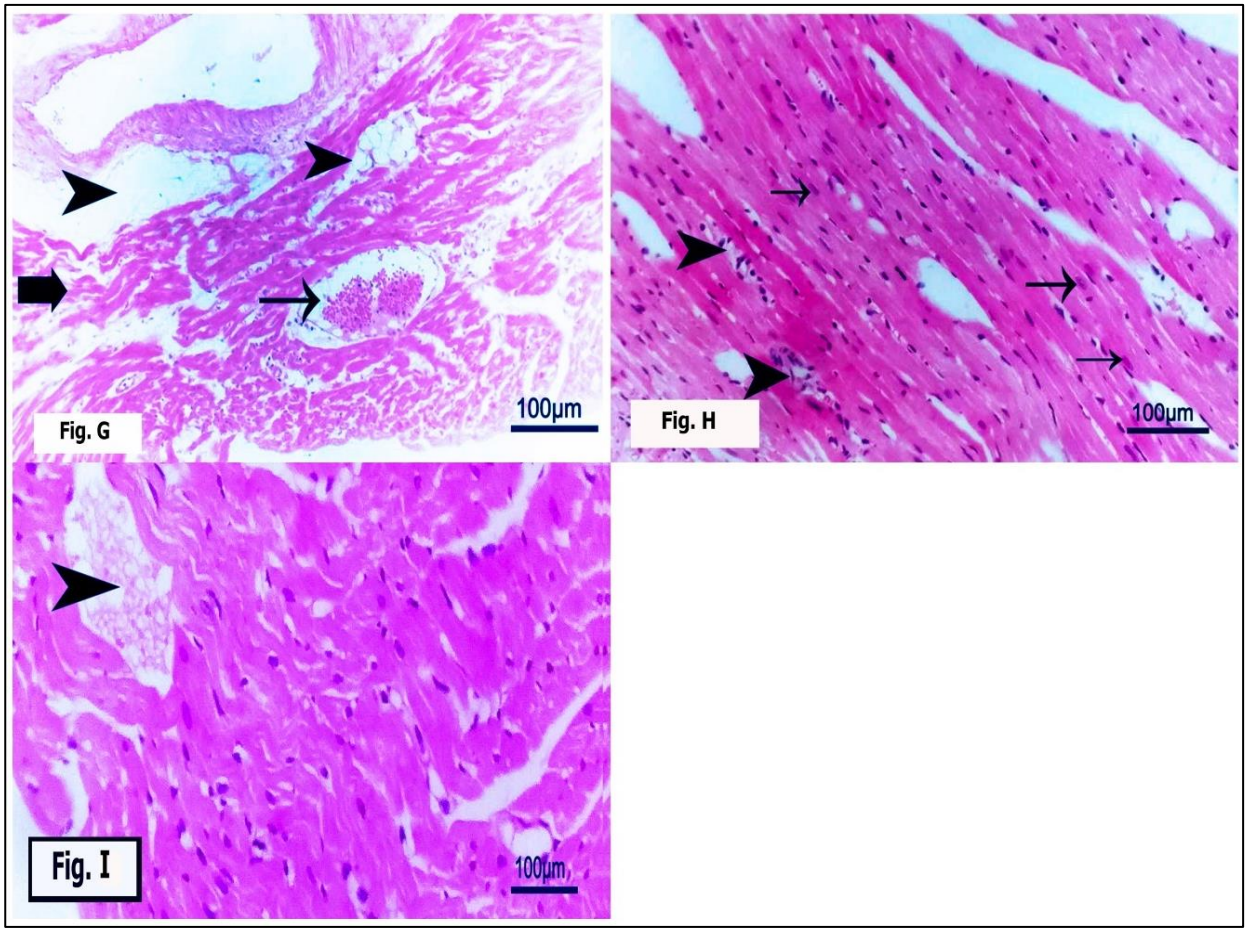
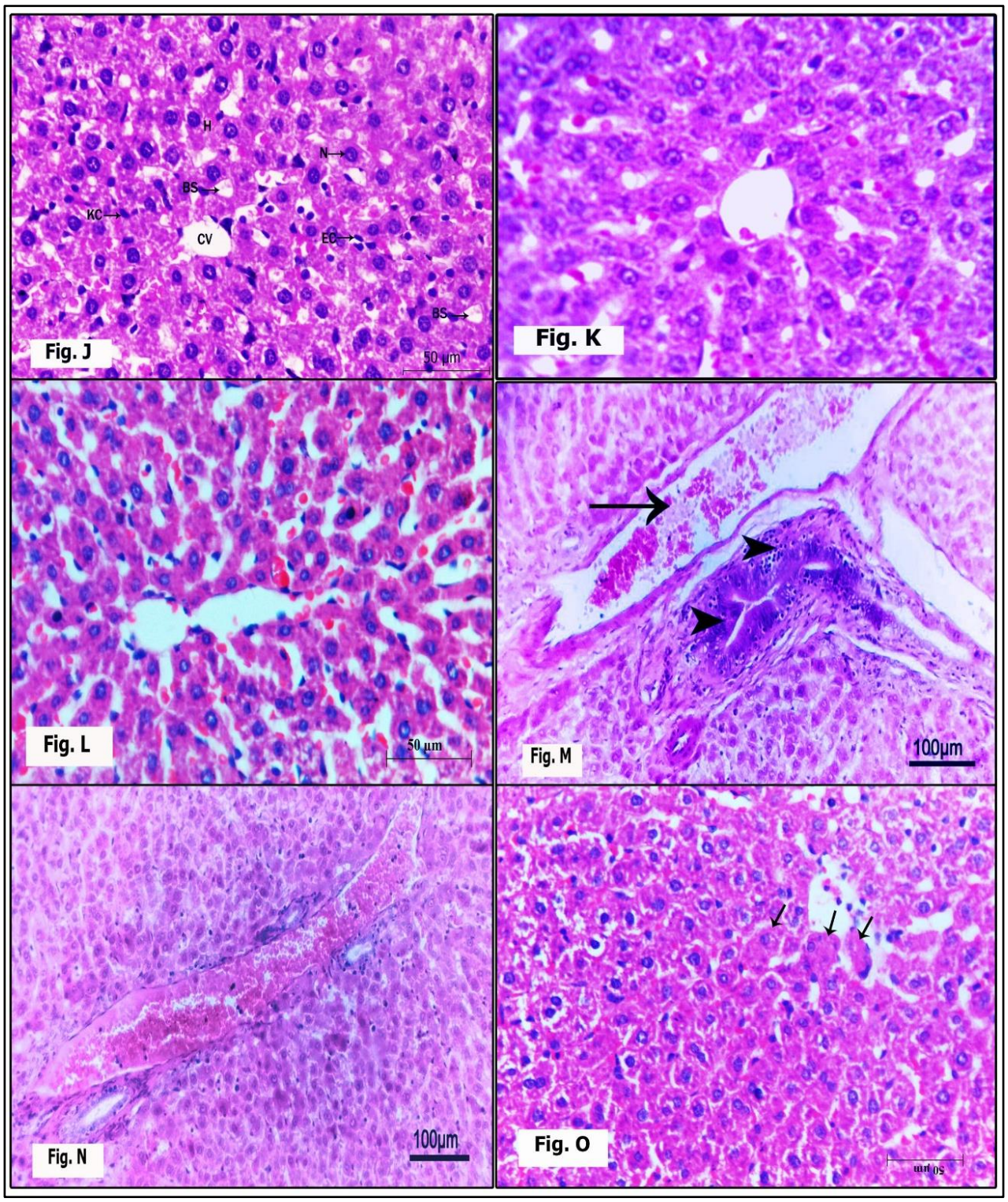


Figs. A-I: Photomicrographs of H- and E-stained sections of rats' hearts. A, B, and C) represent the negative control, the saline-treated, and the resveratrol-treated groups, respectively. The stained sections of these groups show normal myocardium with normal cardio myofibers striation and continuity with intact vasculature. D-G) showing a doxorubicin-treated group. In these photomicrographs: D) showing vascular endotheliosis (arrows) with diffuse Myo Malacia of cardiac fibers (arrows head). E) showing interstitial extravasated erythrocytes (arrows) with mild hyalinization of some cardiac fibers (arrowhead). F) showing severe fibrosis of the vascular wall (thick arrow) with perivascular edema (arrows' heads). G) showing diffuse vacuolation of some cardiac myofibers of mainly fatty degeneration (arrows degeneration) with severe vascular congestion (thin arrow) in addition to discontinuity of some fibers (thick arrow) and losing the normal striation of others. H&I) representing doxorubicin- and resveratrol-treated group. H) shows interstitial inflammatory cells' infiltration (arrowheads) in addition to mild proliferation of Anitschkow cells (thin arrows), and I) shows mild vascular congestion (arrowhead) with focal normal myocardium and intact fibers, (scale bar =100µm).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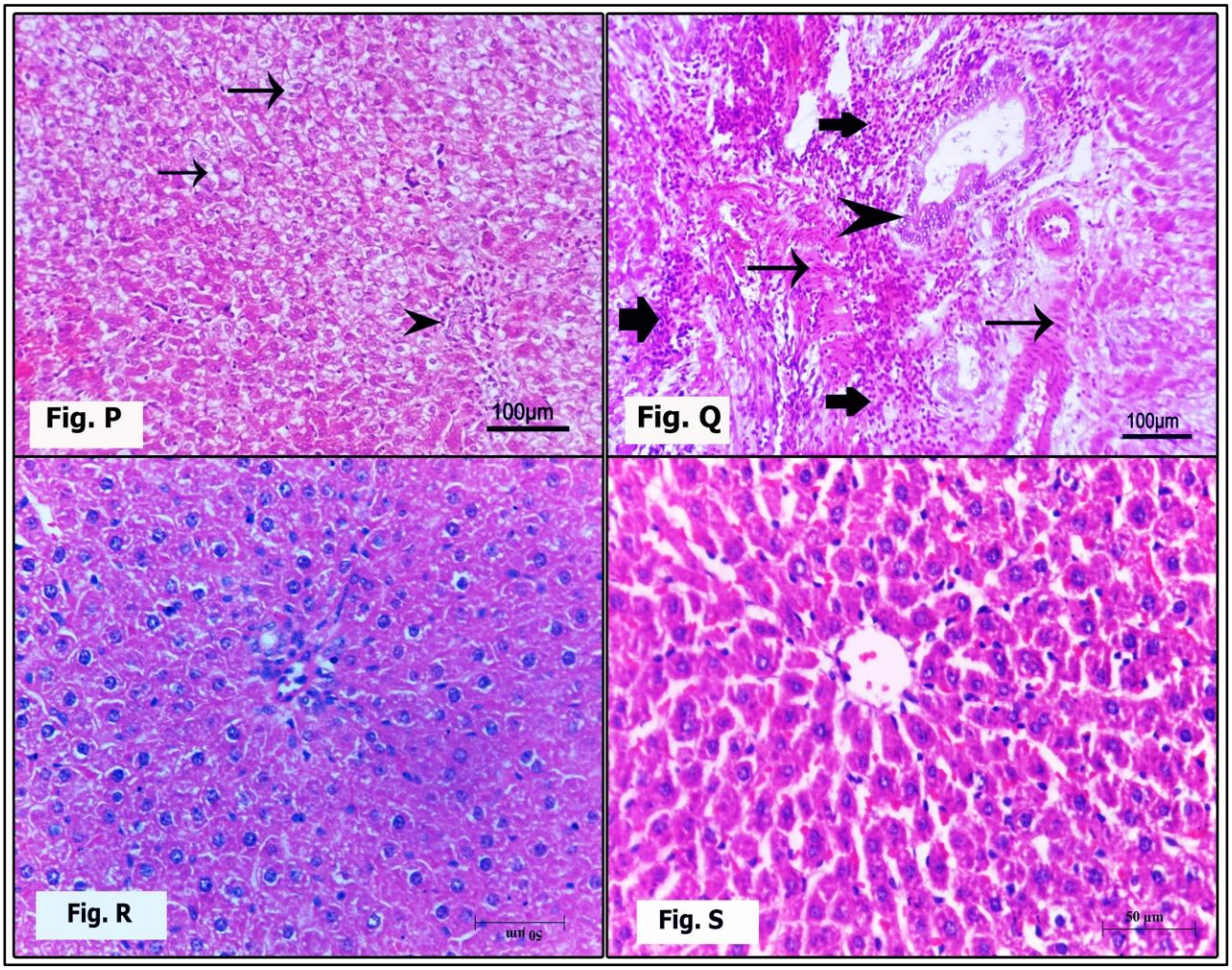

Figs. J-S: Photomicrographs of H- and E-stained liver sections of male adult albino rats. J, K, and L) show normal tissue architecture, cellular details, and intact hepatic vasculature and represent groups I, II, and III, respectively. M-Q) showing a doxorubicin-treated group. In these photomicrographs: M) showing hyperplasia of the biliary epithelium (arrowheads) with vascular congestion (arrow). N) showing severe congestion of the hepatic blood vessel (arrow). O) the hepatocytes' architecture is disrupted. Most hepatocytes are vacuolated with the area of vanished cells characterized by several Langhans giant cells (arrows) that scavenge the remnants of the hepatocytes. P) A disrupted hepatic architecture of hepatocytes with lytic and coagulative necrotic hepatocytes and diffuse mild vacuolation of some hepatocytes (arrows) and inflammatory cells infiltration. Q) showing vacuolation of the biliary epithelium (arrowhead) with focal and perivascular fibrosis (thin arrows), in addition to massive mononuclear cells infiltrating the hepatic parenchyma (thick arrows). R & S) representing the combination group of resveratrol- and doxorubicin-treated rats, in which both photomicrographs showed minimal inflammatory cellular infiltration with almost normal hepatic architecture. Fig. S shows mild widened blood sinusoids.

Discussion

The antineoplastic agent doxorubicin causes severe cardiac and hepatic toxicity mediated through oxidative injury (Attia and Bakheet, 2013). Its toxicity limits its use (Rawat et al., 2021). The current research assessed the protective effect of resveratrol on doxorubicin-induced cardio- and hepatic-toxicity in male adult albino rats with a focus on biochemical and histopathological analysis to provide a comprehensive evaluation of tissue injury. Our findings showed that Dox treatment (Group IV) significantly increased cardiac biomarkers levels) including LDH, AST, troponin, SOD, catalase, MDA, and caspase-3(, together with CK-MB and TAC depletion (Octavia et al., 2012; Songbo et al., 2019; Zhang et al., 2020). These results are in agreement with the earlier studies demonstrating that Dox induces cardiotoxicity by generating an excessive level of reactive oxygen species (ROS) that, in turn, leads to lipid peroxidation, mitochondrial injury, and apoptosis (Lemasters and Neiminen, 2001; Berthiaume and Wallace, 2007; Xiong et al., 2025). These biochemical observations were complemented with histopathological studies, showing an extensive damage in structure of the cardiac tissue. H- &E-stained sections of the Dox group revealed alterations ranging from vascular endotheliosis to diffuse myomalacia of cardiac fibers (Fig. D). In addition to interstitial extravasated erythrocytes with mild hyalinization of some cardiac fibers. Also, severe

fibrosis of the vascular wall, with perivascular edema (Fig. E). In addition to diffuse vacuolation of some cardiac myofibers of mainly fatty degeneration (Fig. F). In Figure "G", the heart section showed severe vascular congestion and discontinuity of some fibers, with loss of the normal striation of others. These cardiac alterations were thoroughly documented by Abdu et al. (2019).

Furthermore, Carvalho et al. (2010) indicated that in their Dox-treated rat model, the oxidation of long-chain fatty acids in cardiac mitochondria was notably reduced and shifted towards glucose metabolism when metabolic genes were transcriptionally suppressed. This shift leads to the accumulation of fat in the heart tissue, a change induced by oxidative stress and signaling related to Dox treatment (Carvalho et al., 2010). Furthermore, in the hearts of rats receiving Dox, hemorrhagic areas were noted between cardiomyocytes, along with increased levels of vascular endothelial growth factor (VEGF). This indicates that Dox has a variety of effects on endothelial cells, including promoting vasodilation and enhancing permeability (Attia et al., 2017). These findings agree with previous reports that doxorubicin induces cardiotoxicity by excessive ROS production, leading to lipid peroxidation, mitochondrial damage, and apoptotic cell death (Octavia et al., 2012; Songbo et al., 2019; Zhang et al., 2020). At the same time, histopathological examination of the hearts of doxorubicin-treated rats revealed severe structural alterations, which were also linked with extensive hepatic disturbances.

Likewise, our findings demonstrated a significant elevation in hepatic biomarkers (ALT, AST, total bilirubin, MDA, and caspase-3) with reductions in TAC, SOD, and catalase, signifying huge oxidative destruction and apoptotic activation in liver tissues (Quiles et al., 2002; Thandavarayan et al., 2010; Tacar et al., 2013; Wang et al., 2025). The hepatocytes' architecture was disrupted (Figs. M-Q). The microscopical examination showed hyperplasia of the biliary epithelium (Fig. M) with vascular congestion.

The sections exhibited severe congestion of the hepatic blood vessels (Fig. N). Most vacuolated hepatocytes were shown around the vanished cells and were characterized by several Langhans giant cells (Fig. O) that invaded the destroyed areas to scavenge the remnants of the hepatocytes. The hepatocytes showed lytic and coagulative necrotic, fibrosis, and vacuolated hepatocytes in addition to vacuolated the biliary epithelium (Figs. P & Q) with inflammatory cells infiltration (Figs. P & Q). It is worth mentioning that nuclear pyknosis is one of the most characteristic features in both organs; heart and liver, as well as one of the characteristic symptoms accompanied by Dox administration according to Adwas et al. (2016). Simultaneously, microscopic changes in the hearts of Dox-treated rats were linked to severe alterations in the liver. It was reported that the mechanism of action involves Dox intercalating into DNA, which disrupts DNA repair processes and generates free radicals, resulting in damaging effects on both nuclear DNA and cell proteins (Adwas et al., 2016). Cytoplasmic vacuolization was found predominant in both hearts and liver treated with Dox compared with the control, saline, and resveratrol groups. The latter alteration was explained by Santucci et al. (2016) and mentioned by Abdel-Ghaffar and Abdelghffar (2022) due to the accumulation of the neutral lipids, which originate at the ER, accumulate in it, and pinched off the ER membrane into the cytosol.

Also, inflammatory cell infiltration whether it is monocellular or giant multicellular as Langhans giant cells is a predominant feature of inflammation in both organs, which indicates chronic inflammation. The previous observation was explained by Michael and Cynthia (2006) as one of the most repeatedly seen features due to severe tissue damage. While Farrag et al. (2020), and Abdel-Ghaffar and Abdelghffar (2022) explained that the drug that caused these changes should be listed among "drug-induced liver injury". The latter type of drugs is defined as "drug-induced critical alterations of hepatocytes that trigger the immune systems of susceptible hosts to infiltrate their livers and assault/damage hepatocytes.

Increased reactive oxygen species lead to lipid radical chain (Chaudhary et al., 2023), which could cause damage to the cell membrane, manifested in increased MDA levels as postulated by Martins et al., 2022 and increased levels of SOD, CAT, and TAC.

Doxorubicin also induces apoptosis through collapse activation via the mitochondrial pathway in cardiomyocytes and hepatocytes and plays an important role in doxorubicin-induced both cardiomyopathy and hepatopathy (Moreira et al., 2014; and Xia et al., 2020). This is confirmed by the work done by AlAsmari et al., (2021). However, another study published by Chen et al. (2017), reported that doxorubicin-induced apoptosis, especially on tissues other than the heart through the mitogen-activated protein kinase family (Micallef and Baron, 2020).

On the other hand, Ferroptosis is a recently identified form of regulated cell death different from apoptosis, it is characterized by iron overload leading to lethal levels of lipid hydroperoxides which has been shown to play an important role in disseminated intravascular coagulation (DIC) (Chen et al., 2024). The measurement of lipid peroxidation products such as MDA, together with a marked reduction in intracellular GSH levels, serve as strong biochemical indicators of ferroptosis.

Moreover, our findings further revealed that resveratrol administration (Group V) exerted partial protection against these disturbances by effectively modulating cardiac and hepatic oxidative stress markers. This can be explained by owning resveratrol, a reactive oxygen scavenging activity as confirmed by Heo et al. (2018) and Constantinescu and Mihis (2023). The cardioprotective and hepatoprotective properties of resveratrol have been attributed to its antioxidant, anti-apoptotic, and anti-inflammatory mechanisms (Zorov et al., 2014; Zordoky et al., 2015; Dolinsky et al., 2013; Chupradit et al., 2022; Alshehri and Alorfi, 2023). These findings raise the possibility that resveratrol's

protective role against oxidative stress and tissue injury due to doxorubicin may indeed be justified. Previous research has demonstrated that the administration of resveratrol can mitigate the oxidative stress-induced cardiac/hepatic tissue injury due to doxorubicin by protecting the cell membrane from peroxidative damage (Fei et al., 2018; Pinyaev et al.,2019; Monahan et al., 2021) and exert protective effects through anti-inflammatory activities (Meng et al., 2021). According to the study made by Constantinescu and Mihis (2023), resveratrol can improve the anti-oxidative potential due to doxorubicin via the reduction of tyrosine-mediated ROS (Cheng et al., 2020). In addition, resveratrol protected against myocardial ischemia-reperfusion injury by inhibiting oxidative stress and ferroptosis (Li et al., 2022). Also, resveratrol has a great effect on endotoxemia as it improves cardiomyocyte injury in lipopolysaccharide-induced endotoxemia by inhibiting ferroptosis (Wang et al., 2022).

Finally, the findings suggest that resveratrol may help mitigate the toxicity of doxorubicin treatment. In conclusion, resveratrol can give hope to improve doxorubicin-related toxicity to a broader extent.

Author contribution statement

RNH: Conceived the study. All authors designed. Performed, analyzed. and interpreted the data of the experiments; as well as; wrote the paper equally.

Competing interest statement

The authors declare no conflict of interest.

Availability of data and materials:

The datasets supporting the conclusions of this article are included within the article.

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الدور الوقائي المحتمل للريسفيراترول في علاج السمية القلبية والكبدية المحدثة بعقار الدوكسوروبيسين فى ذكور الجرذان البيضاء البالغة

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الملخص العربي

المقدمة: يعتبر عقار الدوكسوروبيسين علاج فعالا يعالج سرطان الدم النقوي الحاد وأورام مختلفة ولكنه يرتبط بتسمم كبير في القلب والكبد. **الهدف:** قامت هذه الدراسة بتقييم التأثيرات السامة الدوكسوروبيسين على هذه الأعضاء من الناحية الفيزيولوجية– المرضية والتأثيرات الوقائية المحتملة للريسفيراترول، الذي له خصائص مضادة للأكسدة ومضادة للالتهابات. **المنهجية:** تم تقسيم خمسين من ذكور الجرذان البيضاء البالغة إلى خمس مجموعات للعلاج، بما في ذلك المجموعة الضابطة، والضابطة للمحلول الملحي، والضابطة للريسفيراترول (٢٠ ملجم/كجم/ يوم/فمويا/ ٦ أسابيع), والدوكسوروبين وحدها (٢ ملجم/كجم/ مرتان/اسبوعيا/لمدة ٥ أسابيع), واخيرا المجموعة المعالجة المسبقة بلريسفيراترول (٢٠ ملجم/كجم/ يوم/فمويا/ ٦ أسابيع) يليه الدوكسوروبين (٢ملجم/كجم/ مرتان/اسبوعيا/لمدة ٥ أسابيع) . **النتائج:** أظهرت النتائج أضرارًا مرضية شديدة في القلب (بما في ذلك تلين عضلي منتشر، وتصلب زجاجي خفيف، وانقطاع بعض الألياف، وفقدان التصدع الطبيعي) والكبد (بما في ذلك البنية المضطربة، وخلايا الكبد ذات النخر التحللي والمتخثر، والتليف، وغزو خلايا لانغان العملاقة). لمجموعة الدوكسوروبيسين مقارنة بالمجموعات الثلاث الأولى. لم يلاحظ أي فروق فسيولوجية كبيرة بين مجموعات الضابطة الاولى والضابطة للمحلول الملحي والضابطة للريسفيراترول فيما يتعلق بمستويات مضادات الأكسدة القلبية والكبدية (TAC/SOD/catalase/MDA/and caspase-3) وكذلك القلب (LDH/ CK-MB/AST/ والتروبونين) ومستويات إنزيمات الكبد (ALT/AST/ وTB) **الاستنتاجات:** تشير النتائج إلى أن ريسفيراترول قد يساعد في تخفيف سمية علاج الدوكسوروبيسين. في الختام: ريسفيراترول يمكن أن يعطي الأمل في تحسين السمية المرتبطة بالدوكسوروبيسين إلى مدى واسع.

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