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Cardioprotective Effects of Resveratrol Against Diazinon-Induced Cardiotoxicity: Experiment in Rats

Conflict of interest: nothing to declare.
Authors' contribution: Afrah Talib Saddam – conceptualization, data curation, investigation, methodology, project administration, resources, software, visualization, writing – original draft and editing; Ahmed H. Al-Darraji – conceptualization, data curation, investigation, methodology, supervision, validation, visualization, writing – original draft and editing.
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Abstract

Introduction. Cardiotoxicity, a serious health concern, can be exacerbated by exposure to harmful substances like organophosphate pesticides, such as diazinon. Natural antioxidants polyphenols like resveratrol, offer promising potential to mitigate the adverse effects of such toxins.
Purpose. To investigate the protective effects of resveratrol against DZN-induced cardiotoxicity in rats.
Materials and methods. Thirty adult male albino rats were randomly divided into five groups. Each receives different doses of diazinon, resveratrol, vitamin C, or distilled water. Throughout the study, rats were monitored for body weight and general health status. At the end of the 30-day treatment period, rats were euthanized. Blood samples were collected for biochemical analysis, and hearts were excised for the assessment of glutathione peroxidase activity, interleukin-1β levels, and histopathological examination.
Results. All treated and control groups exhibited an increase in body weight. Exposed to diazinon, there were elevations in troponin, LDH, and CK levels and deterioration of the lipid profile indicative of cardiac damage. Pre-treatment with resveratrol reduced these biomarkers and improved the lipid profile, indicating enhanced antioxidant capacity and reduced pro-inflammatory mediators.
Conclusion. These findings suggest that sub-acute administration of pharmacological doses of resveratrol demonstrated cardioprotective effects against diazinon-induced myocardial injury in rats.
Keywords: diazinon, resveratrol, antioxidants, cardiotoxicity, troponin

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Кардиопротекторное действие ресвератрола при кардиотоксичности, вызванной диазиноном: экспериментальное исследование на крысах

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Резюме

Введение. Кардиотоксичность представляет собой серьезную проблему для здоровья, которая может усугубляться при воздействии вредных веществ, таких как фосфорорганические пестициды, в частности диазинон. Природные антиоксиданты полифенолы, к которым относится ресвератрол, обладают большим потенциалом в плане противодействия негативному воздействию таких токсинов.
Цель. Исследовать протекторное действие ресвератрола в отношении кардиотоксичности, вызванной диазиноном, в эксперименте на крысах.
Материалы и методы. 30 взрослых самцов крыс-альбиносов были случайным образом разделены на 5 групп. Каждая из групп получала различные дозы диазинона, ресвератрола, витамина С или дистиллированной воды. На протяжении всего исследования оценивали массу тела и общее состояние крыс. В конце 30-дневного периода лечения крысы были подвергнуты эвтаназии. Образцы крови были взяты для биохимического анализа, а сердцá извлечены для проведения оценки активности глутатионпероксидазы, уровня интерлейкина-1β и гистопатологического исследования.
Результаты. Во всех экспериментальных и контрольной группах было отмечено увеличение массы тела крыс. При воздействии диазинона наблюдалось повышение уровня тропонина, креатинкиназы и лактатдегидрогеназы, а также ухудшение липидного профиля, свидетельствующее о повреждении сердца. Предшествующий прием ресвератрола способствовал снижению уровня этих биомаркеров и улучшению липидного профиля, что указывает на повышение антиоксидантной активности и снижение уровня провоспалительных медиаторов.
Заключение. Применение фармакологических доз ресвератрола в подострый период оказывает кардиопротекторное действие при диазинон-индуцированном повреждении миокарда у крыс.
Ключевые слова: диазинон, ресвератрол, антиоксиданты, кардиотоксичность, тропонин

■ INTRODUCTION

Diazinon (DZN) is an organophosphorus pesticide used in agriculture to control various pests, like flies, lice, and ground insects. The World Health Organization classifies it as a moderate hazard still it poses significant health risks to humans and animals [1], due to its cardiotoxicity, which can lead to cardiac complications and potentially life-threatening arrhythmias [2].

One strategy for protecting against pesticide toxicity is to use natural antioxidants. Antioxidants are crucial in protecting cells from damage caused by free radicals. Classified as enzymatic such as catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx), break down harmful free radicals, while non-enzymatic like vitamins C and E, plant polyphenols neutralize them [3].

Studies showed that increased intake of polyphenolics in vegetables and fruits may reduce cardiovascular disease incidence. Resveratrol, a polyphenolic compound found in plants, has antioxidant, anti-inflammatory, and metabolic effects. It scavenges free radicals, enhances endogenous antioxidant enzyme activity like GPx, and influences multiple signaling pathways, such as the Sirtuin and Mitogen-Activated Protein Kinase (MAPK) pathways, leading to improved mitochondrial function, enhanced fat metabolism, reduced apoptosis. Resveratrol inhibits nuclear factor κB (NF-κB), a key regulator of the inflammatory response, and activates the Nuclear factor erythroid 2-related factor 2 (NRF2) pathway, which upregulates the expression of antioxidant genes [3, 4].

■ PURPOSE OF THE STUDY

To investigate the protective effects of resveratrol against DZN-induced cardiotoxicity in rats. By exploring resveratrol's protective mechanisms, the study intends to shed light on its therapeutic potential in countering the adverse cardiovascular effects associated with pesticide exposure, thereby contributing to safer agricultural practices and improved public health.

■ MATERIALS AND METHODS

Experimental Animals

The experiment was conducted at the University of Basra's College of Pharmacy, in the animal Facility, with the Ethical Committee (EC 40) approval on 10-2023.

Thirty adult male albino rats (weighted average 250–350 gm), aged (2–3 months). The animals were obtained from breeding research, in Baghdad, Iraq. The rats were placed in medium-sized plastic boxes, where the boxes were lined with wood shavings. They were provided Water and food, with the wood shavings being changed every 3 days. Four rats were placed in each box and kept in suitable environmental conditions of temperature and humidity, and avoid exposing the rats to any stress. The rats were exposed to 12 hours of normal light and 12 hours of darkness. As for the food, they were allowed to eat freely during the day and fasted during the night. After two weeks the animals' weights were recorded before administering any treatment and starting the experiment.

The materials and chemicals used in these experiments were Diazinon 10% EC liquid, bought from Endimaj for the specialized chemical and pharmaceutical industry.CO., Jordan. Resveratrol powder was purchased from Xi an LY Health Technology Co., Ltd. China. Vitamin C tablet 1000 mg was from Nutritionl L.L.C., USA. Chloroform was from Thomas Baker, India. Formaldehyde was from Loba Chemie PVT. LTD, India.

Experiment Design

Rats were randomly divided into five groups (n=6 in each group):

- Group 1: Diazinon-induced toxicity animals were administered 20 mg/kg Diazinon with an equal amount of vehicle (distilled water).
- Group 2: 20 mg/kg resveratrol was administered concomitantly before delivery of 20 mg/kg Diazinon.
- Group 3:10 mg/kg resveratrol was administered concomitantly before 20 mg/kg Diazinon was delivered.
- Group 4: 100 mg/kg vitamin C was administered before 20 mg/kg Diazinon.
- Group 5 (control): administered distilled water equivalent volume to the volumes of the agents delivered to the other groups.

Following a 30-day diazinon and treatment period, rats fasted overnight. The following day (31 days), their weights were recorded after the experiment's completion.

To euthanize the animals, the rats were anesthetized by placing them in a sealed container with a cotton ball saturated with an anesthetic agent(chloroform). Once anesthesia was confirmed, the rats were removed from the container, their chests were opened, and the heart and blood were extracted for analysis.

Blood Sampling Preparation

After opening the rats' chests, blood was drawn from a vena cava of the heart, placed in tubes for biochemical measurement, centrifuged at 3000 rpm for 15 minutes, and the clear supernatant layer was collected [5].

Tissue Sampling Preparation (Homogenate)

The rat's hearts were extracted, washed, dried, and ground into small pieces. The tissues were then homogenized, centrifuged at 5000 rpm for 5 minutes to collect the supernatant in Eppendorf tubes, and stored at –20 °C for biochemical tests [6].

Histopathological Preparation

The hearts were histopathologically evaluated by washing them with phosphate-buffered saline (PBS), drying them, measuring their weight, placing them in a 10% neutral buffered formalin solution, and stored at room temperature for 3 to 5 days for histopathological examination [7].

Evaluation of Body Weight and Organs

The experiment involved taking the weights of all animals before and after administering the treatment and diazinon and retaking them weekly. The relative weight was calculated using the equation (organ weight/animal weight) *100 [1].

Cardiac Biomarkers

The study evaluated serum troponin, lactate dehydrogenase (LDH), and creatinine kinase (CK) levels in all groups, including the control group,(1) using spectrophotometric methods. The results of LDH were analyzed using the Abbott ARCHITECT c4000 clinical chemistry analyzer. The results of both troponin and CK were analyzed using the Abbott Architect i1000SR Immunoassay System. of serum from tubes used (Blood Sampling preparation).

Measurements of Lipid Profile

Serum cholesterol and triglyceride levels were evaluated using spectrophotometric methods, (8) including the Abbott ARCHITECT c4000 clinical chemistry analyzer, in all groups, including the control group, using blood sampling preparation.

Estimation of Tissue Glutathione Peroxidase Levels

GPX was measured in heart tissue as an antioxidant parameter, by using a previously prepared sample (homogenate) using the Rat Glutathione Peroxidase ELISA Kit [9].

Estimation of Tissue Interleukin-1β Level

IL-1β was measured in heart tissue as an inflammatory marker, by using a previously prepared sample (homogenate) using the Rat Interleukin1 B ELISA Kit [10].

Histopathological Examination

Using a previously prepared sample (Histopathological preparation sample) Histopathological examination occurs for heart tissues.

Statistical Analysis

The study's results were presented as the mean value and the standard error of the mean (SEM). One-way ANOVA and Tukey post hoc test were used in the statistical analysis to determine significant differences between the treated and the control groups. A p-value of (≤0.05) was considered statistically significant, and the analysis was done using Graph Pad Prism software, version 10.2.3(403) [11].

■ RESULTS

Effect of Treatments on Relative Heart Weight

There were no significant differences in relative heart weight between all experiment groups and between the control group and the treatment groups (Diazinon, Vit. C, RES 10 mg, RES 20 mg). Non-significant elevated relative cardiac weight was seen in group vitamin C (Fig. 1A).

Cardiac Effects

Effect of Treatments on Serum Troponin Levels. As illustrated in Fig. 1B, there is a statistically significant difference in troponin levels among different groups, with the diazinon group having higher levels, compared to the control group, and the vitamin C and resveratrol groups showing lower levels, compared to diazinon.

Effect of Treatments on Serum LDH Levels. The diazinon group significantly increased LDH levels, but no significant differences were found among all experiment groups. Vitamin C did not significantly reduce LDH levels, and the resveratrol 20 mg group tended to lower LDH levels but did not significantly reduce them, compared to the diazinon group (Fig. 1C).

Effect of Treatments on Serum CK Level. Fig. 1D demonstrates a significant statistical difference in serum CK levels among all groups, with diazinon groups having higher levels. Vitamin C and resveratrol groups significantly reduced CK levels, while the resveratrol 20 mg group showed lower levels, compared to the diazinon group.

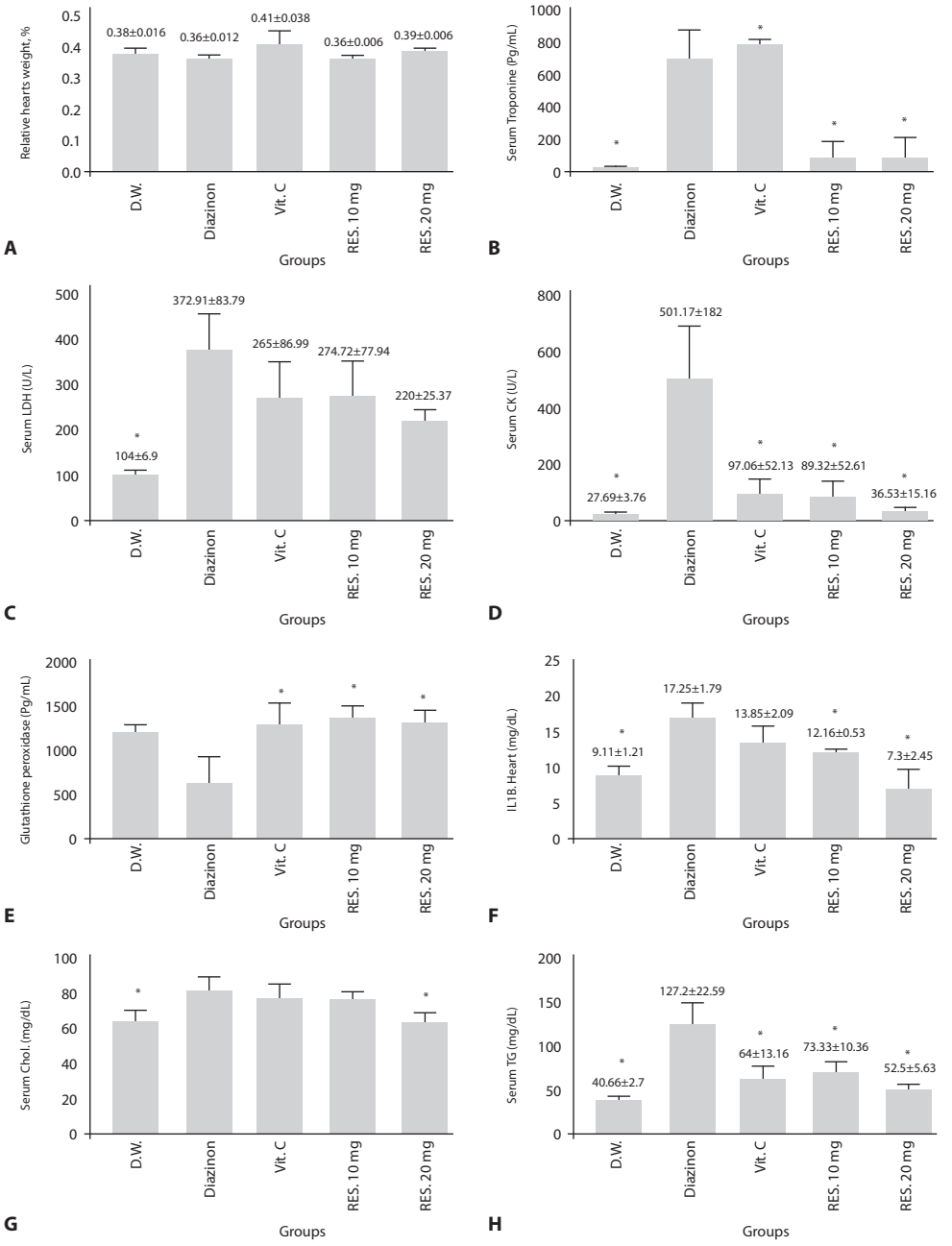


Fig. 1. A – Comparison of cardiac weight showing the effect of Resveratrol and vitamin C after Diazinon administration; B – Comparison of troponin levels showing the effect of Resveratrol and vitamin C; C – Comparison of LDH levels showing the effect of Resveratrol and vitamin C; D – Comparison of CK. Levels showing the effect of Resveratrol and vitamin C; E – Comparison of myocardial GPX levels showing the effect of Resveratrol and vitamin C; F – Comparison of myocardial IL-1β levels showing the effect of Resveratrol and vitamin C; G – Comparison of cholesterol levels showing the effect of Resveratrol and vitamin C; H – Comparison of triglycerides levels showing the effect of Resveratrol and vitamin C

Effect of Treatments on Cardiac Tissue GPX Levels. While no overall differences in GPx levels between groups, a trend toward reduced GPx in the diazinon group. Both vitamin C and resveratrol significantly elevated GPx levels, compared to the diazinon group (Fig. 1E).

Effect of Treatments on Cardiac Tissue IL-1β **Levels.** The study found a significant relationship between exposure to diazinon and IL-1β levels, with the vitamin C group reducing IL-1β levels but not significant. Both doses of resveratrol significantly decreased IL-1β levels, with higher doses showing greater efficacy, compared to the diazinon group (Fig. 1F).

Effect of Treatments on Lipid Profiles

Effect of Treatments on Cholesterol Serum Levels. The experiment demonstrated that diazinon significantly elevated serum cholesterol levels. While vitamin C and 10mg resveratrol did not significantly decrease cholesterol levels, resveratrol with higher doses has significantly reduced cholesterol, compared to the diazinon group (Fig. 1G).

Effect of Treatments on Triglyceride Serum Levels. In this experiment, all groups' relationships were statistically significant. The diazinon group exhibited significantly higher serum triglyceride (TG) levels. Conversely, the Vitamin C and resveratrol groups significantly decreased serum TG levels compared to the Diazinon group (Fig. 1H).

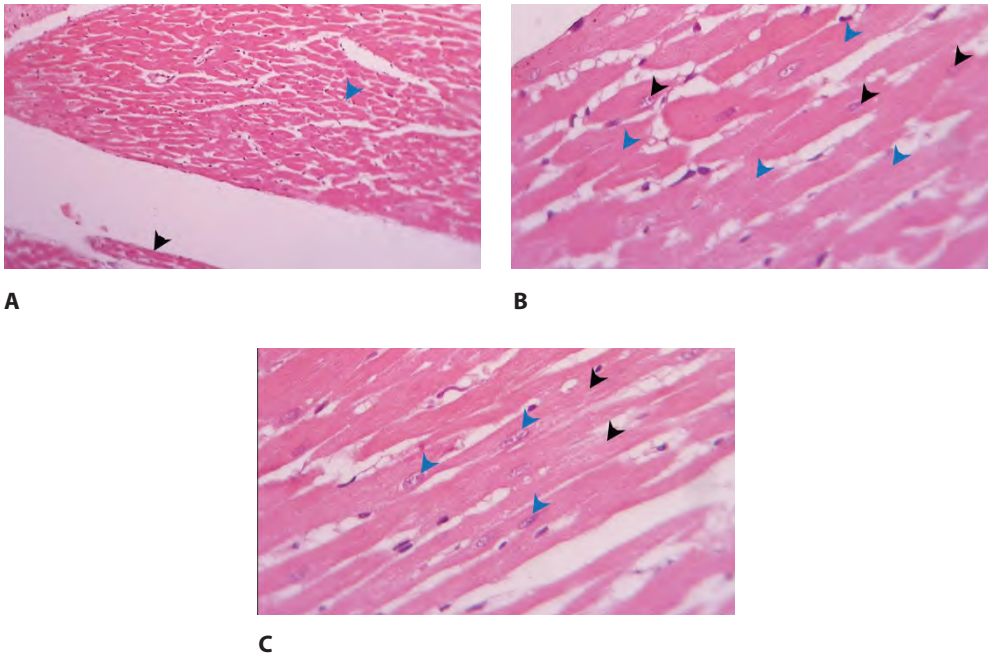


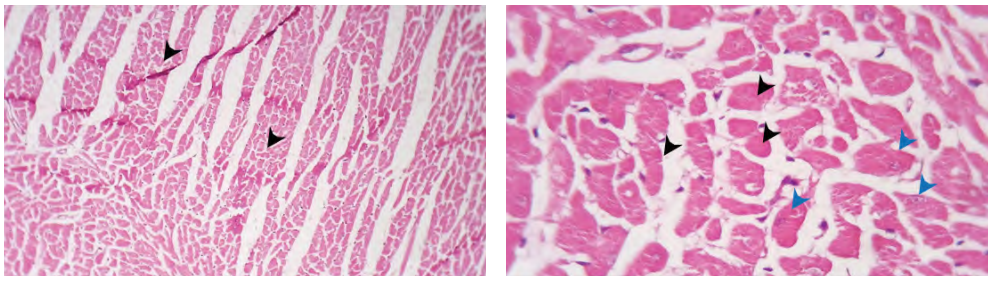
Fig. 2. A – Heart of control group shows normal longitudinal myocardial muscle fibers (black arrow), normal transverse muscle fibers (blue arrow), 10X; B – Heart of control group shows normal transverse muscle fibers (blue arrow), normal nuclei (black arrow), 40X; C) Heart of control group shows normal longitudinal myocardial muscle fibers (black arrow), normal nuclei (blue arrow), 40X (H&E)

Effect of Treatments on Cardiac Histopathology

The study examined the myocardial architecture of heart tissue in different groups. The control group had normal striated, cylindrical morphology Fig. 2A–C, while the diazinon group showed necrosis Fig. 3. In vitamin C-treated groups about half (50%) of the myocardial fibers in the examination field at 40X magnification consisted of necrotic fibers with nucleus loss (Fig. 4), in Resveratrol (10 mg) there were 23% necrotic fibers and 7% of fibers showed vacuolar degeneration (Fig. 5), while Resveratrol (20 mg) treated group there were only normal myocardia fibers in the field and no any microscopic changes were seen in the heart of this group (Fig. 6).

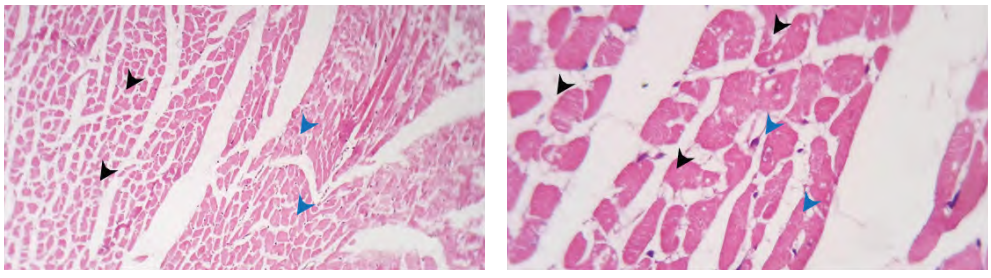
■ DISCUSSION

This study explored the cardioprotective effects of resveratrol against diazinon-induced cardiotoxicity in rats. The rats were divided into five groups: a control group, a diazinon group, and three groups receiving diazinon with either vitamin C or resveratrol in two doses. Researchers monitored various health markers throughout the experiment. Results showed that diazinon caused heart damage, reflected in elevated blood markers such as troponin, LDH, CK, and lipid profile. Also, there is an increase in IL-1β and a decrease



A **B**

Fig. 3. A – Heart of diazinon group shows necrotic myocardial muscle fibers (black arrow), 10X; B – Heart of diazinon group shows necrotic myocardial muscle fibers (black arrow), others are appearing normal (blue arrow), 40X (H&E)



A **B**

Fig. 4. A – Heart of Vit C treated group shows some necrotic myocardial muscle fibers (black arrow), others are appearing normal (blue arrow), 10X; B – Heart of Vit C treated group shows some necrotic myocardial muscle fibers (black arrow), others are appearing normal (blue arrow), 40X (H&E)

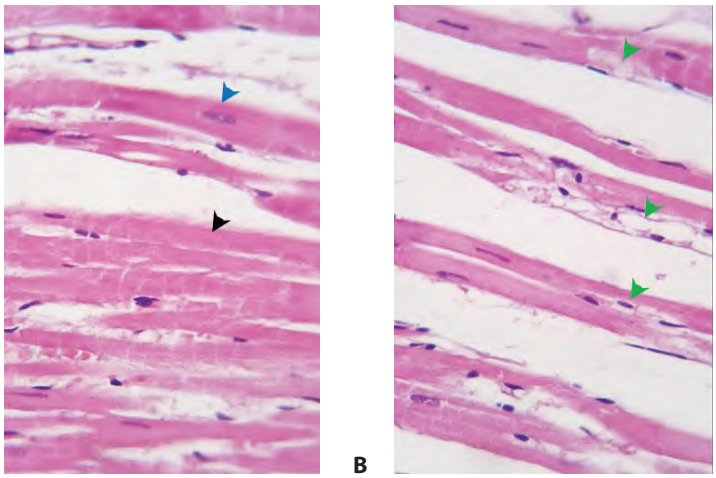


Fig. 5. Heart of resveratrol (10 mg) treated group shows vacoulation of myocardial cells (green arrow), some of them appear necrotic (black arrow), others are normal (blue arrow), H&E. A – 10X; B – 40X

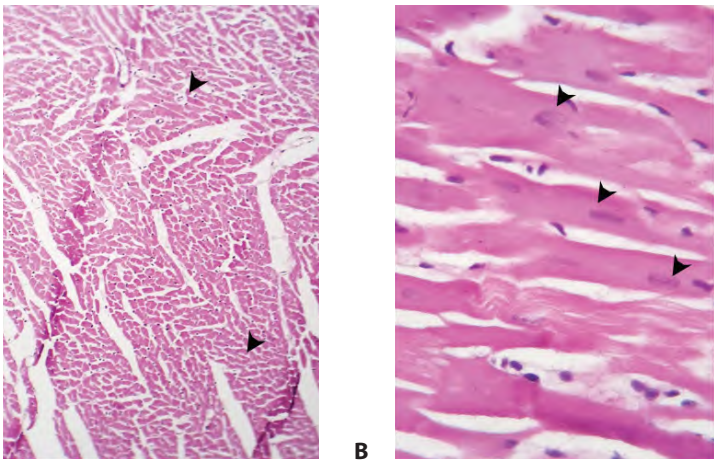


Fig. 6. Heart of resveratrol (20 mg) treated group shows normal myocardial muscle fibers (black arrow), H&E. A – 10X; B – 40X

in GPX in heart tissue. Both vitamin C and resveratrol helped protect against these effects. Vitamin C has positively affected heart function, with some improved heart tissue observed in histological analysis. Resveratrol, at both doses, has protected the heart, with the higher dose showing better results. Rats in the resveratrol groups exhibited better overall health and heart functions were significantly improved. Histological examination revealed no pathological changes in the heart of rats treated with resveratrol compared to the Diazinon group which exhibited pathological changes in necrosis, and infiltration to neutrophils within the necrotic tissue.

The findings of this experiment demonstrate that the combined administration of resveratrol or vitamin C following diazinon treatment can decrease the levels of cardiac enzymes, including troponin I (CnTnI), creatine kinase-MB (CK-MB), Lactate dehydrogenase (LDH), and lipid profile in the bloodstream. Decrease in IL-1β and increase in GPX in heart tissue.

Cardiac toxicity is a condition where certain drugs or substances cause heart damage, often exacerbated by inflammation. Leading to impaired heart function, increased oxidative stress, and heart failure or arrhythmias [12].

Diazinon, an organophosphate compound, is linked to cardiovascular toxicity due to Primarily inhibiting acetylcholinesterase enhances acetylcholine accumulation, which activates inflammatory pathways like p38 MAPK, extracellular signal-regulated kinase (ERK), and NF-κB, and NLRP3 inflammasome, leading to caspase-1 activation and IL-1β secretion [13], and reduced antioxidant enzyme (GPx) levels, depletion of the essential substrate glutathione (GSH) [9]. This leads to oxidative stress, inflammation, and cell death, causing heart dysfunction and failure [14]. Diazinon exposure also increases blood lipid levels [8] and increases inflammation, exacerbated by immune responses, oxidative stress, and damaging heart cells. This is supported by histological alterations in heart tissue, such as necrosis and the infiltration of inflammatory cells [15].

Resveratrol, a polyphenolic compound found in plants like grapes, has cardioprotective effects by reducing oxidative stress, inflammation, lipid metabolism, and cellular protection. Its anti-inflammatory action inhibits key inflammatory pathways like NF-κB and MAPK [16], and lowers pro-inflammatory cytokine production like IL-1β, by preventing the kappa kinase (IκB) degradation, blocking toll-like receptor 4 (TLR4) signaling, activating silent information regulator T1 (SIRT1), inhibiting the NLRP3 inflammasome [17]. Resveratrol also targets pro-inflammatory enzymes like cyclooxygenase 2 (COX-2), and inducible nitric oxide synthase (iNOS), further contributing to its anti-inflammatory profile [4,18].

Resveratrol has antioxidant properties by neutralizing free radicals, reducing reactive oxygen species (ROS) production, alleviating oxidative stress, and protecting myocardial cells [19]. This is achieved through increased GPx levels [20], activation of transcription factors like Forkhead box (FOXO) [21], and enhancement of GSH synthesis [22].

Resveratrol significantly impacts lipid metabolism [23, 24] reducing blood lipid levels by inhibiting Cholesteryl ester transfer protein (CETP), upregulating reverse cholesterol transport, and downregulating HMG-CoA reductase. By preventing LDL oxidation, provides a balanced lipid profile.

Resveratrol protects cardiomyocytes by preventing apoptosis and activating survival pathways such as phosphatidilinositol-3-kinase/protein kinase B (PI3K/AKT), and Glycogen synthase kinase 3 beta (GSK3B) phosphorylation [25]. It enhances endothelial function, improving vasodilation and blood flow [26]. Resveratrol can restore normal cardiac architecture [27, 28], by reducing ROS production, mitigating Transforming growth factor-beta (TGF-β) overexpression, and enhancing protective proteins like S100A1, contributing to overall cardioprotection.

■ CONCLUSION

Resveratrol is a naturally occurring compound found in the skin of grapes and certain other plants, is a potent antioxidant, according to the current study, Resveratrol exhibited superior cardioprotective effects compared to vitamin C against heart injury caused by

diazinon, an organophosphorus compound. Resveratrol significantly lowered troponin, CK, LDH, and triglyceride cholesterol to near-control levels. Moreover, resveratrol markedly reduced pro-inflammatory cytokine IL-1β levels below those of the control group, while simultaneously elevating antioxidant enzyme GPX levels above normal. Histological examination showed no significant heart pathological changes. Its effectiveness in preclinical studies requires further investigation in human clinical trials to estimate Resveratrol's potential therapeutic benefits.

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