

# Protective effect of *Tulbaghia violacea* extract on cardiac damage: deep circulatory arrest rat model

Bişar Amaç<sup>1</sup>, Nazım Kankılıç<sup>2</sup>, Fatih Güngören<sup>3</sup>, Mehmet Salih Aydın<sup>2</sup>, Yusuf Çakmak<sup>4</sup>, Muhammet Emin Güldür<sup>5</sup>, İsmail Koyuncu<sup>6</sup>, Emine Zeynep Tarini<sup>7</sup>, Mesut Engin<sup>8</sup>, Senol Yavuz<sup>8</sup>

<sup>1</sup>Department of Cardiovascular Surgery, Division of Perfusion, University of Health Sciences, Mehmet Akif Inan Research and Training Hospital, Sanliurfa, Turkey; <sup>2</sup>Department of Cardiovascular Surgery, Harran University School of Medicine, Sanliurfa, Turkey, <sup>3</sup>Department of Cardiology, Harran University School of Medicine, Sanliurfa, Turkey, <sup>4</sup>Animal Experiment Application and Research Center (HDAM), Harran University, Sanliurfa, Turkey, <sup>5</sup>Department of Pathology, Harran University School of Medicine, Sanliurfa, Turkey, <sup>6</sup>Department of Medicinal Biochemistry, Harran University School of Medicine, Sanliurfa, Turkey, <sup>7</sup>Department of Pathology, University of Health Sciences, Mehmet Akif Inan Research and Training Hospital, Sanliurfa, Turkey, <sup>8</sup>Department of Cardiovascular Surgery, University of Health Sciences, Bursa Yüksek İhtisas Training, and Research Hospital, Bursa, Turkey

## ABSTRACT

**Objectives:** Total circulatory arrest (TCA) technique is a method used in cardiac surgery accompanied by cardiopulmonary bypass (CPB). It has been shown that *Tulbaghia violacea* extract increases antioxidant capacity, regulates blood pressure, decreases lipid peroxide, and reduces atherosclerosis. In this experimental study, we aimed to investigate the effect of *T. violacea* extract administration on serum oxidative stress parameters (Total antioxidant status [TAS], total oxidant status [TOS] and oxidative stress index [OSI] and deoxyribonucleic acid [DNA] damage level with 8-Hydroxy-2-Deoxyguanosine [8-OHdG]) and histopathological changes in the heart and other organs in rats with deep circulatory arrest model.

**Methods:** In this study, 48 Wistar Albino adult rats, 24 female and 24 male, obtained from Harran University Experimental Animals Research Center were used. The average weight of female rats was 250-300 g, and the average weight of male rats was 450-500g. These rats were randomly divided into four groups. 6 male and 6 female rats were used in each group (Group 1 = Sham, Group 2 = Injury, Group 3 = Treatment and Injury, Group 4 = Treatment).

**Results:** As a result of this experimental study, the changes in the biochemical 8-OHdG, TOS, OSI and TAS levels of the groups were found to be statistically significant ( $p < 0.001$ ). In the subgroup analyzes of the data, 8-OHdG level, which is an oxidative DNA damage marker in Group 2 was higher than the Group 1, Group 3 and Group 4 and there was a statistically significant difference ( $p < 0.001$ ,  $p = 0.027$  and  $p < 0.001$ ; respectively). The TOS level of the injury group was higher than Group 1, Group 3 and Group 4 and there was a statistically significant difference ( $p < 0.001$ ,  $p = 0.003$  and  $p < 0.001$ ; respectively).

**Conclusions:** As a result of our study, we revealed that *T. violacea* extract has a protective effect on organ and tissue damage in the TCA model.

**Keywords:** Circulation, arrest, protective agent, plant derived, *Tulbaghia violacea* extract

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**Address for correspondence:** Mesut Engin, MD., University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Cardiovascular Surgery, Mimar Sinan Town, Emniyet Street, Yıldırım, Bursa, Turkey. E-mail: mesut\_kvc\_cor@hotmail.com, Tel: +90 224 2955000, Fax: +90 224 2756767

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Cardiac diseases have an important place among the causes of morbidity and mortality all over the world [1]. It will continue to be an important health problem in the future [2]. Cardiac surgery has an important role in the treatment of these diseases, and most of cardiac surgeries are performed using cardiopulmonary bypass (CPB). In addition, the total circulatory arrest (TCA) technique is performed in cardiac surgery accompanied by CPB, especially in aortic arch surgery [3]. The deep hypothermic TCA method is the method in which the body temperature is lowered below 20 °C and the blood circulation is temporarily stopped. It is preferred in thoracic aortic lesions associated with aortic arch, complex congenital pathologies, pulmonary thromboembolism and sometimes intracerebral aneurysm surgeries other than cardiovascular surgery. After hypothermic circulatory arrest, adverse events related to many organs, especially neurological and cardiac damage, may occur. They are localized ischemic infarcts that develop as a result of global ischemia or embolism as a result of localized stroke, infarction, insufficient flow or protection [4, 5]. In order to prevent these negative situations, cardioplegic arrest for the heart and hypothermia and various medical treatments are used for other organs [6].

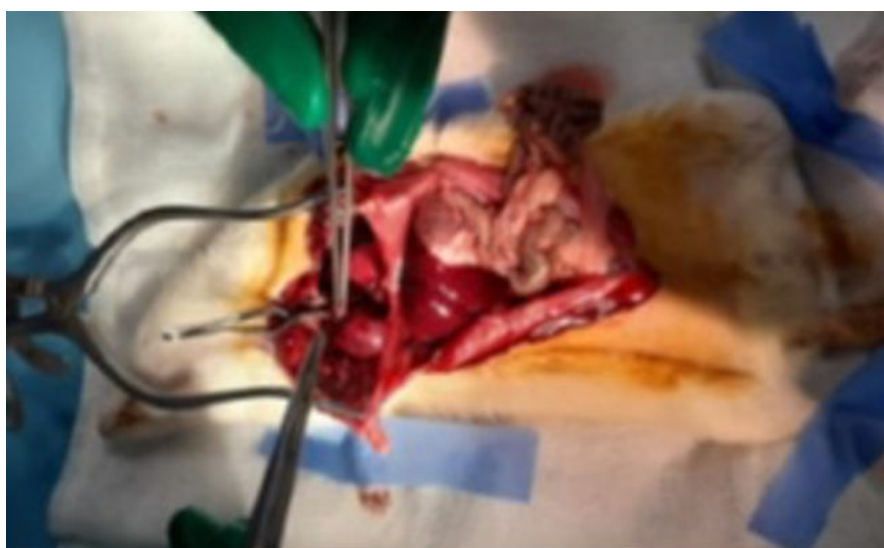
*Tulbaghia violacea* plant is a perennial ornamental plant with green leaves in summer and winter, its leaves and flowers give a garlic odor when rubbed, are edible, have a garlic flavor. This plant contains active compounds such as tannins, terpenoids, flavonoids,

saponins, proteins, steroids, cardiac glycosides, phenols and coumarins [7]. It has been shown that *T. violacea* increases antioxidant capacity, regulates blood pressure, decreases lipid peroxide, and reduces atherosclerosis [8].

In this experimental study, we aimed to investigate the effect of *T. violacea* extract administration on serum oxidative stress parameters (Total antioxidant status [TAS], total oxidant status [TOS] and oxidative stress index [OSI] and deoxyribonucleic acid [DNA] damage level with 8-Hydroxy-2-Deoxyguanosine [8-OHdG]) and histopathological changes in the heart and other organs in rats with deep circulatory arrest model.

## METHODS

This research was carried out as a doctoral thesis by the Perfusion Technology Program of the Department of Cardiovascular Surgery, Institute of Health Sciences, Harran University. Approval was obtained from Harran University Animal Experiments Local Ethics Committee on 11/12/2020 (Session no: 2020/0006, Decision: 01-17). After the approval of the Ethics Committee, a scientific research project was prepared. The project support of the study was approved by Harran University Scientific Research Projects Coordination Unit on 29/04/2021 (HUBAK Project No: 21130). Experimental study was carried out between 17/06/2021-02/07/2021 in Harran University Experi-



**Fig. 1.** Controlled ischemia in the heart by applying a cross-clamp to the aorta in a rat who underwent laparotomy and sternotomy.

mental Animals Laboratory. The blood and pathology samples taken as a result of the experimental study were stored under appropriate conditions and the data were obtained by working in the laboratories of Medical Biochemistry and Medical Pathology of Harran University.

### Experimental Animals

In this study, 48 Wistar Albino adult rats, 24 female and 24 male, obtained from Harran University Experimental Animals Research Center were used. The average weight of female rats was 250-300 g, and the average weight of male rats was 450-500 g. These rats were randomly divided into four groups. 6 male and 6 female rats were used in each group. Animal experimentation and care of all rats were carried out in accordance with the principles of "Regulation on Working Procedures and Principles of Animal Experiments Ethics Committees" and "Care Principles of Experimental Animals" shaped by the National Association for Medical Research.

### Deep Circulatory Arrest Model

Before the study, rats were fasted for 8 hours. During this time, they were allowed to drink water. All applications were performed under anesthesia. Ketamine (60 mg/kg) (Ketazol<sup>®</sup> 10%, 10ml, Richter Pharma AG 4600 Wels, Austria) and xylazine (40 mg/kg) intraperitoneally (ip) for anesthesia purposes (Rompun<sup>®</sup> 2%, 25ml, Bayer Healthcare LLC. Kansas 66201), USA) was applied. If necessary, an additional dose of 3/1 of the application dose was planned. Midline laparotomy and sternotomy were performed on rats whose skin was prepared aseptically (the abdominal skin was cleaned with povidone iodine after shaving), and the heart was reached. Before cardiac arrest, 0.1 ml of heparin (Koparin<sup>®</sup> 25000 IU/5ml, Koçak Farma İlaç ve Kimya Sanayi A.Ş. Kapaklı, Tekirdağ) was administered to all rats with an insulin injector from the right atrium while the heart was working [9]. Then, controlled ischemia was created in the heart by placing a cross-clamp on the aorta (Fig. 1). Immediately after the application of cross-clamp to the aorta, cardiac arrest was achieved by administering 0.2 ml of potassium chloride (KCL) (Turktipsan Potassium Chlorür<sup>®</sup> 750 mg/10ml, Turktipsan Turizm Eğitim ve Tic. AS. Akyurt, Ankara) from the right atrium or aortic root with an insulin injector [10, 11]. In some groups, total

circulatory arrest was created for 20 minutes. Cardiac damage was created with this circulatory arrest [12, 13]. Then, blood was drawn from the hearts (right atrium) of all rats and their hearts were surgically removed. Tissues and blood samples were stored at -80 °C for histopathological and biochemical studies until the study.

### Working Groups

Group 1 (Sham group, n = 12): They were fed with standard rat chow and tap water for 15 days. On the 16th day, all rats in this group were sacrificed under deep anesthesia (Ketamine (90 mg/kg) and xylazine (10 mg/kg)-i.p) and their blood and all tissues were removed.

Group 2 (Injury group [TCA group], n =12): An experimental cardiac injury model was created with TCA in rats after similar feeding and anesthesia. After TCA, the blood sample and all tissues were removed.

Group 3 (Treatment+Injury group [*T. violacea* extract+TCA group], n = 12): Different from group 2, *T. violacea* extract (500 mg/kg/day) dissolved in 0.9% saline for 15 days was given to this group by oral gavage. administered directly into the stomach.

Group 4 (Treatment group [*T. violacea* extract group], n = 12): In this group, unlike Group 3, blood and tissue samples of the rats were extracted without applying the TCA model.

### Histopathological Examination

As a result of the experimental study, the tissues taken from the rats were grouped and numbered, and the heart tissues were fixed separately in 10% buffered neutral formaldehyde solution for histopathological examination. Afterwards, the samples were embedded in paraffin blocks and sections of 5 micron meters were taken. These sections were stained with hematoxylin-eosin dye and examined with Nikon Eclipse<sup>®</sup> NI DS-FI2, JAPAN microscope. Interstitial edema, inflammatory cell infiltration and presence of necrosis were evaluated in the histopathological examination.

### Biochemical Evaluation

As a result of the experimental study, the blood taken from the rats was grouped and numbered and collected in heparinized yellow capped gel-free tubes. Collected blood was centrifuged at 4000 rpm for 10 minutes. The serum portion from the centrifuged

blood was transferred to eppendorf tubes and stored at -80 oC until the study day. Then, changes in oxidative stress parameters (TAS, TOS, OSI) and DNA damage level (8-OHdG) at blood serum levels were examined.

### Statistical Analysis

Statistical analyzes were performed using the SPSS® package program (IBM Corp. Released 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.). Mean and standard deviations were calculated for continuous and ordinal data. Data were given as mean and standard deviation. Kolmogorov Smirnov test and Shapiro-Wilk test were used to evaluate the normality distribution. One Way ANOVA test was used to compare the four groups. Tukey test was used for subgroup analysis of the data. Statistically  $P < 0.05$  values were considered significant.

## RESULTS

As a result of this experimental study, the changes in the biochemical 8-OHdG, TOS, OSI and TAS levels of the groups were found to be statistically significant ( $p < 0.001$ ) (Table 1).

In the subgroup analyzes of the data (Table 2), 8-OHdG level, which is an oxidative DNA damage marker in Group 2 was higher than the Group 1, Group 3 and Group 4 and there was a statistically significant difference ( $p < 0.001$ ,  $p = 0.027$  and  $p < 0.001$ ; respectively). The TOS level of the injury group was higher than Group 1, Group 3 and Group 4 and there was a statistically significant difference ( $p < 0.001$ ,  $p = 0.003$  and  $p < 0.001$ ; respectively).

The OSI level of Group 2 was higher than Group 1, Group 3 and Group 4 and there were statistically

significant differences ( $p < 0.001$ , for all). TAS levels in Group 1, Group 3 and Group 4 were higher than Group 2 and there were statistically significant differences ( $p < 0.001$ ,  $p = 0.004$  and  $p < 0.001$ ; respectively).

### Cardiac Tissue Histopathological Findings (Fig. 2)

As a result of the experimental study, the regular structure in the heart tissue of the rats was examined in the histopathological examination of the heart tissues taken from the rats. No pathological finding was detected. A regular heart muscle is observed in the sample of Group 1 (Fig. 2A). Histopathological examination of Group 2 reveals localized areas of necrosis and edema in the myocardial tissue in the tissue sections (Figs. 2B and 2C). In the histopathological examination of Group 3 significant improvement was observed in the areas of edema and focal necrosis in the muscle fibers (Fig. 2D). Histopathological examination of Group 4 revealed regular muscle fibers (Fig. 2E).

### Histopathological Findings of Liver and Kidney Tissues (Fig. 3)

In Group 1, hepatic (Fig. 3A) and renal parenchyma (Fig. 3B) are observed in a regular histopathological structure. Focal lytic necrosis in the liver tissue of Group 2 is indicated by the green arrow ( $\times 400$ ) (Figure 3C). In the histopathological examination of Group 2, hemorrhage in the renal parenchyma, interstitial tissue between the tubules, glomerulosclerosis (Blue arrow), inflammatory infiltration in the stroma (Fig. 3D) ( $\times 100$ ), Group 3, significant improvement in periportal fibrosis in liver tissue (Fig. 3E), renal parenchyma ( $\times 100$ ) containing regular glomerular structures with minimally thrombosed vascular structures (Fig. 3F).

**Table 1. The change of oxidative parameters of the experimental rat groups**

	Group 1 (Sham)	Group 2 (Injury)	Group 3 (Treatment/Injury)	Group 4 (Treatment)	p value
8-OHDOG (ng/mL)	1.8 ± 0.59	6.22 ± 1.5	4.58 ± 2.14	1.55 ± 0.47	< 0.001
TOS (µmol H2O2 Eqv/1)	10.66 ± 2.15	15.85 ± 1.71	13.13 ± 1.81	10.29 ± 1.32	< 0.001
OSI (µ)	0.69 ± 0.17	1.4 ± 0.23	0.93 ± 0.18	0.65 ± 0.11	< 0.001
TAS (mmol Trolox Eqv/1)	1.57 ± 0.27	1.14 ± 0.12	1.41 ± 0.13	1.6 ± 0.17	< 0.001

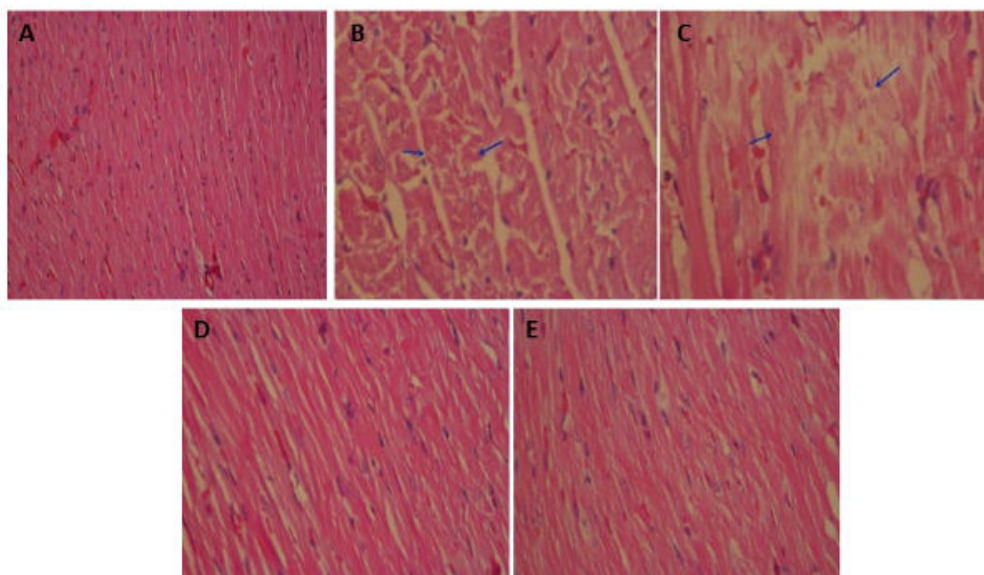
One Way Anova test was used to compare the four groups. Data were given as mean and standard deviation. 8-OHdG = 8-hydroxy-2'-deoxyguanosine, TOS = Total oxidant status, OSI = Oxidative stress index, TAS = Total antioxidant status.



**Table 2. Subgroup analysis of the data of the experimental groups**

<b>8-OHDOG (ng/mL)</b>	Group 1 vs Group 2 <i>p</i> < <b>0.001</b>	Group 1 vs Group 3 <i>p</i> < <b>0.001</b>	Group 1 vs Group 4 <i>p</i> = 0.973
	Group 2 vs Group 3 <i>p</i> = <b>0.027</b>	Group 2 vs Group 4 <i>p</i> < <b>0.001</b>	Group 3 vs Group 4 <i>p</i> < <b>0.001</b>
<b>TOS (µmol H2O2 Eqv/1)</b>	Group 1 vs Group 2 <i>p</i> < <b>0.001</b>	Group 1 vs Group 3 <i>p</i> = <b>0.007</b>	Group 1 vs Group 4 <i>p</i> = 0.956
	Group 2 vs Group 3 <i>p</i> = <b>0.003</b>	Group 2 vs Group 4 <i>p</i> < <b>0.001</b>	Group 3 vs Group 4 <i>p</i> = <b>0.002</b>
<b>OSI (aµ)</b>	Group 1 vs Group 2 <i>p</i> < <b>0.001</b>	Group 1 vs Group 3 <i>p</i> = <b>0.01</b>	Group 1 vs Group 4 <i>p</i> = 0.949
	Group 2 vs Group 3 <i>p</i> < <b>0.001</b>	Group 2 vs Group 4 <i>p</i> < <b>0.001</b>	Group 3 vs Group 4 <i>p</i> = <b>0.002</b>
<b>TAS (mmol Trolox Eqv/1)</b>	Group 1 vs Group 2 <i>p</i> < <b>0.001</b>	Group 1 vs Group 3 <i>p</i> = 0.175	Group 1 vs Group 4 <i>p</i> = 0.988
	Group 2 vs Group 3 <i>p</i> = <b>0.004</b>	Group 2 vs Group 4 <i>p</i> < <b>0.001</b>	Group 3 vs Group 4 <i>p</i> = 0.091

Tukey test was used for subgroup analysis of the data. Group 1 = Sham, Group 2 = Injury, Group 3 = Treatment/Injury, Group 4 = Treatment, 8-OhdG = 8-hydroxy-2'-deoxyguanosine, TOS = Total oxidant status, OSI = Oxidative stress index, TAS = Total antioxidant status

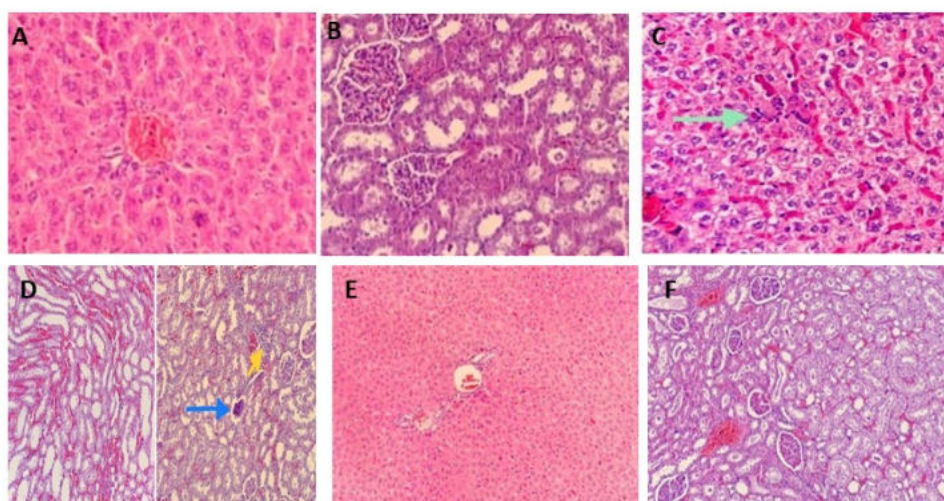


**Fig. 2.** (A) Regular cardiac muscle is observed in the sample belonging to the Sham group (B, C) Histopathological examination of the injury group (Group 2), necrosis and edema areas in the myocardium in tissue sections in the histopathological examination (D) Histopathological examination of the Treatment+Injury group (Group 3) Significant improvement in edema and focal necrosis in muscle fibers in the examination (E) Regular muscle fibers in the histopathological examination of the treatment group (Group 4).

## DISCUSSION

Aortic cross clamp and TCA applications are fre-

quently performed in operations where CPB is used. Oxidative stress occurs as a result of insufficient oxygenated blood to the tissues [14]. CPB is also an im-



**Fig. 3.** (A) liver from sham group, (B) kidney from sham group, (C) focal lytic necrosis in liver tissue in injury group, (D) (left side) hemorrhage in intertubular interstitial tissue in renal parenchyma, right side glomerulosclerosis (blue arrow), inflammatory infiltration in the stroma (yellow arrow), (E) reduced periportal fibrosis in the damage and treatment group, (F) renal parenchyma containing regular glomerular structures with minimal thrombosed vascular structures with treatment damage.

portant factor for the formation of oxidative stress. The reason for this is neutrophils, catecholamines, which are activated as a result of contact of blood with nonendothelial circuit elements, activation of the complement system and cytokines released as a result of activation of neutrophils [15]. In these operations, various medical treatments are applied along with hypothermia to ensure the continuation of organ vitality, especially the heart. In this experimental deep circulatory arrest model, we showed that oxidative stress parameters (TAS, TOS, OSI, 8-OHdG), histopathological damage in heart, kidney and liver tissue decreased by administering *T. violacea* extract to rats with organ damage.

It is known that oxidative stress causes damage by causing lesions such as base and sugar modifications, single and double chain breaks, DNA-protein cross-linking on deoxyribo nucleic acid by different mechanisms [16]. In our study, 8-OHdG, a marker of oxidative DNA damage, was found to be higher in the damage group (Group 2) than the other groups. We think that this is due to the insufficiency of existing antioxidant mechanisms as a result of ischemia and TCA. In the groups given *T. violacea* extract, the lower 8-OHdG level can be explained by the external antioxidant effect of *T. violacea* extract [8].

Murugesan *et al.* [17] investigated the protective role of *T. violacea* extract on isoproterenol-induced myocardial necrosis in rats. In their study, they treated

rats with *T. violacea* extract (60 mg/kg body weight) daily for 30 days. Myocardial necrosis was induced by subcutaneous injection of isoproterenol (85 mg/kg body weight) on days 29 and 30 in rats. On the 31st day, the rats were sacrificed under anesthesia and their blood and tissues were collected. In the results of myocardial necrosis induced by isoproterenol; stated that cardiac markers, lipid peroxidation products and heart rate levels increased significantly, while plasma enzymatic antioxidants decreased significantly. At the end of the study, they stated that the treatment of myocardial necrosis with *T. violacea* extract showed significant effects on all biochemical and molecular studies. They also found that *T. violacea* extract increased antioxidant production and had a protective effect on isoproterenol-induced myocardial necrosis in rats [17]. In our study, we found positive effects of *T. violacea* extract on cardiac damage (oxidative stress and DNA damage) caused by circulatory arrest.

Modeley *et al.* [18] investigated the cardiovascular effects of TV methanolic extract in Dahl salt sensitive rats. In their study, Dahl salt was administered intraperitoneally in rat groups. After that, distilled water (3 ml/kg) to the control group; captopril (25 mg/kg) to one group; and *T. violacea* methanolic extract (50 mg/kg) to one group were administered for 7 weeks. As a result of their study, they stated that besides many positive effects, *T. violacea* extract, when applied for a long time, showed an antihypertensive effect in rats

sensitive to Dahl salt [18]. Raji *et al.* [19] aimed to investigate the effect of *T. violacea* extract on blood pressure and heart rate in aging normotensive rats and adult spontaneously hypertensive rats. As a result of their study, they stated that *T. violacea* extract significantly and dose-dependently reduced systolic and diastolic blood pressure, and mean arterial pressure in both rat groups [19].

In some studies, it has been shown that *T. violacea* extract has antithrombotic and anticoagulant effects [20, 21]. Davison *et al.* [20] investigated the properties such as platelet aggregation, adhesion and protein secretion in both in vitro and ex vivo rat models to determine the effects of *T. violacea* extract on platelets in their study. In their study, they stated that *T. violacea* extract had a higher inhibition on platelet aggregation and agglutination than aspirin. They stated that in the prothrombin time test, it decreased the coagulation times, but prolonged the coagulation time in the activated partial thromboplastin time (aPTT) experiment in the ex vivo model, which showed its antithrombotic ability. They found that the *T. violacea* extract increased D-dimer and fibrinogen-C concentrations in the in vitro model, but had no effect on D-dimer concentrations. In the ex vivo model, they found that it decreased fibrinogen-C values. As a result, they revealed that *T. violacea* extract has a beneficial effect on the modulation of platelet activation by decreasing fibrinogen levels, increasing the aPTT duration, and through the glycoprotein receptor IIb in platelets [20]. There are also studies showing the protective effect of *T. violacea* extract on other organs (kidney, liver) and tissues (aortic tissue) [22- 24]. In their study, Olorunisola *et al.* [22] investigated the protective effect of *T. violacea* extract in rats fed on an atherosclerogenic diet (4% cholesterol, 1% cholic acid and 0.5% thiouracil). They also investigated serum lipid profile, tissue antioxidant enzyme depletion, endothelial dysfunction, histopathological changes in the aorta and liver of rats. In the groups treated with *T. violacea* extract compared to the atherogenic control group; There is a significant decrease in the activities of serum markers of liver (Lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin) and kidney (creatinine and bilirubin) damage. They stated that the extract confirmed its protective properties. They also stated that *T. violacea* extract protected against the development

of fatty streak plaques (aorta) and fatty changes in hepatocytes in their histopathological evaluation of aortic sections [22]. Similarly, positive effects of *T. violacea* extract were observed in the histopathological evaluation of liver and kidney tissues in our study.

### Limitations

The lack of budget-based biochemical parameters in our study is among the limitations of our research. In addition, the mini CPB circuit was not used in our study. Despite this limitation, beneficial effects of *T. violacea* extract have been demonstrated in the arrest model. Our work needs to be supported by new studies using mini CPB circuits.

### CONCLUSION

The application of aortic cross-clamp and TCA methods in cases performed with CPB in cardiac surgery causes signs of cardiac damage due to ischemia in the heart tissue. Although cardioplegia solutions form the basis of myocardial protection, it is obvious that a holistic approach is required. For this purpose, all pre-operative, intraoperative and postoperative variables should be evaluated. In the light of these results, we think that *T. violacea* extract is protective against cardiac damage and other organ damage and may be a potential therapeutic agent. We also think that these data will form the basis for further experimental and clinical studies.

### Authors' Contribution

Study Conception: BA, NK; Study Design: BA, NK; Supervision: BA, NK; Funding: BA, NK; Materials: BA, NK, FG, MSA YÇ, MEG, İK, EZT, ME, ŞY; Data Collection and/or Processing: BA, NK, FG, MSA YÇ, MEG, İK, EZT, ME, ŞY; Statistical Analysis and/or Data Interpretation: BA, NK, FG, MSA YÇ, MEG, İK, EZT, ME, ŞY; Literature Review: BA, NK, FG, MSA YÇ, MEG, İK, EZT, ME, ŞY; Manuscript Preparation: AEY and Critical Review: BA, NK, FG, MSA YÇ, MEG, İK, EZT, ME, ŞY.

### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.



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### Ethics Committee Approval

This study was prepared as a doctoral thesis. Our study was approved by Harran University Animal Experiments Local Ethics Committee (Date: 11/12/2020, Session no: 2020/0006, Decision:01-17).

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