EXPERIMENTAL STUDY

The effect of rutin on experimentally induced acute heart contusion in rats: Biochemical and histopathological evaluation

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ABSTRACT

BACKGROUND: Acute cardiac contusion induced by trauma is known with its high mortality and morbidity. The role of oxidative stress and inflammation in its pathophysiology has led to the investigation of antioxidant and anti-inflammatory substances in non-surgical treatment. In this study, the effects of rutin which has these two features on acute cardiac contusion were investigated.

METHODS: Thirty male albino Wistar rats were divided into three equal groups as healthy (HG), contusion (CG), and rutin + contusion (rutin + CG). A heart contusion was created dropping 200 g weight from 1-m height onto anterior thorax of CG (n=10) and Rutin + CG (n=10) group animals by anesthetizing with intraperitoneal administration of 60 mg/kg ketamine and xylazine inhalation at appropriate intervals. Thirty minutes after contusion was applied, rutin at the dose of 50 mg/kg was administered orally to the stomach by gavage to the rutin + CG group animals. The rutin was used once a day for 2 days. Rats were killed at the end of 48 h. Heart tissues were removed and examined biochemically and histopathologically. Troponin I (TP I) and creatine kinase-MB (CK-MB) were measured in blood samples taken from the tail veins just before the rats were killed.

RESULTS: TP I, CK-MB, malondialdehyde, total oxidant status, and nuclear factor-kappa B levels increased in the CG when compared to the HG, and Rutin application prevented this increase, total glutathione (eGSH) and total antioxidant status levels decreased, and rutin application prevented this decrease. Histopathological findings also supported these findings.

CONCLUSION: Rutin had a protective effect on heart tissue.

Keywords: Blunt thoracic trauma; heart contusion; rat; rutin.

INTRODUCTION

Acute cardiac contusion results from non-penetrating chest trauma such as motor vehicle accidents, sports injuries, and falls from height.[1] The heart is squeezed between the ribcage and the spine with a high-energy impact effect,[2] and this compression causes damage in cardiac structures, decreases in coronary blood flow,[3] and life-threatening arrhythmias.[4] According to experimental trauma models, mitochondrial dysfunction[5] and an increase in reactive oxygen radicals (ROS) occur in myocardial cells, in which blood flow and oxygenation are impaired.[6] In addition, traumatic injury is associated with the initiation of the cardiac inflammatory response.[7] Initiating the acute inflammatory response in the injured

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tissue is the increase in vascular permeability.[8] Therefore, the possible protective effects of antiedema, anti-inflammatory, and antioxidant properties against myocardial damage have gained importance to alleviate the response in the early phase of acute inflammation.

The rutin, in which we will try its protective effect against acute cardiac contusion, is a type of flavonoid known as Vitamin P.[9] The previous studies have reported that rutin has a cardioprotective effect,[10] and this effect is due to its antioxidant properties.[11] In addition, it has been reported that rutin preserves barrier integrity against pro-inflammatory cytokines in vascular endothelial cells and prevents PNL adhesion.[12,13] Our study aims to investigate whether the antioxidative, anti-inflammatory, and anti-edema properties of rutin are beneficial in acute cardiac contusion.

MATERIALS AND METHODS

Animals

In the experiment, 30 male Albino Wistar rats weighing 225–235 g and 6–7 months old were used. All rats were obtained from Atatürk University Medical Experimental Application and Research Center. Animals were housed and fed under suitable conditions at normal room temperature (22°C) in a suitable laboratory environment. The protocols and procedures were approved by the local Animal Experimentation Ethics Committee (Number: 75296309-050.01.04-E.2000272275, Date: 02.11.2020).

Chemicals

Rutin, one of the drugs used in our experiment, was supplied from Solgar (USA), while ketamine was obtained from Pfizer (Turkey).

Experimental Groups

The experimental animals were divided into three equal groups as the healthy group (HG), the contusion-induced group (CG), and the group administered with rutin after inducing contusion (rutin + CG).

Experimental Procedure

The cardiac contusion procedure in rats was administered by anesthetizing with intraperitoneal administration of 60 mg/kg ketamine and xylazine inhalation at appropriate intervals. After ketamine injection, rats were kept waiting for the appropriate period to occur. The period animals' immobility in the supine position was accepted as a suitable anesthesia period for the procedure.[14] During the anesthesia period, cardiac contusion was created dropping 200 g weight from 1-m height onto anterior thorax of CG (n=10) and rutin + CG (n=10) group animals. The resulting energy was calculated to be 1.96 joules with the formula of E=mgh (E: energy, m: reduced weight, 0.2 kg, g: gravity, 9.8 m/s2, h: height, 100 cm). As result, cardiac contusion was induced by applying 1.96 joules of energy to rats.[15] Thirty minutes after contusion was applied, rutin at the dose of 50 mg/kg was administered orally to the stomach by gavage to the rutin + CG group animals. The rutin was used once a day for 2 days. Normal saline (0.9% NaCl) was administered orally in the same volume as a solvent to the non-contused HG (n=10) group. At the end of this period, the animals were killed by high dose (120 mg/kg) ketamine anesthesia, and their heart tissues were removed. Removed heart tissues were examined biochemically and histopathologically. Troponin I (TP I) and creatine kinase-MB (CK-MB) were measured in blood samples taken from tail veins just before the animals were killed. The evaluation was made comparing the results obtained from the rutin + CG group and biochemical and histopathological results obtained from CG and HG groups.

Preparing the Samples

At this stage of the study, 0.2 g from each removed tissue was weighed. Tissues were homogenized in an icy environment completing 1.15% potassium chloride solution for malondialdehyde (MDA) determination to 2 mL in phosphate buffer pH=7.5 for total glutathione (tGSH), total oxidant status (TOS), total antioxidant status (TAS), and nuclear factor kappa B (NF-kB) measurements. It was, then, centrifuged at +4°C and 10000 rpm for 15 min.

Protein Measurement

Protein concentration measurement was made according to the Bradford MM method.[16] The measuring principle is based on measuring the absorbance at 595 nm of the colored complex formed by the binding of the Coomassie Brilliant Blue G-250 dye to proteins. All tissue analysis results were standardized by dividing them into protein.

MDA Determination

The MDA levels were determined spectrophotometrically at 532 nm according to the method described by Ohkawa et al.[17] This method is based on spectrophotometric measurement of absorbance of colored complex which is formed by thiobarbituric acid and MDA at a high temperature (95°C). Tissue MDA concentration unit was given as µmol/g protein.

tGSH Determination

5.5'-dithiobis (2-nitrobenzoic acid) (DTNB) in the measurement environment was a disulfide chromogen and was easily reduced by compounds with sulfhydryl groups. The resulting yellow color was measured spectrophotometrically at 412 nm wavelength.[18] Tissue tGSH concentration unit nmol/g protein was calculated.

Measurements of TOS and TAS

TOS and TAS levels of tissue homogenates were determined using a novel automated measurement method and commercially available kits (Rel Assay Diagnostics, Turkey), both devel-

oped by Erel.[19,20] Tissue TOS unit was given as μmol H_2O_2/g protein and TAS unit as mmol Trolox equivalent/g protein.

NF-κB Determination

Tissue-homogenate NF-κB concentration was measured using rat-specific sandwich enzyme-linked immunosorbent assay. Rat NF-κB ELISA immunoassay kits (Cat. No:201-11-0288, SunRed). Tissue NF-κB concentration was calculated as μg/g protein.

TP I Determination

TP I levels in plasma obtained from animals were measured in VIDAS TP I Ultra kit using ELFA (Enzyme-Linked Fluorescent Assay) technique. All steps of the test were performed automatically on VIDAS device using the test reagents that were available in the kit. Plasma TP I concentration unit was given as μg/mL.

CK-MB Determination

CK-MB determination in plasma obtained from animals was measured in Roche/Hitachi cobas c701 system. Plasma CK-MB activity unit was given as U/L.

Histopathological Examination

Cardiac tissues removed from rats were fixed in 10% formalin solution for 24 h. Samples were then treated with a conventional grade of alcohol (70%, 80%, 90%, and 100%) to remove the water within tissues. Tissues were then passed through xylol and embedded in paraffin. After routine tissue treatment, 4–5 micron thick sections were obtained from the paraffin blocks and stained with Hematoxylin and Eosin. All sections were evaluated under a light microscope (Olympus BX 52, Tokyo, Japan) by two pathologists who were blind to treatment protocols. The histopathological damage severity in each cardiac tissue section was scored between grades 0 and 3 (0-normal, 1-mild damage, 2-moderate damage, and 3-severe damage).

Statistical Analysis

For statistical analysis, IBM SPSS 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used. The results were presented as mean±standard error of the mean. The normality assumption was confirmed with the Kolmogorov–Smirnov test. For comparison of groups, one-way ANOVA was used. After ANOVA, according to homogeneity of variances, Tukey's HSD or Tamhane's tests were used as *post hoc*. While variables were not normally distributed, Kruskal–Wallis test was used with Dunn's test as a *post hoc* test. The statistical level of significance for all tests was considered to be 0.05. In the histopathological examination, the differences between the groups were determined by Kruskal–Wallis test and groups that exhibited differences were determined by the Dunn test. P<0.05 was considered significant.

RESULTS

Biochemical Findings

MDA Analysis Results

As shown in Figure 1, when MDA levels measured were compared between the groups, an increase was observed in the CG when compared to the HG, and a statistically significant difference was found between the two groups (p<0.001). It was observed that this increase induced by contusion was prevented with rutin, and a significant difference was found between the CG and rutin + CG (p<0.001).

tGSH Analysis Results

A decrease in tGSH level was observed in the CG when compared to the HG, and a significant difference was found between these two groups (p<0.001). In the rutin + CG, it was observed that the decrease in tGSH level was prevented, and a significant difference was found between the CG and the rutin + CG (p<0.001) (Fig. 2).

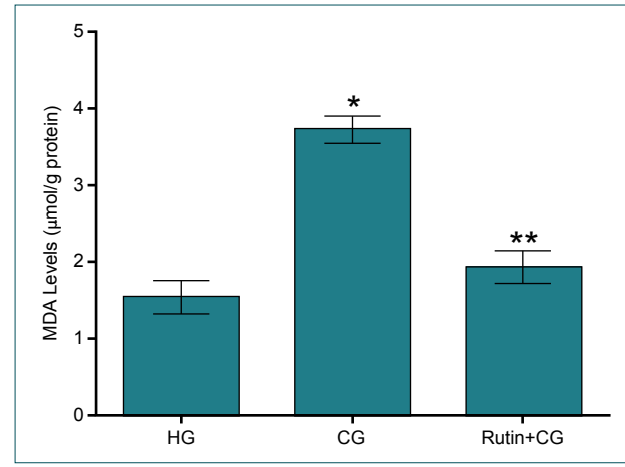

Figure 1. MDA levels of groups HG (heathy), contusion induced (CG), and rutin + contusion (rutin + CG). *P<0.001 according to HG, **p<0.001 according to CG. Tukey's HSD test was used as *post hoc*.

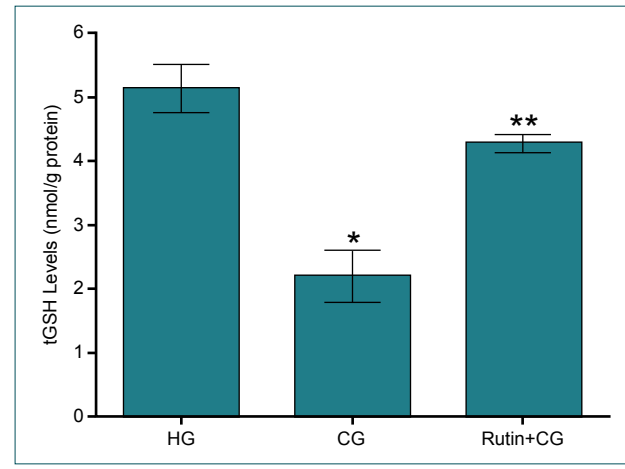

Figure 2. tGSH levels of groups HG (heathy), contusion induced (CG), and rutin + contusion (rutin + CG). *P<0.001 according to HG, **p<0.001 according to CG. Tamhane's test was used as *post hoc*.

TOS and TAS Analysis Results

As shown in Figures 3 and 4, whereas the TOS value increased in the CG when compared to the HG, the TAS value decreased. There was a statistically significant difference between the HG and CG in terms of TOS and TAS values ($p<0.001$). With rutin application, it was noticed that the values observed in the CG reversed, and the increase in TOS value and decrease in TAS value in the rutin + CG were prevented. A statistically significant difference was found between the CG and rutin + CG in terms of TOS and TAS values ($p<0.001$).

NF-κB analysis results

It was observed that the level of NF-κB increased in the CG when compared to the HG, and the increase in NF-B level was prevented with rutin and regressed to the HG level. There was a statistically significant difference between the CG and the HG ($p=0.001$), and similarly, there was a significant difference between the CG and the rutin + CG ($p=0.013$), as well. NF-κB levels were found close to each other between the HG and Rutin+CG, and there was no statistically significant difference ($p=0.387$) (Fig. 5).

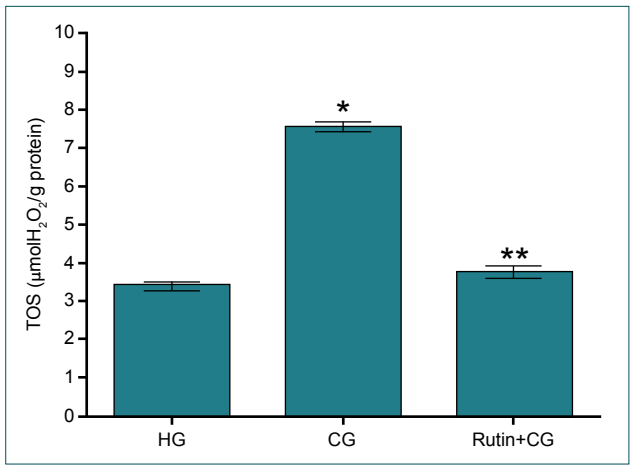

Figure 3. TOS levels of groups HG (healthy), contusion induced (CG), and rutin + contusion (rutin + CG). *P<0.001 according to HG, **p<0.001 according to CG. Tukey's HSD test was used as *post hoc*.

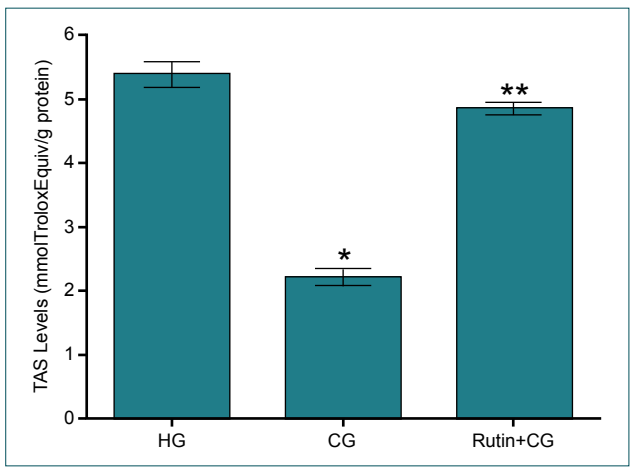

Figure 4. TAS levels of groups HG (healthy), contusion induced (CG), and rutin + contusion (rutin+CG). *P<0.001 according to HG, **p<0.001 according to CG. Tukey's HSD test was used as *post hoc*.

Plasma TP I and Plasma CK-MB Analysis Results

As shown in Figures 6 and 7, plasma TP I and plasma CK-MB levels increased in the CG when compared to the HG, and there was a statistically significant difference between the two groups ($p<0.001$). These findings supported the occurrence of cardiac tissue damage in our experiment. In the rutin applied group, these increased values were reversed, and a significant difference was found between the CG and the rutin + CGs ($p<0.001$). TP I values of the HG and rutin + CG were found to be similar, and there was no statistically significant difference between the two groups ($p=0.159$).

Histopathologic Findings

Histopathologically, Figure 8a indicated healthy cardiac mus-

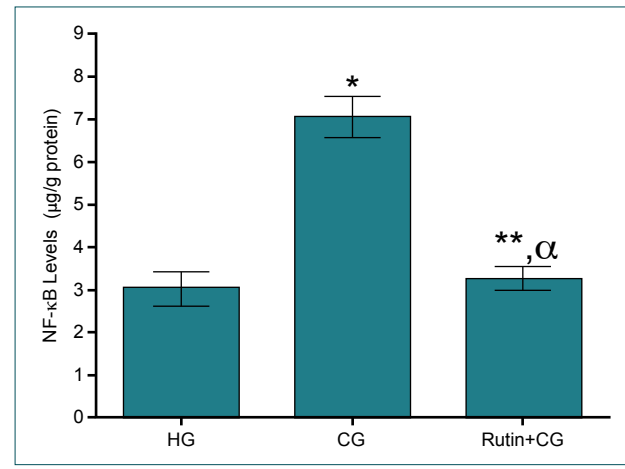

Figure 5. NF-κB levels of groups HG (healthy), contusion induced (CG), and rutin + contusion (rutin + CG). *P<0.001 according to HG, **p<0.001 according to CG, α = p>0.05 according to HG. Kruskal–Wallis test was used with Dunn's test.

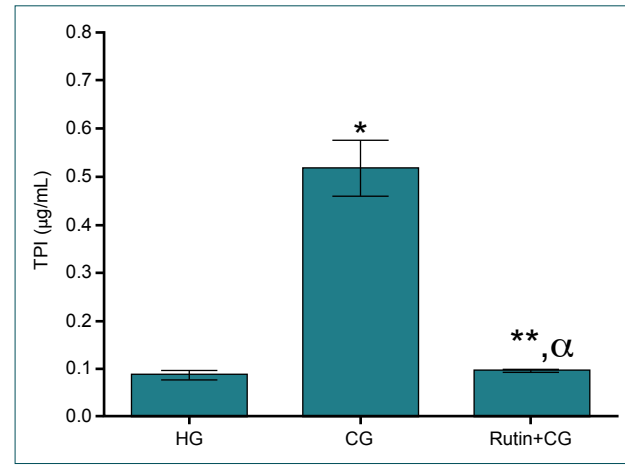

Figure 6. TP I levels in the plasma of groups HG (healthy), contusion induced (CG), and rutin + contusion (rutin + CG). *P<0.001 according to HG, **p<0.001 according to CG, α = p>0.05 according to HG. Tamhane's test was used as *post hoc*.

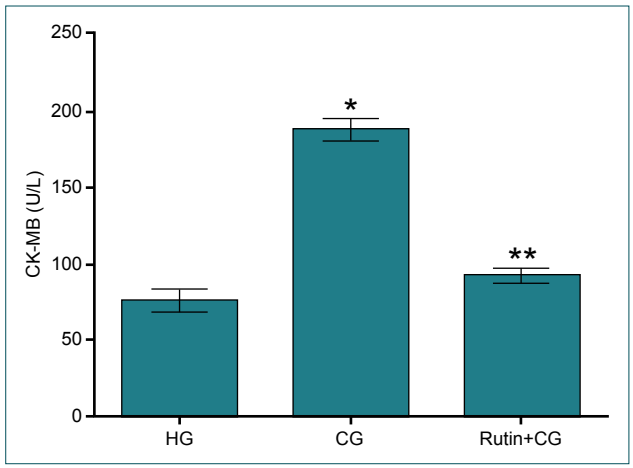

Figure 7. CK-MB levels in the plasma of groups HG (healthy), contusion induced (CG), and rutin + contusion (rutin + CG). *P<0.001 according to HG, **p<0.001 according to CG. Tukey's HSD was used as *post hoc*.

Table 1. Histopathological results of the study groups

	HG (n=10)	CG (n=10)	Rutin+CG (n=10)
	Mean±SD	Mean±SD	Mean±SD
PNL infiltration	0.0±0.0	2.9±0.32[a]	0.1±0.32[b]
Edema	0.0±0.0	3.0±0.0[a]	0.7±0.48[b]
Hemorrhage	0.0±0.0	2.8±0.42[a]	0.0±0.0[b]
Necrosis	0.0±0.0	2.7±0.48[a]	0.1±0.32[b]
Degeneration	0.0±0.0	2.9±0.32[a]	0.2±0.42[b]
Congestion	0.0±0.0	2.6±0.52[a]	0.6±0.52[b]

Statistically significant ($p<0.05$) when compared with [a]HG, with [b]CG. Kruskal Wallis test was used and Dunn test was performed as post hoc. HG: Healthy group; CG: Contusion-induced group; SD: Standard deviation; PNL: Polymorphonuclear leukocytes

cle tissue. PNL, edema, hemorrhage areas, muscle necrosis, myocardial degeneration, and dilated congested blood vessels were noticed in the contused damaged heart tissue (Fig. 8b-c). In the rutin + CG, mildly dilated congested blood vessels and mild edema were seen (Fig. 8d). The differences in histopathological changes between groups are shown in Table 1. Accordingly, all histopathological changes in the CG are statistically significant when compared with the HG. In the rutin+CG, it was observed that these histopathological changes regressed, and the findings were found to be statistically significant compared to the CG.

DISCUSSION

Cardiac injury is more common than expected in patients with blunt chest trauma and is possible to cause significant morbidity and even mortality.[21] Impairment of coronary blood flow due to compression of the heart between the ribcage and spine[2] can increase tissue damage causing hy-

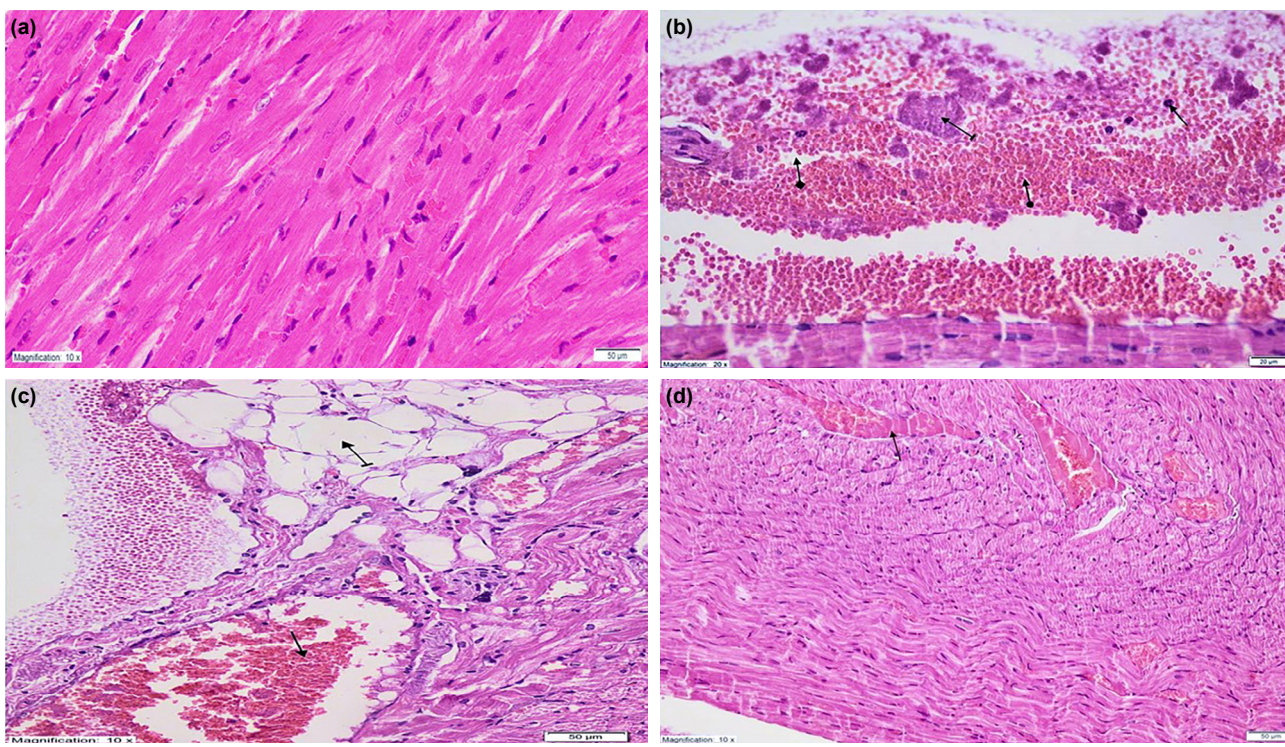

Figure 8. Histopathological preparation images of the study groups. **(a)** Healthy cardiac muscle tissue (H and E ×200). **(b)** Contusion-induced group: PNL (straight arrow), hemorrhage areas (circle arrow), edema (square arrow), muscle necrosis, and degeneration (line arrow) (H and E ×400). **(c)** Contusion-induced group: dilated congested blood vessels (straight arrow), degeneration of myocardial tissue (striped arrow) (H and E ×200). **(d)** Rutin+Contusion group: Mildly dilated congested blood vessels (H and E ×200).

poxia in the heart.[5] With the impairment of oxygenation in the myocardium, mitochondrial dysfunction and an increase in the amount of ROS occur.[6] As known, ROS induces LPO and causes the formation of cytotoxic products such as MDA.[10] The previous studies have revealed that MDA is the end product of LPO increases in myocardial contusion.[22] In our study, an increase in MDA levels was observed in the heart CG supporting the induction of oxidative stress in myocardial tissue.

GSH is known to regulate many biological processes such as ion transport and enzyme activity, signal transduction is a multifunctional tripeptide.[23] It is known that GSH, also known as antioxidant defense in cardiomyocytes, rapidly decreases with the development of oxidative stress and increases at ROS.[24] The previous studies have reported that GSH depletion in heart muscle begins a few minutes after oxidative stress occurring before abnormalities in electrical function.[25] In our study, it was found that tGSH decreased in the heart tissue with a contusion in accordance with the literature.

TOS and TAS levels of the sample are measured wince it is not practical to measure different oxidant and antioxidant molecules separately.[19,20] It has been revealed that increased TOS can increase reperfusion arrhythmias, necrosis of myocytes, and coronary endothelial dysfunction.[26] On the other hand, it has been reported that as TAS increases, free radicals are removed from biological systems and macromolecules are protected from damage.[27] In our study, it was observed that TOS increased, and TAL decreased in the CG when compared to the HG, and the results supported the development of oxidative stress.

The role of inflammation in post-traumatic cardiomyocyte damage has also been emphasized.[28,29] NF-κB plays an active role in the initiation and regulation of local and systemic inflammatory response after trauma.[30,31] NF-κB is activated by the formation of ROS and inflammatory cytokines in myocardial tissue.[32] The previous studies have shown that myocardial damage is exacerbated by the activation of the NF-κB signaling pathway.[33] In our study, parallel to previous studies, it was observed that NF-κB levels increased through administering contusion.

TP I, an indicator of cardiac damage, is a low molecular weight protein component of the myofibrillary contractile apparatus of cardiomyocytes.[34] The increase in plasma TP I levels is closely related to the severity of myocardial damage.[35] CK-MB, an enzyme released into the plasma in case of myocardial damage, is a cytosolic enzyme found in cardiomyocytes.[36] In the studies carried out on cardiac contusion induced by blunt trauma, TP I and CK-MB levels have been revealed to increase when compared to the HG.[37] In our study, it was observed that administering contusion caused an increase in TP I and CK-MB levels. Our findings supported the occurrence of cardiomyocyte damage in accordance with the literature.

In the studies examining cardiac damage histopathologically, myofibrils separated due to diffuse degeneration and bleeding in the heart muscle,[38] PNL infiltration and edema density[39] were described. In a myocardial contusion study carried out with dogs, extravasation of blood was characterized histopathologically.[40] The histopathological findings in our study were consistent with these findings in the literature. Histopathological findings of the CG were defined as intense PNL infiltration, hemorrhage areas, edema, muscle necrosis, and myocardial degeneration.

It was reported in almost all in vitro and in vivo studies that rutin could reduce oxidative stress due to its antioxidative properties.[41] In a study, in which oxidative stress was induced in the heart, it was reported that rutin reduced the level of oxidative stress markers such as MDA in the tissue.[42] In our study, MDA values were found to be lower in the rutin + CG when compared to the CG, and the results supported the decrease of oxidative stress.

In the literature, it was reported in studies of cardiac injury induced by fluoride[43] and isoproterenol[44] that rutin increased tissue tGSH levels and thus reduced cardiac toxicity. In our study, GSH levels were found to be higher in the group administered with rutin treatment when compared to the untreated group, and the findings were consistent with the literature. Further studies have been needed to determine whether the decrease in MDA and the increase in GSH have depended on the dose of the rutin.

Rutin has been known to reduce oxidative stress preventing the decrease of antioxidants in myocardial ischemic reperfusion.[45] In a study, it was reported that the tissue TOS value was significantly lower and the TAS value was significantly higher in the rutin-treated group.[46] In our study, the increase in TOS and decrease in TAS in the cardiac tissue in the CG seemed to be prevented by rutin treatment, and the findings were consistent with the literature.

In a study indicating that rutin also had effects on the inflammatory response through NF-κB, it was reported that rutin treatment caused a significant downregulation in NF-κB mRNA expression.[47] In this study, it was revealed that rutin treatment prevented NF-κB activation and reduced inflammation.[47] In another study, it was mentioned that the decrease in NF-κB levels was greater when the dose of rutin treatment was increased.[48] In our study, the fact that NF-κB levels in tissue homogenates were lower in the routinely applied group when compared to the CG could indicate that rutin prevented cardiac hyperinflammatory response.

TP I and CK-MB levels which were the most important biochemical markers indicating cardiac tissue damage were proven to be significantly decreased in a study investigating rutin treatment.[49] In another study, it was revealed that rutin decreased increasing TP I and CK-MB levels depending on the

dose.[50] In our study, TP I and CK-MB levels were lower in the group that was given rutin after cardiac contusion when compared to the group that was not treated. This could be interpreted as the fact that starting the rutin early was possible to reduce cardiomyocyte damage.

It has been well known that the initiator of inflammation has increased vascular permeability.[40] In a study in which cardiac damage was induced, changes such as cardiomyocyte necrosis, inflammatory cell infiltration, edema, and hemorrhage were histopathologically reported to be almost completely resolved with rutin treatment.[51] In our study, the findings of PNL infiltration, hemorrhage areas, edema, muscle necrosis, and myocardial degeneration which occurred in the CG histopathologically were remarkably reduced with rutin treatment.

Conclusion

In our study, it was observed that cardiac contusion due to blunt trauma caused oxidative stress and inflammation, and as result, it caused an increase in MDA, TOS, NF-B, TP I and CK-MB levels, and a decrease in tGSH and TAS levels. Furthermore, cardiac damage induced by blunt trauma was demonstrated histopathologically. Biochemical and histopathological findings caused by trauma were found to be improved with rutin application. The findings suggested that rutin could be useful in treating traumatic cardiac injury complications.

Ethics Committee Approval: This study was approved by the Atatürk University Animal Experiments Local Ethics Committee (Date: 02.11.2020, Decision No: 75296309-050.01.04-E.2000272275).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: B.E., H.S.; Design: B.E., H.S.; Supervision: B.E., H.S.; Resource: B.E., Ş.Y., Y.B.; Materials: R.M., B.G., A.Ç.; Data: R.M., B.G., A.Ç.; Analysis: R.M., B.G., A.Ç.; Literature search: B.E., Ş.Y., Y.B.; Writing: B.E., Ş.Y.; Critical revision: H.S., R.M.

Conflict of Interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZ*

Rutinin sıçanlarda deneysel olarak oluşturulan akut kalp kontüzyonuna etkisi: Biyokimyasal ve histopatolojik değerlendirme

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AMAÇ: Travmaya bağlı gelişen akut kalp kontüzyonu yüksek mortalite ve morbiditesi ile bilinir. Patofizyolojisinde oksidatif stres ve enflamasyonun rol oynaması, cerrahi dışı tedavide antioksidan ve antienflamatuvar özellikli maddelerin araştırılmasına yol açmıştır. Bu çalışmada, sözkonusu iki özelliğe sahip olan rutinin akut kalp kontüzyonu üzerine etkileri araştırılmıştır.

GEREÇ VE YÖNTEM: Albino Wistar türü 30 adet erkek sıçan, sağlıklı (HG), kontüzyon (CG) ve rutin+kontüzyon (rutin+CG) olmak üzere üç eşit gruba ayrıldı. İntraperitoneal yolla 60 mg/kg ketamin verilerek ve uygun aralıklarla ksilazin koklatılarak sağlanan anestezi yoluyla CG (n=10) ve rutin+CG (n=10) grubu hayvanların toraks ön duvarı üzerine 1 metre yükseklikten 200 gram ağırlık düşürülerek kalp kontüzyonu oluşturuldu. Kontüzyon işlemi uygulandıktan 30 dakika sonra rutin+CG grubu hayvanlara oral yoldan 50 mg/kg dozunda rutin, gavajla mideye verildi. Rutin günde bir defa olmak üzere iki gün kullanıldı. Sıçanlar 48 saatin sonunda öldürüldü. Kalp dokuları çıkarılarak biyokimyasal ve histopatolojik olarak incelendi. Sıçanlar öldürülmeden hemen önce kuyruk venlerinden alınan kan örneklerinde troponin I (TP I) ve kreatin kinaz MB (CK-MB) ölçümü yapıldı.

BULGULAR: Kontüzyon grubunda sağlıklı gruba kıyasla TP I, CK-MB, malondialdehit (MDA), total oksidan status (TOS), nükleer faktör-kappa B (NF-κB) düzeyleri artmış ve rutin uygulaması bu artışı engellemiş; total glutatyon (tGSH) ve total antioksidan status (TAS) düzeyleri azalmış ve rutin uygulaması bu azalmayı engellenmiştir. Histopatolojik bulgular da bu bulguları desteklemektedir.

TARTIŞMA: Rutin, kalp dokusu üzerine koruyucu etki göstermiştir.

Anahtar sözcükler: Kalp kontüzyonu; künt torasik travma; rutin; sıçan.

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