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Protective Effect of Resveratrol and Vitamin B17 on 8-iso-Prostaglandin F2α and Raftlin-1 Levels in an Experimental Acute Urinary Retention in Rat

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ABSTRACT

Background: The incidence and complications of bladder disorders due to ischemia-reperfusion (I/R) injury constitute an important public health problem. The harmful effects of the disease–could be reduced or completely eliminated by using natural antioxidant agents. In this study, the effect of preconditioning with Resveratrol and B17 vitamin, on bladder I/R damage was evaluated by the levels of 8-iso-prostaglandin F2α (8-iso-PGF2α) and raftlin-1 (RFTN-1) biomarkers.

Methods: A total of 42 Wistar Albino male rats were used in the study which were divided in 6 groups (Group 1: Control, Group 2: Sham, Group 3: I/R, Group 4: Treatment 1 (RSV), Group 5: Treatment 2 (B17), Group 6: Combined treatment (RSV+B17). The effect of RSV and B17 valuated as the therapeutic group. Clamping the penile urethra of the rats, diuresis was forced and overdistension was achieved. After being kept in overdistension for 30 minutes, the rat bladder was emptied with a 3F catheter. The reperfused bladder was kept in this way for 30 minutes and the rats were sacrificed. 8-iso-PGF2α and RFTN-1 levels were measured in bladder tissue by ELISA.

Result: In the I/R rat bladder tissue, we detected severe tissue injuries ($p<0.05$). As compared to the control group; It was observed that 8-iso-PGF2α and RFTN-1 values increased statistically significantly in sham, I/R and treatment 2 groups ($p<0.05$). 8-iso-PGF2α and RFTN-1 values were statistically significantly decreased in the therapeutic groups (Treatment 1, Treatment 2, Combined treatment compared to the I/R and sham group ($p<0.05$). A statistically significant decrease was observed in the treatment 1 group compared to the treatment 2 group in terms of 8-iso-PGF2α and RFTN-1 values ($p<0.05$).

Key words: Bladder, Ischemia-reperfusion injury, Raftlin-1, Resveratrol, Vitamin B17, 8-iso PGF2α.

INTRODUCTION

Oxygen hemostasis is vital in human physiology. Oxygen must be constantly delivered to the tissues. Ischemia is considered as the inability to provide enough oxygen and metabolites to the tissue and the inability to expel the harmful metabolites formed in the tissues (Eltzschig and Collard, 2005; Delibas *et al*., 2018). The duration of ischemia is also very important. In cases where the duration of ischemia is prolonged, swelling, acidosis and significant changes in ion concentrations occur in the cells (Kumar *et al*., 2007). The severity of cell membrane damage and mitochondrial dysfunction determine whether post-reperfusion ischemic tissue damage is reversible or irreversible (Hensley *et al*., 2000; Lohiya *et al*., 2017). In cases of reperfusion accompanying prolonged ischemia, cell damage is exacerbated and results in cell death. The level of damage to the tissues increases with reperfusion. It is observed that more harmful metabolites are formed in reperfusion (Anaya-Prado *et al*., 2002). The function of the bladder is to store urine and empty it at an appropriate time. For the homeostasis of the bladder and the continuity of its proper function, adequate oxygen and nutrient support from the arterial flow is required and at the same time, waste products must be removed by venous drainage. Bladder ischemia-reperfusion (I/R) is observed in cases of vasospasm, embolization, atherosclerosis and advanced age. Histopathological studies have shown that I/R significantly impairs bladder function (Bean *et al*., 2009).

Antioxidant substances containing phenolic compounds have positive effects on preventing ischemia-reperfusion or minimizing I/R damage (Avnioglu *et al.,* 2022). Grape seed (RSV) contains high amounts of proanthocyanidins in terms of both quantity and quality. Proanthocyanidins; it is the main factor of red color in plants (Ben-Ari *et al*., 2007). Resveratrol (RSV) is an active compound that can dissolve in water and ethanol and can be absorbed from the human intestine and spread to all tissues and unlike other antioxidant substances,

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it can remain in the plasma or tissues for 7-15 days. In this regard, RSV is considered to be a very powerful antioxidant and anti-inflammatory agent. Vitamin B17 (B17) is a cyanogenic vitamin found in abundance in plants belonging to the Prunus genus of the Rosaceae family. It is found in large amounts in the seeds of fruits such as apricots, almonds, cherries and pears (Barceloux, 2009). B17 is an active compound that has recently been used in alternative medicine for the treatment of anemia, asthma, high blood pressure, atherosclerosis, diabetes, migraine and tumors characterized by the loss of red blood cell production (Aghadavod, 2016).

Isoprostaglandins, whose *in vivo* formation was first demonstrated by Morrow *et al*. (1990), are specific indicators of lipid peroxidation induced by free radicals (Morrow *et al*., 1990). Among the isoprostaglandin isomers formed, the most important is 8-iso-prostaglandin F2α (8-iso-PGF2α). Determining the level of 8-iso-PGF2α in body tissues, which has biological effects such as vasoconstriction and bronchoconstriction, is reported increases in 8-iso-PGF2α levels are observed in body tissues in various pathological conditions such as diabetes, atherosclerosis, cirrhosis (Ito *et al*., 2019) to be the most reliable approach for lipid peroxidation determination (Kurutas, 2016)., alcoholism and hypercholesterol, which are caused by the activities of free radicals (de Faria *et al*., 2016). One of the inflammatory biomarker used to determine the level of oxidative stress is raftlin-1 (RFTN-1) (Belce *et al*., 2022). RFTN-1 is called the main lipid protein found in B cells. In addition to regulating the signaling of the B cell antigen receptor (BCR), it has functions such as the formation of autoimmune response and vascular inflammatory response (Saeki *et al*., 2009).

In this study, we aimed to examine the urinary retention seen in humans on the bladder I/R model we examined in mice. In the experimental I/R model, the levels of 8-iso-PGF2α and RFTN-1, which are biomarkers of lipid peroxidation were evaluated. The study aimed to see the effect of bladder I/R injury on reactive oxygen species (ROS) and to determine to what extent this effect can be prevented with different antioxidant compounds.

MATERIALS AND METHODS

This study was carried out in the Medicinal Biochemistry Laboratory of Kahramanmaras Sutcu Imam University between 01 January and 31 June 2021.

Animals

Wistar albino rats weighing between 220-300 g were used in this study. Animals were kept under optimum conditions (21±1°C, 40 to 70% humidity, 12/12 darkness cycle) at Kahramanmaras Sutcu Imam University's Laboratory Animal Unit and were allowed to eat and drink water. This study was approved by the Local Ethics Committee of Kahramanmaras Sutcu Imam University. The operative procedure use of anesthesia and animal care methods in the experiments were consistent with the guidelines in the National Institute of Health's Guide for the Care and Use of Laboratory Animals (NIH publication No. 86-23, revised 1985. Bethesda, MD, USA).

Experimental Groups

Subjects were randomly divided into 6 groups and working groups were formed. The subjects were anesthetized with ketamine (50 mg/kg) by intramuscular injection (i.m.).

Control group (n=7)

Nothing was administered to the rats in this group.

Sham group (n=7)

Intraperitoneal administration of 1 mL saline (0.9% NaCl) was begun two days before the procedure and 30 min of ischemia and 30 min of reperfusion created. Following the reperfusion, 1 mL (single dose) of saline was given again.

I/R group (n=7)

Only ischemia-reperfusion group. Following the intervention and surgery the bladder was subjected to 30 min of ischemia and 30 min of reperfusion.

Treatment 1 group (n=7)

This group began with intraperitoneal administration 1 mL saline (0.9% NaCl) two days before the procedure, with 30 min ischemia and 30 min of reperfusion performed. Folowing the reperfusion, 1 mL of saline (single dose) was administered again. Intraperitoneal administration of 1 mL of RSV 50 mg/kg was initiated two days before the procedure and surgery was performed. Thirty minutes of ischemia and 30 minutes of reperfusion were performed in the bladder after surgery. Following the reperfusion, 1 mL (single dose) of RSV was given again.

Treatment 2 group (n=7)

Intraperitoneal administration of 1 mL of B17 vitamin 50 mg/kg was initiated two days before the procedure and surgery was performed. Thirty minutes of ischemia and 30 minutes of reperfusion were performed in the bladder after surgery. Following the reperfusion, 1 mL (single dose) of B17 was given again.

Combined treatment (RSV+B17) group (n=7)

Intraperitoneal administration of 1 mL of RSV+B17 50 mg/kg was initiated two days before the procedure and surgery was performed. Thirty minutes of ischemia and 30 minutes of reperfusion were performed in the bladder after surgery. Following the reperfusion, 1 mL (single dose) of RSV+1 mL (single dose) of B17 was given again.

Establishment of ischemia-reperfusion

Ischemia model was performed using the method described by (Saito and Miyagawa, 2001; Leppilahti *et al*., 1999). The bladder of male rats anesthetized with ketamine (50 mg/kg im) was emptied through the urethral route with a 3F catheter and the penile urethra was clamped with an aneurysm clamp

with a holding force of 145 g. Afterwards, diuresis was forced and maximum bladder distension was achieved. Thus, the bladder has become palpable in the lower abdomen. The bladder, which entered ischemia as a result of overdistension, was waited for 30 minutes and the urethral clamp was removed and emptied with a 3F catheter. Thus, the reperfused bladder with increased blood supply was made ready for evaluation 30 minutes after decompression (Leppilahti *et al*., 1999).

At the end of the experiment, animals were sacrificed and bladder tissues were removed and subjected to biochemical and histopathological examinations.

Preparation of homogenate

Bladder were homogenized with three volumes of ice-cold 1.15% KCl. RFTN-1 and 8-iso-PGF2α levels were measured in the supernatant obtained from centrifugation at 14.000 rpm.

Biochemical analysis

8-iso-PGF2α levels were measured ELISA commercial kits (Cayman Chemical, MI, USA) enzyme-linked immunosorbent assay (ELISA) method. Read using the ELISA system (Elx-800; Bio-Tek Instruments Inc, Vermont). RFTN-1 levels in samples were meausured at 450 nm using the commercial kit (Human Raftlin-1 ELISA Kit, USA). Kit reference intervals of 100-2500 pg/mL.

Histopathological analysis

Small bladder tissue specimens for histological examination were fixed in 10% formalin, embedded in parafin wax on the oriented edge and cut into 5um thick sections. All tissue sections were stained with hematoxylin and eosin for histological examination.

Statistical analysis

SPSS (Statistical Package for Social Sciences) 25.0 was used for statistical analysis. Our results were given as mean±standard deviation. Since the results did not show normal distribution, nonparametric One-Way ANOVA test was used. Non-parametric Kruskal-Wallis test was used to examine the differences between the groups. A p value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Biochemical analysis results

Table 1 shows the mean±standard deviation (SD) values of the RFTN-1 and 8-iso-PGF2α results obtained after the model applied in the Sham, control, I/R and treatment groups and the distribution of the lower and upper values according to the groups.

Considering the RFTN-1 and 8-iso-PGF2α values; It was observed that the values of the sham, I/R and treatment 2 groups statistically significantly increased as compared to the control group ($p<0.05$). The RFTN-1 value of the I/R group was found to be significantly increased compared to the sham group ($p<0.05$). Although an increase in 8-iso-PGF2α value was observed in the I/R group compared to the sham group, no significant difference was found ($p>0,005$). It was observed that the RFTN-1 and 8-iso-PGF2α values of the treatment 1 and combined treatment groups were significantly decreased compared to the sham group ($p<0.05$). It was observed that the RFTN-1 and 8-iso-PGF2α values of the treatment 2 group decreased compared to the sham group, but only the 8-iso-PGF2α values varied statistically ($p<0.05$). RFTN-1 and 8-iso-PGF2α values of the tratment 1, treatment 2 and combined treatment groups were found to be significantly decreased compared to the I/R group ($p<0.05$). 8-iso-PGF2α value of the treatment 1 group was statistically decreased compared to the treatment 2 group ($p<0.05$). It was found that both RFTN-1 and 8-iso-PGF2α values of the combined treatment group were statistically significantly decreased compared to the treatment 2 group ($p<0.05$).

Histopathological results

Conjoined dilated structures, pericapillary and inflammatory cells were seen in the Sham and I/R groups. In addition, edema formation and fibrinoid necrosis were observed in the I/R group. Few pericapillaries and mild inflammation was seen in treatment 2 group. Decreased pericapillary and inflammatory cells, mild dilatation of vascular structure were observed treatment 1 group. Significant improvement was seen in the combined treatment (B17+RSV) group (Fig 1). It was observed that there was no edema, hemorrhage and infection in the combined treatment group (Table 2).

The results obtained from our study showed that the combined treatment of RSV and B17 may be effective in reducing both bichemical and histopathological damage due to bladder I/R injury. One of the most important target structures of free radicals formed as a result of I/R is lipids. Lipid peroxidation is considered by some researchers to be the key to I/R injury (Sahna *et al*., 2006). 8-iso-PGF2α, a product of lipid peroxidation, are usually checked. 8-iso-PGF2α is chemically more stable than other isoprostanes and studies were shown that it was a reliable marker that could be measured as an indicator of oxidative stress in plasma and tissue samples (Bratslavsky *et al*., 2003).

In our study, 8-iso-PGF2α value was lower in the treatment 1 and treatment 2 groups compared to the I/R group ($p<0.05$). In addition, the most decrease in 8-iso-PGF2α value was observed in the combined treatment (RSV+B17) group ($p<0.05$). The antioxidant role of RSV is to compete with coenzyme Q, capture O2-(Superoxide radical) and inhibit lipid peroxidation (Avnioglu *et al.,* 2022). In our study, the low levels of 8-iso-PGF2α in the treatment group may suggest that RSV inhibits lipid peroxidation as a strong antioxidant *in vivo*. The high level of 8-iso-PGF2α value in the I/R group indicates that tissue damage occurs due to lipid peroxidation and leukocyte activation after I/R injury. In addition, the 30-minute ischemia and reperfusion time we applied in our study suggests that it may be effective in the high level of 8-iso-PGF2α. In our study, the

Table 1: RFTN-1 and 8-iso-PGF2α values of the groups.

Groups	RFTN-1 Mean±SD (pg/mL)	8-iso-PGF2α Mean±SD (ng/mL)
Control	271.57±66.23	11.43±2.42
Sham*0"	501.57±99.35	19.59±1.69
I/R	690.86±126.47**	21.76±2.37
#Treatment 1 (RSV)**	324.00±49.42	12.20±1.49
#Treatment 2 (B17)	409.57±40.24	16.37±0.71**
#Combined therapy (RSV+B17)**	270.71±56.02	11.34±2.05

SD: Standart deviation

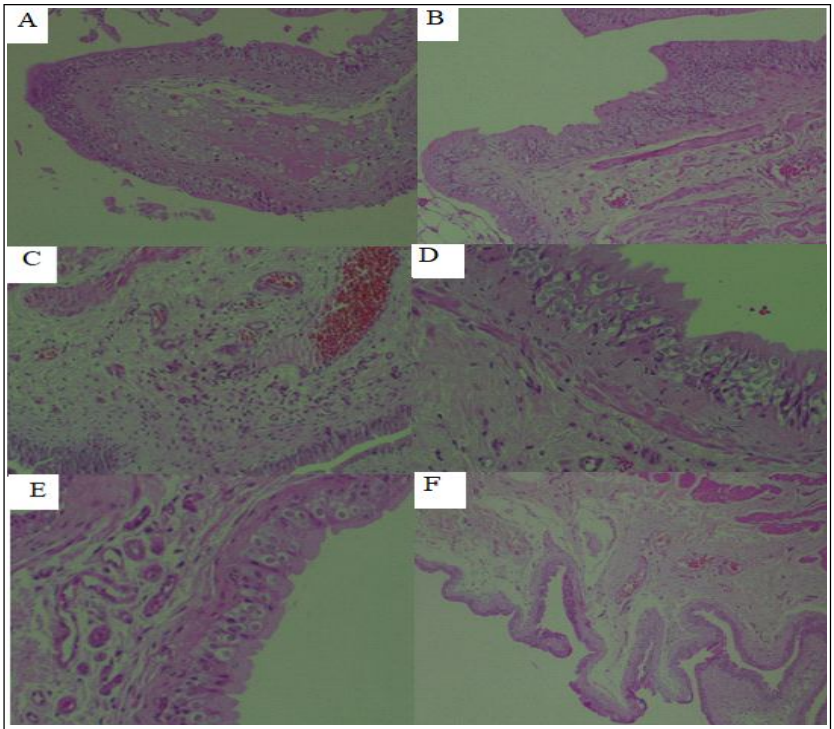
*There is a statistically significant difference with the control group ($p<0.05$).

**There is a statistically significant difference with the sham group ($p<0.05$).

#There is a statistically significant difference with the I/R group ($p<0.05$).

Table 2: Histopathological grade of the groups.

	Inflammatory cells	Edema	Necrosis	Hemorrohage
Control	0	0	0	0
Sham	1	1	0	0
I/R	2	1	1	3
Treatment 2	1	0	0	0
Treatment 1	1	0	0	0
Combined therapy	0	0	0	0



A: Control group: Normal bladder tissue; B: Sham group: Moderately congested dilated structures, pericapillary and inflammatory cells; C: I/R group: Edema, scattered inflammatory cells, fibrinoid necrosis; D: Treatment (B17) Group: Few pericapillaries and mild inflammation; E: Treatment (RSV) group: Decreased pericapillary and inflammatory cells; mild dilatation of vascular structure; F: Combined Therapy (B17+RSV) Group: No edema, hemorrhage and inflammation.

Fig 1: Histopathological results of the groups.

highest increase in 8-iso-PGF2α value occurred at the 30th minute of reperfusion. Similar evaluations regarding this period are recorded in the literature (Guler *et al*., 2004; Lin *et al*., 2000).

Another parameter used in this study was RFTN-1. Saeki *et al*. (2003) reported that RFTN-1 modulates lipid rafts and has some enzymatic activities related to lipid metabolism. RFTN-1 is a biochemical parameter used to diagnose inflammatory diseases and characterize the immune response. In this present study, RFTN-1 levels were found to be high in the I/R and sham groups, while RFTN-1 levels were found to be lower in the therapeutic groups (treatment 1 and 2). But, it was observed that RFTN-1 levels decreased significantly, especially in the treatment 1 group ($p<0.05$). This is the first study to investigate the protective effect of RSV and B17 on RFTN-1 against bladder I/R injuries. This situation contributes to the originality of our study. However, in literature, there were studies evaluating different vitamins in I/R models (Jing *et al*., 2013; Jarrod, 2000).

Although the dose of RSV varies between $10^{(-6)}$ mg/kg and 20 mg/kg in the literature, there are studies in which different doses are applied (Gedik *et al*., 2008). In our study, we used resveratrol at a dose of 50 mg/kg and showed that resveratrol at this dose significantly reduced tissue damage (Table 1).

In our study, it was observed that RSV and B17 showed similar protective effects histopathologically. The histopathologically mild inflammation and the presence of a small number of pericapillaries in the B17 applied groups indicate that it is effective in tissue repair. Pericapillary and inflammatory cells decreased in treatment 1 group. Histopathologically significant improvement occurred in the combined therapy (RSV+B17) group.

As a result, bladder I/R injury and ROS formation occur due to changes in the blood flow of the bladder during filling and emptying of the bladder. In this study, we showed with biochemical data that RSV and B17 can play an active role in injuries related to bladder I/R. In addition, our research, supported by histopathological data, has clinically demonstrated that RSV and B17 have a healing effect in injuries related to bladder I/R.

Conclusion

In present study, significant improvement in histopathological damage was demonstrated in the groups treated with RSV and B17. Especially in the combined (RSV+B17) treatment group, it was observed that edema, hemorrhage and inflammation formation in the tissue were prevented. In conclusion, our compatible biochemical and histopathological results show that RSV and B17 are protective against bladder I/R injury with their free radical scavenging effect. This study focused on the antioxidant protective properties of RSV and B17 against bladder I/R injury.

Conflict of interest: None.

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