Effect of Resveratrol and Quercetin on Intestinal Ischemia Reperfusion Injury in Rats

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Abstract

Aim: Intestinal ischemia reperfusion (I/R) injury is an emergency condition with a high mortality rate and early diagnosis is very difficult. In this study, we aimed to examine the biochemical and histopathological effects of resveratrol and quercetin on intestinal I/R injury model.

Methods: In our study, 56 male Sprague-Dawley rats weighing 250-300 g were randomly divided into 7 groups consisting of 8 rats. Groups were control group (group 1), saline group (group 2), ethanol group (group 3), resveratrol group (group 4) (30mg/kg), quercetin group (group 5) (30mg/kg), resveratrol+quercetin group A (group 6) (15 mg/kg+15 mg/kg), resveratrol+quercetin group B (group 7) (30 mg/kg+30 mg/kg). At the end of the experiment rats intestinal tissues were divided into 2 parts for biochemical and histopathological examination. Total oxidant level (TOS), total antioxidant level (TAS), total thiol [(-SH)+(-S-S-)] (TT), native thiol [-SH] (NT), and protein content levels were measured spectrophotometrically, oxidative stress index (OSI) and disulfide [-S-S-] levels were calculated.

Results: A statistically significant difference was found between the groups in terms of TOS, OSI, TT, NT and disulfide levels ($p < 0.05$). No statistically significant difference was observed between the groups in terms of TAS levels ($p > 0.05$). A significant improvement in histopathological scoring was observed in all treatment groups compared to saline and ethanol groups ($p < 0.05$).

Conclusions: Resveratrol and quercetin have protective effects in reducing oxidative stress in intestinal I/R damage.

Keywords: *Ischemia-reperfusion, resveratrol, quercetin, intestinal tissue damage*

1. Introduction

Mortality rates due to acute intestinal I/R injury have decreased in recent years but they still remain at high levels. 26% of these patients who are hospitalized live less than 1 year (1). Although the relevant mechanisms have not been fully elucidated, studies show that free radical attack originating from toxic oxygen metabolites is effective in the pathophysiology of intestinal I/R injury[1-3].

Increased blood flow in I/R injury causes an increase in tissue oxygenation and thus the production of reactive oxygen species (ROS) such as superoxide radical ($O_2^{\bullet-}$), peroxynitrite ($ONOO^-$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^\bullet$) (4). While low ROS levels are effective in ischemic preconditioning, excessive elevation of ROS plays a role in the deterioration of the antioxidant system, mitochondrial membrane permeability, protein structure, lipid oxidation and deoxyribonucleic acid (DNA) damage. Thus, it causes an increase in cell membrane permeability and apapoptosis[4,5].

TOS is used as a cumulative indicator of oxidative stress in the body. TAS is used as a marker showing the amount of antioxidants produced in the body against oxidative stress[6]. The TOS/TAS ratio gives the OSI and is a parameter that shows whether the balance between antioxidants and oxidants increases on the oxidant side or on the antioxidant side[2,3,6,7].OSI index value of 1 indicates a healthy balance,

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while a value greater than 1 indicates an increase in oxidative stress or a decrease in the amount of antioxidants[6].

Thiols are molecules containing sulfhydryl (-SH) group and are effective in preventing the occurrence of oxidative stress. While thiols reduce oxidant substances, they themselves oxidize and turn into disulfide. Native thiol, dynamic disulfide and total thiol are among the parameters used in thiol disulfide balance measurement. NT shows antioxidant activity, and disulfide dynamic shows oxidant activity[8].

Antioxidants are used to prevent local or systemic effects caused by I/R injury. Studies have shown that both resveratrol and quercetin have high antioxidant capacity[9,10].

Resveratrol is a natural polyphenolic compound found mainly in peanuts, grapes, mulberries and red wine. With its antioxidant effect, it reduces the pathological progression in many diseases[11-13]. It is also stated that resveratrol has a protective effect on I/R damage[11]. Resveratrol has antioxidant activity by scavenging $OH^{\cdot}$ and $O_2^{\bullet-}$ and inhibiting lipid peroxidation caused by $OH^{\cdot}$ radical[9,10]. It is effective against oxidative stress by chelating copper (II) and phagocytizing free oxygen radicals[13].

Quercetin is a flavone derivative polyphenol found in many vegetables and fruits such as tea, apples, onions, strawberries and red grapes[4,5,14]. Its antioxidant activity is quite strong compared to other flavonoids[15]. It has the ability to scavenge free radicals via the Fenton reaction by chelating transition metals such as Fe^{2+} and Cu^{+} ions[5,11,16].

The protective properties of resveratrol and quercetin against intestinal I/R injury have not been adequately studied to date. The aim of this study is to investigate whether resveratrol and quercetin have anti-oxidant effects and histopathologically protective effects on intestinal tissue in I/R injuries.

2. Materials and methods

Ethics committee approval of this study was obtained by Kahramanmaraş Sütçü İmam University Experimental Animals Ethics Committee with the decision dated 26.12.2018 (Decision No: 02).

The study was carried out in Kahramanmaraş Sütçü İmam University Experimental Animals Laboratory. In all animal procedures used, care was taken to strictly comply with the "European Convention on Animal Care and the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals".

2.1. Subjects

In the study, 56 Sprague Dawley type male rats weighing between 250-300 grams were used. The groups were randomly divided into 7 groups of 8 rats in each group; control group, saline group, ethanol group, resveratrol (30 mg/kg) group, quercetin (30 mg/kg) group, resveratrol+quercetin group (A) (15 mg/kg+15 mg/kg), resveratrol+quercetin group (B) (30 mg/kg) kg+30 mg/kg). All rats were fed standard laboratory chow until the day of the experiment and were weighed before the experiment. Before the study, the rats were allowed to drink water but were fasted for 12 hours before the experiment. Surgery was performed in all rats under intraperitoneal ketamine (40 mg/kg) and xylasine (50 mg/kg) anesthesia. The rats were allowed to breathe spontaneously throughout the experiment.

2.2. Design of experimental groups:

Following ketamine anesthesia, median laparotomy was performed in all groups, and the superior mesenteric artery (SMA) was reached by entering the abdominal cavity.

Then, intestinal tissue samples were taken from the control group (n=8).

In other groups, 60 minutes ischemia damage is created and intraperitoneally; was given 0.3 ml of saline to the saline group; 5% ethyl alcohol (0.3 ml) to the ethanol group; resveratrol at a dose of 30 mg/kg dissolved in 5% alcohol to the resveratrol group[17]; to the quercetin group, quercetin at a dose of 30 mg/kg dissolved in 0.3 ml of saline[18]; resveratrol+quercetin group (A) (15 mg/kg + 15 mg/kg) intraperitoneally at a dose of 15 mg/kg of resveratrol dissolved in 5% alcohol and 15 mg/kg of quercetin dissolved in 0.3 ml of saline; 30 mg/kg resveratrol dissolved in 5% alcohol and 30 mg/kg quercetin dissolved in 0.3 ml saline to resveratrol+quercetin group (B) (30 mg/kg + 30 mg/kg). Afterwards, 60 minutes of reperfusion was applied to these groups and intestinal tissue samples were taken.

2.3. Conducting the Experiment and Taking Samples:

The rats were anesthetized by the intraperitoneal (IP) route. After shaving the abdominal skin of the rats, it was cleaned with an antiseptic solution and then laparotomy was performed with a midline incision. After entering the abdominal cavity, reaching the small intestines and temporarily removing the small intestines, the SMA was reached and the artery was carefully dissected and isolated from the surrounding tissues. The blood flow was stopped by placing an atraumatic microvascular clamp on the SMA, and then 60 minutes of ischemia and then 60 minutes of reperfusion were applied, and the ileum segment of approximately 2 cm, 15 cm proximal to the ileocecal valve was resected and tissue samples were taken[19]. All rats were sacrificed after the procedure. Tissue samples taken were divided into two and one part of each was stored at –80 °C for biochemical analysis. The other part of the samples was placed in 10% formaldehyde and used for histopathological examination. In our study, one rat in the quercetin group died during the experiment.

2.4. Biochemical Analysis:

Tissue samples reserved for biochemical studies were left to melt at +4 ˚C on the working day. Before the analysis, the tissues were weighed and homogenized on ice with 0.15 molar KCl at a ratio of 1/10 (Ultra turrax, 60 sec at 13500 rpm). Then, the supernatants were separated by centrifugation at 4000 rpm at + 4˚C for 20 minutes. TOS, TAS, TT, NT and protein levels were analyzed by spectrophotometric method (Shimadzu UV-1800).

2.5. Total oxidant/antioxidant level (TOS/TAS) and oxidative stress index (OSI):

Spectrophotometric analyzes were performed in Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Medical Biochemistry Research Laboratory.

TOS (Rel Assay) and TAS (Rel Assay) levels were analyzed spectrophotometrically, adhering to the commercial kit content. The results obtained as a result of TOS analysis were calculated as μmol H_2O_2 Eq/L and given as umol/L/mg protein, the results obtained as a result of TAS analysis were calculated as μmol Trolox Eq/L and given as mmol/L/mg protein.

OSI is the percentage degree of the ratio of TOS to TAS. In the calculation of OSI, the unit of TOS and TAS value is equal to μmol.

2.6. Total thiol-native thiol and thiol / disulfide balance:

TT (Rell Assay, Product Code: 0178) and NT (Rell Assay, Product Code: RL0185) levels were analyzed spectrophotometrically, adhering to the commercial kit content. The amount of dynamic disulfide bonds was obtained by calculating half of the difference between the TT and NT groups (μmol/L) .

2.7. Protein analyzes:

Protein analyzes were performed using the Lowry[20] method and the results were given in proportion to protein values.

2.8. Histopathological Analyzes:

At the end of the experiments, the jejunums of the sacrified rats were placed in 10% buffered formol and then routinely followed up with tissue. Then, 4.5 μm sections were taken and stained with hematoxylin-eosin dye, and then the groups were evaluated by a histologist

under the light microscope (Olympus BX41). Used in the histopathological evaluation of intestinal I/R injury, Chiu et al.[21] is a scoring system in which intestinal I/R damage and the effect of antioxidant agents used against it can be evaluated[16,21].

2.9. Statistical Analysis:

2.9.1. For biochemical analysis:

SPSS 21.0 (SPSS Inc. Chicago, USA) program was used for statistical analysis of research data. In the descriptive statistics part, continuous variables are presented with mean±standard deviation (mean±SD). Mann-Whitney U test was used for comparison analyzes between two independent groups and Kruskal Wallis test was used for comparison analysis between three groups. Statistical significance level was accepted as $p<0.05$.

2.9.2. For histopathological analysis:

Data were collected using SPSS 17 software (SPSS® version 17.0; SPSS, Chicago, IL, USA). Numerical variables are presented as mean±SD. The groups were compared using the ANOVA test, and within-group evaluations were made using the Tucey HSD method. Statistical significance level was accepted as $p<0.05$.

3. Results

3.1. Biochemical Findings:

In our current study, a statistically significant difference was observed between the groups in terms of TOS, OSI, TT, NT and disulfide values ($p<0.05$). There was no significant difference between the groups in terms of TAS (mmol/L/mg protein) values ($p=0.518$) (Table 1).

3.2. Histopathological Findings:

In the histopathological examination, intestinal appearance was normal in the control group (Figure 1). In the saline and ethanol groups, intestinal appearance compatible with Stage 3 and 4 was observed in Chiu scoring. Histopathology consistent with Stage 1 was observed in the quercetin and resveratrol groups. While there was no significant difference between resveratrol and quercetin group (A) (15 mg/kg+15 mg/kg), resveratrol and quercetin group (B) (30 mg/kg+30 mg/kg) groups, histopathology compatible with Stage 0 and 1 was observed. It has been shown statistically that quercetin, resveratrol and their combined low and high doses have a protective effect on the intestine (Table 2).

Table 1

TOS, TAS, OSI, TT, NT, disulfide levels of the groups (mean±SD.)

	Control (Group 1) (n=8)	Salin (Group 2) (n=8)	Ethanol (Group 3) (n=8)	Resveratrol (Group 4) (n=8)	Quercetin (Group 5) (n=7)	R+Q (A) (Group 6) (n=8)	R+Q (B) (Group 7) (n=8)	p1
TOS umol / L / mg Protein	0,11±0,01	0,22±0,05a	0,24±0,06a	0,15±0,03abc	0,14±0,02abc	0,15±0,01abc	0,14±0,03abc	< 0,001
TAS mmol /L/ mg Protein	0,03±0,01	0,03±0,00	0,03±0,00	0,03±0,00	0,03±0,00	0,03±0,00	0,03±0,00	0,518
OSI	0,31±0,05	0,77±0,23a	0,81±0,20a	0,51±0,06abc	0,44±0,05abcd	0,47±0,05abc	0,42±0,08abcd	< 0,001
TT [(-SH)+(-S-S-)] / Protein	5,78±0,76	3,4±0,21a	3,52±0,42a	3,91±0,61a	4,46±0,36abc	4,27±0,65abc	4,76±0,68abcd	< 0,001
NT (-SH) / Protein	5,27±0,68	2,51±0,18a	2,69±0,41a	3,15±0,58ab	3,72±0,43abcd	3,56±0,66abc	4,12±0,69abcd	< 0,001
Disulfide (-S-S-)	0,26±0,14	0,45±0,07a	0,41±0,12a	0,38±0,06b	0,37±0,11	0,35±0,06b	0,32±0,08b	0,016

Notes: p1 Kruskal Wallis test. aCompared to Group 1, bCompared to Group 2, cCompared to Group 3, dCompared to Group 4 (Mann-Whitney U test). R+Q: resveratrol + quercetin. TOS: Total oxidant level, TAS: total antioxidant level, OSI: oxidative stress index, TT: total thiol, NT: native thiol.

Figure 1

Intestine view of the groups

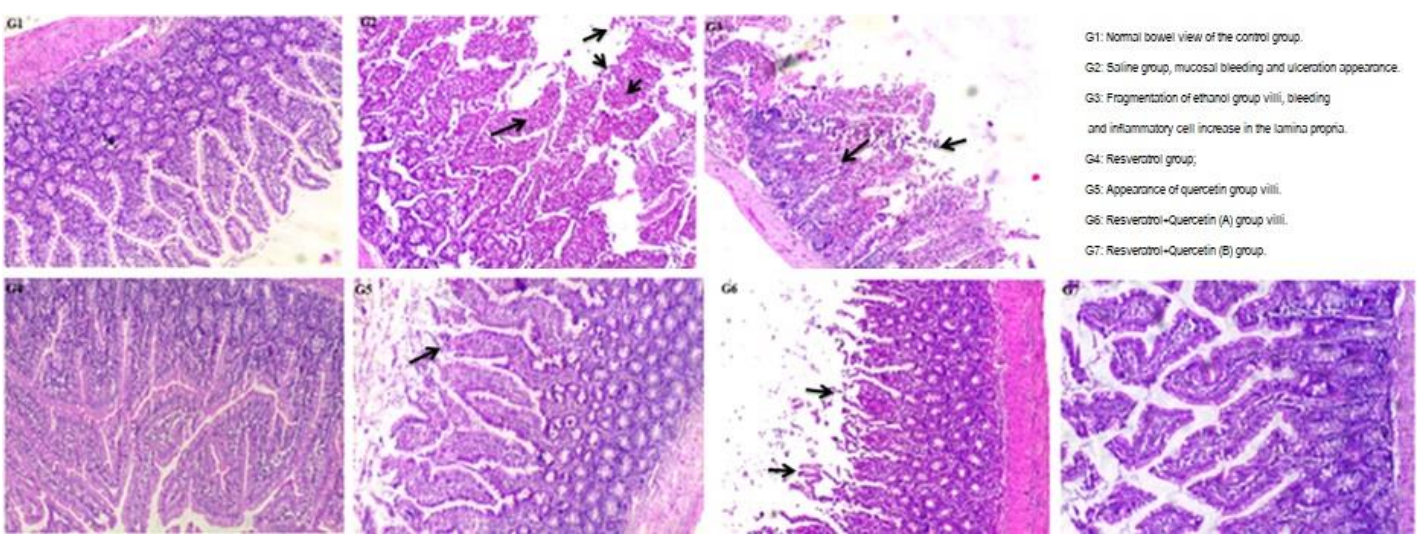

Table 2

Histopathological data of the groups (mean±SD)

	Control (Group 1) (n=8)	Salin (Group 2) (n=8)	Ethanol (Group 3) (n=8)	Resveratrol (Group 4) (n=8)	Quercetin (Group 5) (n=7)	R+Q (A) (Group 6) (n=8)	R+Q (B) (Group 7) (n=8)	p2
Chiu Score	0.62±0.44	4.12±0.83	4.25±0.70	2.87±0.83*	2.75±0.70*	3.50±0.92	2.75±0.70*	< 0,001

*Compared to Group 3 (p2: One Way ANOVA (with Tukey HSD)). R+Q: resveratrol + quercetin.

4. Discussion

One of the most life-threatening conditions in clinical practice worldwide is ischemic bowel disease. The most important approach to salvage intestinal tissue in ischemia is to restore blood flow as soon as possible. However, restoration of blood flow causes a more serious complication such as intestinal I/R injury[1]. After ischemia, reperfusion causes molecular oxygen to enter the tissue, causing rapid production of ROS and serious cellular damage[2,3,7].

In the study of Yazıcı et al.[6], serum OSI levels 2 hours after induction of mesenteric ischemia were found to be significantly higher compared to the control group. However, OSI levels after 6 hours decreased compared to OSI levels after 2 hours. The increase in OSI and TOS values at the 2nd hour was attributed to the changes experienced with oxidative stress. It has been stated that the decrease in these parameters at the 6th hour of ischemia may be due to the opening of the collateral circulation and the activation of systemic antioxidant mechanisms in prolonged ischemia[6]. In the study of Tanyeli et al.[2], it was observed that intestinal tissue TAS levels decreased significantly and TOS and OSI levels increased significantly in the rat group with mesenteric ischemia-reperfusion injury compared to the sham group. It has been seen in many studies that resveratrol has beneficial effects against intestinal I/R damage[14,22-25]. In the study of Yıldız et al.[12], they found that TAS was significantly higher, TOS and OSI were significantly lower in the intestinal tissue in the resveratrol treatment group compared to the control group in intestinal I/R damage. In the study of Tóth et al.[14], it was observed that quercetin reduced the mucosal damage caused by intestinal IR damage in rats. In the study of Bahadır et al.[4], the effects of quercetin on hepatic I/R damage were investigated, and TAS, TOS and OSI values in the sham group were found to be significantly lower than the control and quercetin applied study groups; the mean TAS, TOS and OSI values of the control group were found to be higher than those of the quercetin applied group, but no statistical difference was observed. In this case, it was stated that quercetin may be effective in reducing pro-oxidant production rather than increasing antioxidant capacity. In our current study, we aimed to investigate the effect of naturally occurring antioxidant compounds called polyphenols, resveratrol and quercetin, on I/R damage. For this, we measured the TAS and TOS values in the intestinal tissue and calculated the OSI values to see if there was a difference between the groups. A significant increase was observed in TOS and OSI levels in all other groups when compared to the control group. It is thought that TOS levels increase due to I/R injury in these groups. When compared with saline and ethanol groups, a significant decrease was observed in TOS and OSI levels in all other groups treated with resveratrol and/or quercetin. The significant decrease in OSI values in the quercetin and resveratrol+quercetin (B) applied groups compared to the resveratrol group suggests that quercetin is more effective in preventing oxidative stress than resveratrol. There was no difference between the groups in terms of TAS levels. This may be due to the time of administration of resveratrol and quercetin or the duration of I/R injury, or, as Bahadır et al.[4] said, resveratrol and quercetin may have been effective in reducing pro-oxidant production rather than increasing antioxidant capacity. Or, the measurement of oxidant and antioxidant levels alone may not be sufficient to clearly reveal most of the oxidative stress state[2]. There was no difference between the groups with the dose increase of antioxidants.

Thiols are organic compounds containing -SH group and play a critical role in preventing oxidative stress in cells. The first target in proteins for ROS is amino acids containing the -SH group. -SH groups are oxidized by ROS and -SH groups of two thiol groups combine to form a dynamic, redox sensitive covalent bond, a reversible disulfide bond[26-29]. With the increase in oxidative stress, the consumption of thiols for detoxification also increases[29]. Thus, while the native thiol decreases, the amount of disulfide increases[26]. Disulfide bonds formed by the oxidation of thiols can be reduced to thiol groups with the effect of antioxidants, thus maintaining thiol/disulfide homeostasis[27]. Thiol/disulfide homeostasis plays an important role in regulation of protein function, stabilization of protein structure, protection of cysteine residues of proteins against irreversible oxidation, cellular signal transduction, chaperone function, regulation of enzymatic activity, transcription factors, and apoptosis[27,28]. In normal healthy individuals, more than 50% of the physiological serum antioxidant capacity consists of thiols[29]. In the study of Yıldırım et al.[29], serum thiol values decreased from the first hour of acute mesenteric ischemia; at 3. and 6. hours, serum total thiol and native thiol values decreased significantly in mesenteric ischemia groups compared to control and sham groups, while serum disulfide values increased significantly. In the study conducted by Özçakır et al.[30], although no statistically significant difference was found in the plasma of rats exposed to intestinal ischemia for 60 and 180 minutes in terms of TT, NT and disulfide levels compared to the control group; TT and NT levels decreased and disulfide values increased at the 3. hour. In the study of Olas et al.[31], resveratrol was found to reduce the thiol-reducing effect of platinum compounds in platelets. In our study, there was improvement in the treatment groups in terms of TT and NT, but it did not approach the baseline value. Thus, we can say that resveratrol and quercetin may have a protective effect by reducing disulfide levels.

In intestinal I/R injury, the release of ROS and proteolytic enzymes cause an acute inflammatory response that increases ischemic damage and neutrophil infiltration, lipid peroxidation, apoptosis and necrosis[32]. It has been shown that reperfusion after occlusion of SMA can cause apoptosis in rat intestinal tissue[33]. Pergel et al.[34] and Tas et al.[32] showed that antiapoptotic treatment can be effective in preventing intestinal I/R damage. In the study of Yıldız et al.[12], it was observed that histological tissue damage in intestinal I/R injury was milder in the resveratrol treatment group compared to the control group. In the study of Bahadır et al.[4], no significant difference was found between the control and quercetin applied study groups in terms of necrosis and apoptosis in hepatic I/R injury. In the study of Curgali et al.[35], protective quercetin application before

jejunal I/R induction stimulated faster restoration of the jejunal mucosa. Yıldız et al.[16], after intestinal I/R application, it was observed that the most histopathological damage was in the I/R group among the sham group, quercetin+I/R and I/R groups. Histological damage was significantly reduced in the quercetin group compared to the I/R group. In our current study, when the groups were evaluated in terms of Chiu score, the highest scores were in the rats in group 2 and group 3, and there was no significant difference between the results of these two groups (p=0.975); however, there was a significant difference between group 3 and group 4 (p=0.021), between group 3 with group 5 and group 7 (p=0.008). When the treatment groups were evaluated within themselves, it was seen that the lowest scores were in the rats in group 5 and group 7, but there was no statistical difference within the treatment groups (p>0.05).

5. Conclusions

In the light of the biochemical and histopathological data we have obtained that resveratrol and quercetin have a protective effect on I/R damaged intestinal tissues. However, detailed studies are required to elucidate the mechanism of this effect and its relationship with thiols.

Statement of ethics

The study was approved by the Kahramanmaraş Sütçü İmam University Experimental Animals Ethics Committee with the decision dated 26.12.2018 (Decision No: 02).

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

Study conception and design: Fatma İnanç Tolun, Işıl Yağmur, Selen Dindar; acquisition of data: Selen Dindar, Atilla Yoldaş; analysis and interpretation of data: Fatma İnanç Tolun, Hasan Dağlı, Aslı Yaylalı, Rabia Tural; drafting of manuscript: Rabia Tural, Işıl Yağmur; critical revision: Fatma İnanç Tolun, Işıl Yağmur, Rabia Tural.

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