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Protective effects of quercetin on hepatic ischemia reperfusion injury

Quercetin'in karaciğer iskemi reperfüzyon hasarı üzerine koruyucu etkisi

Halil Mert Bahadır[1], Talha Sarıgöz[2], Ömer Topuz[3], Yusuf Sevim[4], Tamer Ertan[3], İnanç Şamil Sarıcı[5]

Abstract / Öz

Introduction: The present study was designed to evaluate the effects of quercetin on hepatic ischemia-reperfusion injury of rats formed by the Pringle maneuver.

Methods: Five-to-six-month-old, 24 female Wistar-Albino rats weighing 200-250 mg were used in this study. In the sham group, 15 minutes after anesthesia induction, laparotomy was performed. Ischemia was not created. In the other groups, the hepatic pedicle (portal vein, hepatic artery, and bile duct) was explored and ischemia was created using an atraumatic microvascular clamp. Meanwhile, the exposed abdomen was covered with warm gauze soaked in saline. In the study group, quercetin was injected intraperitoneally prior to laparotomy and ischemia-reperfusion. Liver tissue samples from the left lobe were analyzed under a light microscope for liver damage. For the evaluation of hepatic ischemia-reperfusion injury and the assessment of quercetin's effect on the antioxidant systems, total oxidant status and total antioxidant status levels were measured. The oxidative stress index was calculated.

Results: Aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase values of the control group were significantly higher than those of the sham and study groups (p<0.001). Although the mean total antioxidant status, total oxidant status, and oxidative stress index values of the study group were found to be lower than those of the control group, the difference was not statistically significant (p>0.05). Significantly less vacuolization and sinusoidal dilatation were observed in the study group compared to the control group (p<0.05). For necrosis and apoptosis, no significant difference was observed between the control and study groups (p>0.05).

Conclusion: Quercetin, which hosts many molecules within its structure with potential utilities, such as anti-inflammatory, antioxidant, and antiaggregant, may be protective against hepatic ischemia-reperfusion injury.

Keywords: Quercetin, ischemia reperfusion, liver injury, pringle maneuver, rat model, antioxidant

Amaç: Bu çalışma, farelerde oluşturulan karaciğer iskemi-reperfüzyon hasarında quercetinin etkilerini değerlendirmek için tasarlandı.

Yöntemler: 24 adet, 5-6 aylık, 200-250 g ağırlığında dişi Wistar-Albino fare çalışmaya alındı. Sham grubunda anestezi indüksiyonundan 15 dakika sonra laparotomi yapıldı. İskemi oluşturulmadı. Diğer gruplarda Hepatik pedikül (portal ven, hepatik arter, safra kanalı) bulundu ve atravmatik mikrovasküler klemp yardımıyla iskemi oluşturuldu. Bu sırada batına serum fizyolojik ile ıslatılmış gaz serildi. Çalışma grubunda laparotomi ve iskemi-reperfüzyondan önce periton içine quercetin verildi. Karaciğer sol lobdan alınan doku örnekleri ışık mikroskobu altında hasar açısından incelendi. Hepatik iskemi-reperfüzyon hasarı ve Quercetin'in anti-oksidan etkisini değerlendirmek için total oksidan durum ve total anti-oksidan durum değerleri ölçüldü. Oksidatif stres indeks hesaplandı.

Bulgular: Kontrol grubunda, aspartat aminotransferaz, alanin aminotransferaz ve laktat dehidrojenaz değerleri sham ve çalışma grubundan anlamlı olarak yüksek bulundu (p<0.001). Ortalama total anti-oksidan durum, total oksidan durum ve oksidatif stres indeks değerleri çalışma grubunda, kontrol grubundan düşük bulunmasına rağmen bu farklılık anlamlı bulunmadı (p>0.05). Çalışma grubunda kontrol grubuna kıyaslandığında belirgin olarak düşük vakuolizasyon ve sinozidal dilatasyon izlendi (p<0.05). Nekroz ve apoptoz için çalışma ve kontrol grupları arasında anlamlı farklılık görülmedi (p>0.05).

Sonuç: Tüm sonuçlar göz önünde bulundurulduğunda, anti-inflamatuar, anti-agregan ve anti-oksidan özelliklere sahip bir çok molekülü bünyesinde bulunduran Quercetin, hepatik iskemi-reperfüzyon hasarında koruyucu olabilir.

Anahtar Kelimeler: Quercetin, iskemi reperfüzyon, karaciğer hasarı, pringle manevrası, fare modeli, antioksidan

ORCID IDs of the authors: H.M.B. 0000-0003-4050-998X; T.S. 0000-0001-6573-6519; O.T.Z. 0000-0001-8086-4682; Y.S. 0000-0002-2708-1598; T.E. 0000-0003-3721-2253; İ.Ş.S. 0000-0002-2292-1279

[1]Clinic of General Surgery, Erzin State Hospital, Hatay, Turkey
[2]Clinic of General Surgery, Sason State Hospital, Batman, Turkey
[3]Clinic of General Surgery, Kayseri Training and Research Hospital, Kayseri, Turkey
[4]Clinic of General Surgery, Numune Training and Research Hospital, Ankara, Turkey
[5]Clinic of General Surgery, Kanuni Sultan Suleyman Training and Research Hospital, İstanbul, Turkey

Address for Correspondence/Yazışma Adresi: Talha Sarıgöz, E-mail:sarigozt.md@gmail.com

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Introduction

Ischemia-reperfusion (IR) injury is an important cause of liver damage in liver transplantation or liver resections with the Pringle maneuver, and it is the main cause of liver dysfunction (1). Unfortunately, the mechanism of damage is not exactly known, but an inflammatory and oxidative process is proposed in the complex pathophysiology. Many molecules have been studied in animal experiments to reduce hepatic damage, but the improvements are not sufficient.

Quercetin is a flavonoid found mostly in fruits and vegetables. Epidemiological studies with quercetin were started in the 1990s. The molecule is found in a wide variety of plants, such as apples, onions, and berries and in red wine. Quercetin has antioxidative, anti-inflammatory, antiaggregatory, and anticarcinogenic effects (2).

The present study was designed to evaluate the effects of quercetin on hepatic IR injury of rats formed by the Pringle maneuver.

Methods

Experimental design and animals

This study was performed according the "Guide for the Care and Use of Laboratory Animals" (National Research Council Institute for Laboratory Animal Research, US, Washington, National Academies Press, 1996), and the animal protocols were approved by the Animal Ethics Committee of Erciyes University.

Five-to-six-month-old 24 female Wistar-Albino rats weighing 200-250 mg were used in this study. Rats were maintained in standard plastic cages and were fed with standard rat chow and water. They were kept under 12-hour light and dark cycles. The temperature of the room was maintained at 24±2°C.

Preparation and experimental groups

In this study, rats were randomized into three groups. In the laparotomy procedure, 15 minutes after drug administration, the anterior abdominal wall was shaved and then a 3-4 cm midline laparotomy incision was made. Meanwhile, the exposed abdomen was covered with warm gauze soaked in saline. In the sham group, 15 minutes after anesthesia induction, laparotomy was performed but ischemia was not created. In the other groups, the hepatic pedicle (portal vein, hepatic artery, and bile duct) was explored and ischemia was created using an atraumatic microvascular clamp (Vasculostatt-Scanlan, St Luis, USA). In the study group, subjects were administered an appropriate quercetin dose intraperitoneally after general anesthesia prior to ischemia application.

Histopathological study

Liver tissue samples from the left lobe of liver were placed in containers with 10% formalin. The samples were embedded in paraffin blocks and 4-5 µm sections were obtained. Samples were stained using hematoxylin-eosin. Preparations were examined by a blinded expert histopathologist under a light microscope, at a magnification of 50-100X (Table 1).

Biochemical evaluation

Blood samples were collected into tubes for the biochemical analysis to obtain serum and plasma. They were centrifuged at 3000 rpm for 10 minutes and then serum and plasma samples were placed in microcentrifuge tubes. Samples were stored at -20 °C until further measurements. For the evaluation of hepatic IR injury and assessment of quercetin's effect on antioxidant systems, the total oxidant status (TOS) and total antioxidant status (TAS) levels were measured. The oxidative stress index (OSI) was calculated. In addition, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) levels were measured through a colorimetric method using ready kits. For the TOS level analysis, a total oxidant status kit (Rel Assay Diagnostics) and Olympus AU 400 biochemistry autoanalyzer was used. Units were expressed in terms of micromole hydrogen peroxide equivalent per liter (µmol H_2O_2 eqv/L). For the TAS analysis, a total antioxidant status commercial kit (Rel Assay Diagnostics) and Olympus AU 400 biochemistry autoanalyzer was used. The TAS results were expressed as µmol Trolox eqv/L. While calculating the value that indicates the balance of an organism's oxidant/antioxidant capacity, OSI was calculated using the formula:

OSI=100 * TOS (µmol H_2O_2 eqv/L)/TAS (µmol Trolox eqv/L)

Statistical analysis

Biochemical and histopathological values were expressed as mean±standard error of the mean. For histopathological values, average (minimum, maximum) values were used. Data were analyzed using the IBM Statistical Package for Social Sciences 15.0 for Windows (SPSS Inc.; Chicago, IL, USA) and Sigma Stat 3.5 statistical package program. Between the groups, one-way analysis of variance (ANOVA) or Kruskal-Wallis tests were used. From the multiple comparison tests, Tukey's, Dunn-Sidak, and Tamhane's T2 were used. P values <0.05 were considered statistically significant.

Results

Aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase levels

The mean serum AST levels were 141.4±28.2 IU/L, 1166.6±275 IU/L, and 710.9±95 IU/, in the sham, control, and study groups, respectively. The AST values of the control group were significantly higher than those of the sham and study groups (p<0.001).

The mean serum ALT levels were 63.6±964.4 IU/L, 964.4±136.8 IU/L, and 475.6±114.7 IU/L in the sham, control, and study groups, respectively. The ALT values of the control group were significantly higher than those of the sham and study groups (p<0.001).

The mean serum LDH levels were 1368.0±316.7 IU/L, 6576.9±1981.2 IU/L, and 3324.3±2617.4 IU/L in the sham, control, and study groups, respectively. The LDH values of the control group were significantly higher than those of the sham and study groups (p<0.001; Table 2).

Total antioxidant status, total oxidant status, and oxidative

Table 1. Scoring system for IR injury of the liver

Liver Injury Histopathological Properties	Score	Description
Cytoplasmic Vacuolization	0	None
	1	Rarely seen
	2	Scattered in some lobules
	3	Scattered in most lobules
	4	Widespread
Sinusoidal Dilatation	0	None
	1	Rarely seen
	2	Frequent perivenular
	3	Frequent perivenular midzonal
	4	Frequent panlobular
Cell Necrosis	0	None
	1	1-2 Apoptotic Cells
	2	≥3 Apoptotic Cells
	3	1-2 Focal necrosis area
	4	≥3 Focal necrosis area

IR: Ischemia-reperfusion

Table 2. Comparison of AST, ALT, and LDH levels between experimental groups of animals. Data are means±SD from 8 rats per group

	Experimental Groups		
	Sham	Control	Study
AST	141.4±28.2	1166.6±275.2	710.9±95.6
ALT	63.6±964.4	964.4±136.8	475.6±114.7
LDH	1368.0±316.7	6576.9±1981.2	3324.3±2617.4

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; SD: Standard Deviation

stress index

In the sham group, TAS, TOS, and OSI values were found to be significantly lower than those of the control and study groups ($p<0.001$). Although the mean TAS, TOS, and OSI values of the control group were higher than those of the study group, these differences were not statistically significant ($p>0.05$; Table 3).

Histopathological examination

During histopathological examination, in the all groups, cytoplasmic vacuolization, sinusoidal dilatation, apoptosis, and cell necrosis were evaluated. In the sham group, normal histopathological appearance was observed despite presence of minimal sinusoidal dilatation and cytoplasmic vacuolization. Significantly less vacuolization and sinusoidal dilatation were observed in the study group compared to the control group ($p<0.05$). Necrosis and apoptosis also showed a similar pattern in the study group, but it was not statistically different compared to the control and sham groups ($p>0.05$; Table 4).

Discussion

Reduced or complete cessation of blood flow to any organ followed by a reperfusion process leads to the formation of an acute inflammatory response. Inflammatory response results in significant cell damage and causes malfunction. This biological process is defined as IR injury (3). Liver in one of the organs in the human body wherein the abovementioned damage most frequently occurs. After a hemorrhagic shock, liver transplantation, or liver resection, various degrees of hepatic IR injuries are observed (3-5).

Following an IR injury, with the increasing blood flow, tissue oxygenation increases and reactive oxygen species (ROS), such as superoxide anion (O_2^-), peroxynitrite ($ONOO^-$), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-), are produced (6). When hepatocytes are exposed to ROS, which are critical mediators in the pathogenesis of many liver diseases, the expression of various genes; synthesis of cytokine, chemokine, and cell adhesion molecules; permeability of cell and cell organelle; and protein and DNA oxidation are increased (7). These events result in the formation of oxidative stress leading to cell death by creating an irreversible damage or malfunction.

Table 3. Comparison of TAS, TOS, OSI. Data are means±SD from 8 rats per group

	Experimental Groups		
	Sham	Control	Study
TAS	0.96±0.11	1.33±0.08	1.22±0.18
TOS	10.98±0.55	35.2±6.3	26.1±1.7
OSI	1166.6±186.7	2657.3±503.6	2168.5±236.9

TAS: Total Antioxidant Status; TOS: Total Oxidant Status: OSI: Oxidative Stress Index; SD: Standard Deviation

Table 4. Comparison of histopathological results. Data are means (min-max) from 8 rats per group

	Experimental Groups		
	Sham	Control	Study
Sinusoidal Dilatation	0.5(0-1)	3.5(3-4)	1.0(1-2)
Cytoplasmic Vacuolization	0.5(0-1)	2.5(2-3)	1.0(0-2)
Necrosis, Apoptosis	0.0(0-1)	1.0(0-2)	0.0(0-1)

An increase in cell membrane permeability occurs as a result of membrane lipid peroxidation formed by the ROS. After lipid peroxidation, very powerful oxidizing agents, lipid peroxide radicals, and lipid hydroperoxides are released (8). These free radicals damage cell membrane. Final products, such as nitrotyrosine formed after protein oxidation, were detected to be high in various degrees in serum and tissue samples. Therefore, the resulting end products of this oxidation are often used as an indicator of protein oxidation (9, 10). The hepatocyte damage that occurs as a result of varying degrees of all the aforementioned effects or death of hepatocytes manifests as liver dysfunction.

One of the most important complications of liver surgery is intraoperative bleeding, which affects the perioperative conditioning of the patient. To avoid this problem, several vascular occlusion techniques have been used. In a retrospective study by Nakajima Y et al. (11), they investigated surgical techniques used to control bleeding in liver resection; and van der Bilt et al. (12) investigated vascular clamp techniques in liver surgery. The frequency of vascular occlusion techniques were shown in these studies. According to these studies, while hemihepatic vascular clamp technique is based on selective interruption of bloodstream to the lobe to be resected, the Pringle maneuver, which is recommended and used frequently, is applied to the portal triad to cut off the liver bloodstream (13). Again, Gurusamy et al. (14) compared vascular occlusion methods for elective liver resections by complication rates, and the intermittent portal triad clamping technique was found to have more evidence to support the clinical practice. In our experimental study, we used a portal triad clamping technique to create liver ischemia.

Free oxygen radicals have shown to be the main cause of all these changes in liver damage. Many treatment strategies have been focused on either preventing free oxygen radical damage or their formation. In the recent years, various number of local remedies, which have pleiotropic biological activity, have been used as a complementary or alternative therapy in the treatment of different diseases. Glantzounis et al. (15) have shown that the use of antioxidant agents for this purpose was to reduce ROS production and support endogenous antioxidants. One of these agents that we used in our study is quercetin (3, 3', 4', 5, 7-pentahydroxyflavone), which is a plant-derived flavonoid known as phytoestrogen (16). Quercetin exerts its antioxidant effect by scavenging free oxygen radicals and inhibiting lipid peroxidation and xanthine oxidase activity (17). Quercetin's anti-inflammatory action is mediated through the inhibition of lipoxygenase and cyclo-oxygenase enzymes (18, 19).

In their study, Dufour et al. (20) emphasized the sensitivity of transaminases (AST and ALT) and LDH in monitoring hepatocyte injury. Seeto et al. (21) reported that the maximum increase was detected in liver aminotransferase levels 90% percent of the cases with ischemic and toxic damage to the liver. In the same study, in the 80 percent of the cases they also detected high LDH and bilirubin levels. In our workup, we measured ALT, AST, and LDH levels as well, which are the most reliable parameters indicating liver cell damage and destruction in serum. We found significant differences for AST, ALT, and LDH levels in the sham group and study group compared to the control group, and it gave us information about liver damage that was induced in the experimental model. This assessment reveals quercetin's positive impact on liver IR injury.

In this study, to determine the level of oxidative stress, TAS and TOS values were measured and the OSI was calculated. The serum TAS analysis yielded relatively lower values in the study group, which was opposite of the desired. However, serum TOS values and OSI levels were found to be higher in the control group than in the study group. In their study, Costantini et al. (22), indicated that a marker of the antioxidant capacity itself was not sufficient to make assumptions about oxidative stress and suggested association with at least a marker of oxidative damage. In this context these results were interpreted to mean that quercetin, which is known to inhibit lipid peroxidation and xanthine oxidase activity, can reduce pro-oxidant production rather than increasing the antioxidant capacity. Altogether, this study demonstrated that following IR injury, oxidative/antioxidative balance shifted toward oxidative status, and higher oxidative stress was observed in the control group subjects.

Free oxygen radicals and abnormal activation of Kupffer cells play the main role in hepatic injury (23). This leads to the formation of structural and functional changes in the liver (24). In our workup, in addition to biochemical parameters, cytoplasmic vacuolization, sinusoidal dilatation, apoptosis, and necrosis were evaluated to reveal liver damage. Quercetin has been shown to reduce sinusoidal dilatation and cytoplasmic vacuolization significantly and necrosis and apoptosis moderately, and it has been found that quercetin reduced histopathological damage. In the light of these results, quercetin may have a moderate positive effect on the acute phase state of hepatic IR injury.

Conclusion

When considering all the findings, quercetin, which hosts many molecules within its structure with potential utility, such as anti-inflammatory, antioxidant, and antiaggregant, may have protective effect against hepatic IR injury. However, particularly, to recommend it as a stand-alone or preoperative nutritional support for the preparation of surgery, broader comparative studies are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from Erciyes University Animal Ethics Committee (Approval Date: 15.01.2014/Approval No: 14/017).

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