ARAŞTIRMA MAKALESİ/ ORIGINAL ARTICLE

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İntestinal İskemi/Reperfüzyon Hasarının Hafifletilmesinde p-Kumarik asit'in Rolü

Role of p-Coumaric acid in Alleviating of the Intestinal Ischemia/Reperfusion Injury

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ÖZ

GİRİŞ ve AMAÇ: *Bu çalışma intestinal iskemi/reperfüzyon (İ/R) hasarına karşı p-kumarik asit' in koruyucu rolünü araştırmak amacıyla planlandı.*

YÖNTEM ve GEREÇLER: *Bu amaçla, çalışmamızda deneysel intestinal İ/R hasar modeli oluşturuldu. p-Kumarik asit ve İ/R gruplarında, süperior mezenterik arter 1 saat süreyle klemplendi. Bu sürenin sonunda klemp açıldı ve 2 saat süreyle reperfüzyona izin verildi.2 saatin sonunda, sıçanlar sakrifiye edildi ve intestinal doku örnekleri hızlıca toplandı.*

BULGULAR: *İ/R'ye bağlı olarak şiddetli oksidatif hasardan dolayı MPO aktivitesi, MDA seviyesi, TOS and OSI değerlerinin arttığı belirlendi. İlaveten İ/R grubunda TAC değeri ve SOD aktivitesi azaldı. Ayrıca, İ/R + p-kumarik asit (50 ve 100 mg/kg) gruplarında MPO aktivitesi, MDA seviyesi, TOS and OSI değerleri azalırken TAC değeri ve SOD aktivitesi arttı. Dahası, p-kumarik asit 50 mg/kg grubu ile karşılaştırıldığı zaman p-kumarik asit 100 mg/kg grubunda TAC değeri ve SOD aktivitesi daha fazla artarken OSI ve TOS değerleri daha fazla azaldı.*

TARTIŞMA ve SONUÇ: *p-Kumaraik asit' in farklı dozları deney hayvanlarında intestinal İ/R (1saat: 2saat) hasara karşı koruyucu etki gösterdiği söylenilebilir.*

Anahtar Kelimeler: *İntestinal iskemi/reperfüzyon, oksidatif stress, p-kumarik asit, sıçan.*

ABSTRACT

INTRODUCTION: *This study was planned to investigate the protective role of p-coumaric acid against intestinal ischemia/reperfusion (I/R) injury.*

METHODS: *For this purpose, an experimental intestinal I/R model was established in our study. In the p-coumaric acid and I/R groups, superior mesenteric artery was clamped for 1 h. Then, the clamp was removed and reperfusion was allowed for 2 h. At the end of 2h, rats were sacrificed and intestinal tissue samples were collected rapidly.*

RESULTS: *It was determined that MPO activity, MDA levels, TOS and OSI values increased due to severe oxidative damage depending on I/R. In addition, TAC value and SOD activity decreased in the I/R group. Also, TAC value and SOD activity increased while TOS, OSI values, MPO activity and MDA level were reducing in the I/R + p-coumaric acid (50 and 100 mg/kg bw.) groups. Moreover, in the p-coumaric acid 100 mg/kg group, TAC value and SOD activity more increased and OSI, TOS values more decreased compared with p-coumaric acid 50 mg/kg group.*

DISCUSSION AND CONCLUSION: *It can say that the different doses of the p-coumaric acid demonstrated protective effects against intestinal I/R (1hour: 2hour) injury in experimental animals.*

Keywords: *Intestinal ischemia/reperfusion, oxidative stress, p-coumaric acid, rat*

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INTRODUCTION

Intestinal Ischemia/Reperfusion (I/R) is a life-threatening, acute pathology that occurs during various clinical conditions, such as cardiovascular procedures, major trauma, intestinal transplantation operations, abdominal aortic surgery, sepsis and severe shock (1-3). It has a high mortality and morbidity rate due to difficulties in diagnosis and the clinical case (4). Ischemia leads to increased capillary permeability and necrosis as well as the mucosal barrier destruction. In fact, the main causes of intestinal I/R injury are mesenteric artery embolism, thrombus formation in the mesenteric venules, and hypoperfusion of the supporting vessels (3, 5, 6). Among the abdominal organs, intestine is the most sensitive one in I/R injury. Intestinal ischemia-reperfusion causes not only intestinal injury but also disturbance of the vital organs such as mainly lung and liver, less heart, brain and kidneys, due to the toxic products originating from interdependent mechanisms. Moreover, it may cause multiple organ failure (7). Re-establishment of blood flow to the tissue after ischemia causes molecular oxygen entering the tissue. However, rapid production of reactive oxygen species in tissue leads to severe cellular damage. These damages often can be irreversible (8).

p-Coumaric acid, a phenolic acid derivative, is a compound which exists in free or bound form in various mushrooms, fruits and vegetables such as apples, pears, grapes, oranges, tomatoes, and beans (9, 10). Also, it is known that it exhibits many different biological properties. For example, it has anti-oxidant, anti-inflammatory, anti-ulcer, antiplatelet, anti-cancer and anti-mutagenic effects (11, 12). It is reported by various researches that p-coumaric acid has protective effects against 1,2-dimethyldrazine-induced colonic preneoplastic lesions (13), cisplatin-induced neurotoxicity (14), cisplatin-mediated acute liver and renal toxicity (15) (and also it attenuates apoptosis in myocardial infarcted rats (16) due to its different biological activities).

As a result of our literature review, it has been concluded that there is no scientific report on the protective effects of p-coumaric acid against intestinal I/R injury. Therefore, the aim of this article is to exhibit the protective effects of p-coumaric acid against intestinal I/R induced oxidative damage in rats.

MATERIAL AND METHODS

Ethical approval and Animals

This experimental study was approved by Atatürk University Experimental Animal Ethics Committee before the experiment (2018-85). Our experimental study was carried out at Atatürk University Experimental Animals Research and Application Center (ATADEM) by using healthy Wistar-albino rats weighing 250-280 g, obtained from Atatürk University Experimental Animal Research and Application Center. Rats were housed in polypropylene cages in laboratory conditions such as 12-h light/dark cycle, humidity of 55 % and a mean temperature of 25 °C. Rats had access to food and water ad libitum. Animals were food deprived for 12 hours before the experiment but were allowed to drink water. p-Coumaric acid was purchased from Sigma Chemical Co., St. Louis, MO, USA.

Experimental design and groups

In our study, 32 rats were used. They were weighed and divided into 4 groups, including 8 rats in each group;

1.Sham Group; in this group, each rat was placed in a supine position and fixed on the operating board. The abdominal field was shaved and washed via 10 % povidone-iodine, and a 2-cm midline abdominal incision was performed with sterile techniques then the incision area was closed with silk suture without performing intestinal I/R model.

2. I/R (Ischemia/Reperfusion) Group; in this group, each rat was fixed on the operating board in a supine position. The abdominal field was shaved and washed via 10 % povidone-iodine, and a 2-cm midline abdominal incision was performed with sterile techniques. It was performed laparotomy under anaesthesia. The superior mesenteric artery

was found and occluded with an atraumatic clamp to create ischemia for 1 h. The clamp was removed and intestinal reperfusion allowed for 2 h. At the end of the reperfusion period, intestinal tissue samples were collected rapidly.

3.I/R + p-coumaric acid 50 mg/kg; as defined in the I/R group, ischemia model was applied by clamping for 1 hour. 50 mg/kg of p-coumaric acid was administered intraperitoneally before the reperfusion immediately. Then the clamp was removed and the reperfusion period started. At the end of the experiment, rats were sacrificed by high-dose anaesthesia and intestinal tissue samples were collected.

4.I/R + p-coumaric acid 100 mg/kg; as a defined in the I/R group, ischemia model was applied by clamping for 1 hour. 50 mg/kg of p-coumaric acid was administered intraperitoneally before the reperfusion immediately. Then the clamp was removed and the reperfusion period started. At the end of the experiment, rats were sacrificed by high-dose anaesthesia and intestinal tissue samples were collected.

All the experimental steps were completed under controlled and continuous general anaesthesia (ketamine/xylazine 60/10 mg/kg bw, intraperitoneally). At the end of the reperfusion, tissue samples were collected from the I/R (2-3 cm) induced intestinal tissue section and purified by washing with normal cold saline.

Biochemical Analysis

Tissue samples were weighed for 100 mg and homogenized with 2 mL of phosphate buffer. Homogenized tissues were centrifuged at 5000 rpm for 20 minutes at +4 °C and the supernatant was carefully transferred to tubes and maintained at -80 °C. The principle of measurement of MDA, as a result of lipid peroxidation, is based on measuring the absorbance at 532 nm of the pink colour compound formed as a result of the reaction of MDA and thiobarbituric acid (TBA) (17). Total antioxidant status (TAC) value was determined with the commercially available kit (Rel Assay Diagnostics, Product Code: RL0017) Kit. Total oxidant status (TOS) measurement was performed with commercially available kit (Rel Assay Diagnostics, Product Code: RL024). The ratio of TOS to TAC was accepted as the oxidative stress index OSI. OSI value was calculated as follows: OSI = [(TOS, μmol H_2O_2 equivalent L)/(TAC, mmol Trolox equivalent/L) × 10] (18). We used OSI as another indicator of oxidative stress. It has been suggested that OSI may reflect the state of oxidative status more accurately than TOS (19). The measurement of MPO activity is based on the kinetic measurement of the absorbance at 460 nm wavelength of the yellowish-orange coloured complex as a result of the oxidation of o-dianisidine with MPO in the presence of hydrogen peroxide (20). The xanthine oxidase enzyme catalyzes the uric acid from xanthine. The resulting superoxide radical forms the molecular oxygen and hydrogen peroxide with the superoxide dismutase enzyme. The resulting superoxide reacts with the tetrazolium salt to form a formazan dye in situations where the effect of the SOD enzyme is insufficient, and the SOD activity is measured with the inhibition degree of this reaction (21).

Statistical Analysis

TAC, TOS, OSI, MPO, SOD and MDA results obtained from our study were analyzed using a statistical analysis program. One-way ANOVA test was used for this purpose. Then, Tukey HSD test was performed for group comparisons. The results were presented as Mean±Standard error mean. P values < 0.05 were considered significant.

RESULTS

The tissue TAC values of all groups are shown in Figure 1a. We aimed to determine whether there was a difference in tissue TAC values among the groups receiving p-coumaric acid at different doses and the I/R group with intestinal damage. As a result, tissue TAC values were significantly increased in the treatment groups 50 and 100 mg/kg bw., compared with the I/R group ($p< 0.05$). There was an increase in MDA levels, TOS, OSI (values) and MPO activity in the I/R group intestinal tissue compared with the sham group. When the treatment groups and the I/R group are compared, MDA, TOS, OSI and MPO levels decreased in the treatment groups. When the treatment groups are

compared between each other; in the 100 mg/kg group MDA, MPO, TOS, OSI levels decreased more than the 50 mg/kg group. **(See Figures 1a-c, Figures 2a-c).** SOD activity of the groups is presented in Figure 2a. SOD activity was lower in the I/R group compared with the sham group p. In the treatment groups, there was a numerical increase in the SOD enzyme activity compared with the I/R group, but this increase was not statistically significant (p> 0.05).

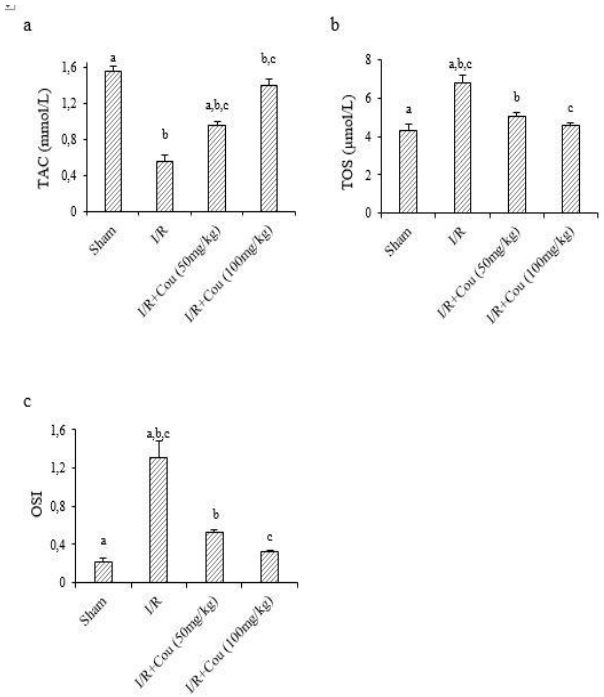

Figure 1.a. The values of TAC (Total Antioxidant Capacity) in all groups, b. The values of TOS (Total Oxidant Status) in all groups, c. The values of OSI (Oxidative Stress Index) in all groups. It represents statistically significant relationships between the groups in the same columns where the same letters appear (p<0.05). I/R: ischemia/reperfusion; I/R+ Cou (50 mg): ischemia/reperfusion + p-coumaric acid 50 mg/kg; I/R+ Cou (100 mg): ischemia/reperfusion + p-coumaric acid 100 mg/kg; I/R + p-coumaric acid 50 mg/kg; TAC: Total Antioxidant Capacity; TOS: Total Oxidant Status; OSI: Oxidative Stress Index; SOD Superoxide dismutase; MPO: (Myeloperoxidase; MDA: Malondialdehyde.

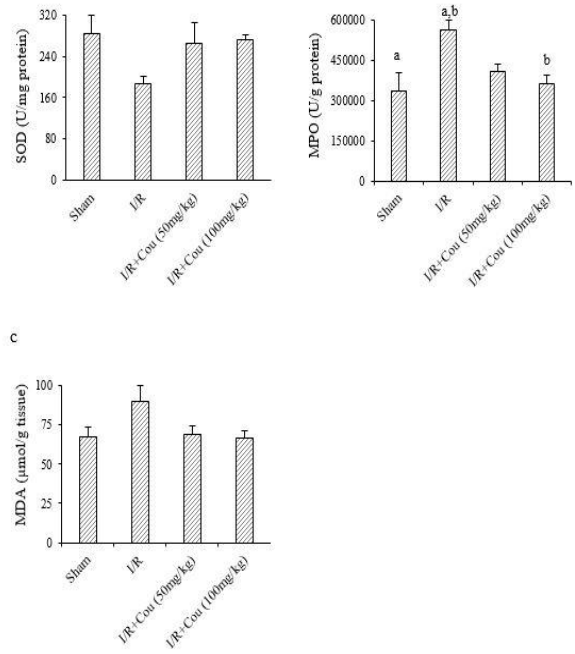

Figure 2. a. The values of SOD (Superoxide dismutase) in all groups, b. The values of MPO (Myeloperoxidase) in all groups, c. The values of MDA (Malondialdehyde) in all groups. It represents statistically significant relationships between the groups in the same columns where the same letters appear (p<0.05). I/R:ischemia/reperfusion; I/R+ Cou (50 mg): ischemia/reperfusion + p-coumaric acid 50 mg/kg; I/R+ Cou (100 mg): ischemia/reperfusion + p-coumaric acid 100 mg/kg; I/R + p-coumaric acid 50 mg/kg; TAC: Total Antioxidant Capacity; TOS: Total Oxidant Status; OSI: Oxidative Stress Index; SOD Superoxide dismutase; MPO: (Myeloperoxidase; MDA: Malondialdehyde.

DISCUSSION

During I/R injuries, numerous pathophysiological mechanisms containing a decreased oxygen and adenosine-triphosphate (ATP) amount, energy production via an anaerobic metabolism, accumulation of lactic acid, lowering intracellular pH, and generation of reactive oxygen species may actualize (22, 23). Metabolic product accumulation, as a result of I/R phase, causes functional disorders in cells. Oxidant-antioxidant balance is disrupted by common inflammatory processes and free radicals. The oxidative stress is a result of disruption in this balance. It can induce dysfunction of organs (8, 24). Free oxygen radicals and hypoxia are responsible for the pathogenesis of I/R. Inadequate blood supply to the tissue during ischemia leads the migration of neutrophils towards the extracellular space.

The myeloperoxidase (MPO) enzyme, released from neutrophils, leads to the capillary pore space expansion. In addition, as a result of hypoxia, xanthine dehydrogenase transforms into xanthine oxidase, which is involved in the production of free oxygen radicals during reperfusion. Intestinal tissue is one of the most abundant xanthine oxidase inclusive tissues which is also the major source of free oxygen radicals as I/R damage initiator (25, 26). Free oxygen radicals initiate lipid peroxidation, which in turn disrupts the lipid structure of the cell membrane and causes tissue damage (27, 28). Lipid peroxidation is a chemical action triggered by free radicals, which results in the oxidation of polyunsaturated fatty acids in membrane phospholipids, thereby altering membrane lipid structure and disrupting cell structure and function (29-32). MDA, the end product of lipid peroxidation, reflects the status for the level of reactive oxygen species. In the process of I/R injury, the activated neutrophils migrate towards the inflammation site, increase the severity of tissue damage by the formation of reactive oxygen species and the release of some toxic enzymes such as MPO (22). SOD is an enzyme with metalloproteins structure and effective in dismutation reaction, which converts the superoxide radical to hydrogen peroxide (30). The determination of TOS value provides a precision index of lipid peroxidation and oxidative stress. TAC, as an antioxidant, can preserve the tissue against the IR-induced oxidative damage through scavenging free radical species. OSI is a parameter that indicates whether the oxidant and antioxidant balance is increased on the oxidant or the antioxidant side. It is determined by proportioning total oxidants into total antioxidants. The use of OSI is more valuable than the use of oxidants and/or antioxidants alone. Increased OSI value due to increased oxidants or reduced antioxidants, triggers uncompensated free radicals production which leads to the peroxidation of lipids, oxidation of proteins and DNA damage.

There is an endogenous antioxidant defence system in the body that protects the tissues against damage caused by free oxygen radicals (30, 33, 34). The most important components of this system are SOD, glutathione peroxidase, catalase enzymes, and A, C and E vitamins. However, this system is unable to eliminate the high amount of free oxygen radicals occurred during the reperfusion phase. Therefore, various antioxidants have been tested in the treatment of I/R injury. A large number of agents have been used to alleviate intestinal I/R injury (35, 36). Terzi et al. investigated the protective effect of Nigella sativa on intestinal I/R and obtained decrease in TAC value, increase in TOS and OSI values in intestinal I/R group, but they reported that these values have changed positively depending on the treatment of Nigella sativa (37). It was determined that the TAC, TOS, and OSI measurements do not only show the oxidative and/or antioxidative conditions during the diagnosis but they also play a role in the monitoring of the treatment (38). Another study reported that in intestinal I/R group, MPO activity and Thiobarbituric Acid Reactive Substances levels were significantly elevated and SOD activity decreased. But MPO activity and TBARS level were reduced and the antioxidant enzyme activity increased depending on the antioxidant treatment (39). Zhang et al. have attested that oxidative stress occurs on intestinal IR injury in mice, declared by a significant increase in serum MDA level and a decrease in serum (SOD level (40). In addition, in another mesenteric ischemia-reperfusion study was raported that MDA, TOS and OSI levels increased and TAC value decreased in the ischemia-reperfusion group but MDA, TOS and OSI levels decreased and TAC value increased due to the antioxidant treatment (41) In a study investigating the effects of leflunomide on intestinal I/R injury, it was shown that MDA level and MPO activity significantly increased in intestinal I/R group, contrary to, leflunomide which is an antioxidant agent, significantly reversed these findings (36). Augustin et al. showed that vitamin E prevents free radical formation caused by neutrophil accumulation after intestinal I/R and reduces lipid peroxidation. This study also revealed that MPO activity, which increased about 15 times after intestinal I/R, approximates the normal level via vitamin E (42). In a different study which investigated the effects of lutein on small intestinal I/R injury in rats, it was found that the increase in lipid peroxidation after I/R was significantly reduced with lutein treatment (43). In our study, we

measured MPO activity as a marker of polymorphonuclear leukocyte accumulation and MDA levels as a marker of lipid peroxidation, SOD activity as one of the antioxidant primary enzymes and TAC, TOS and OSI levels which indicate the oxidant and antioxidant balance values in the intestinal tissue.

CONCLUSION

As a conclusion, MDA levels were numerically higher in the I/R group than the sham group but there was no statistically significant difference. It was determined as consistent with the findings of many studies in the literature that the elevation of SOD activity, the reduction of lipid peroxidation and MPO activity, the increase of TAC value and decrease of TOS and OSI values by administrations of p-coumaric acid at doses of 50 and 100 mg/kg before intestinal reperfusion. Our results also indicated that the p-coumaric acid, as associated with its anti-inflammatory and anti-oxidative activities, demonstrated protective effects on alleviating I/R injury by reducing the neutrophil infiltration and the free radical formation.

Conflict of interest

There is no conflict of interest.

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