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ORIGINAL RESEARCH

The effect of quercetin on cerulein-induced acute pancreatitis

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OBJECTIVE: The aim of this study was to evaluate the protective and therapeutic effects of quercetin on pancreatic injury in cerulein-induced acute pancreatitis.
METHOD: Thirty-two rats were randomly divided into four groups, eight per group: (CT): untreated controls, (CER) treated with cerulein, 50 µg/kg body weight; (Q+CER) pre-treatment with quercetin, 100 mg/kg body weight, followed by cerulein, 50 µg/kg; (CER+Q) post-treatment, cerulein followed by quercetin, same doses. Cerulein was divided into four doses, given at 1-hour intervals by intraperitoneal injection. Quercetin was given either 1-hour before (in pre-treatment group) or 1-hour after (in post-treatment group) cerulein. Pancreatic malondialdehyde (MDA), carbonyl, myeloperoxidase (MPO), tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), reduced and oxidized glutathione (GSH and GSSG, respectively) were measured. Histology of the pancreas was studied.
RESULTS: (1) MDA, carbonyl, MPO, TNF-a and IL-6 levels were significantly higher in CER vs CT rats. (2) MDA, carbonyl, MPO and TNF-α decreased significantly in pre-treated rats vs. CER. (3) MDA, MPO, TNF-α, IL-6 were significantly lower in post-treated rats vs. CER. (4) The reduced vs. oxidized glutathione ratio (GSH/GSSG) of was significantly lower CER vs. CT rats. (5) Pre- and post-treatment with quercetin significantly increased this ratio. (6) Pancreatic histology showed that quercetin had no significant effect on the histological image of the pancreas
CONCLUSION: These results suggest that quercetin can attenuate the severity of cerulein-induced acute pancreatitis by acting as an antioxidant and anti-inflammatory agent and combating oxidative stress. Further studies are needed to clearly explain its utility on acute pancreatitis.

KEYWORDS: Acute pancreatitis, cerulein, quercetin, oxidative stress.

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INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease which is characterized by activation of leukocytes, macrophages and digestive proteases, inflammatory cell infiltration, the release of various inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6).[1-4] The digestive enzymes of pancreas lead to auto-digestion of the gland. The auto-digestion is a key event in the pathogenesis of AP. After auto-digestion, a massive infiltration of neutrophils and macrophages lead to a local and systemic inflammatory response.[3,5] This is partially caused by the release of cytokines from acinar cells. Reactive oxygen substances (ROS) may also contribute to the damage of pancreatic acinar cells.[4,6-10] Previous studies have confirmed the participation of ROS at early stages of AP, regardless of the underlying cause.[11-13] The characteristics of the pancreatitis induced by cerulein (a decapeptide and cholecystokinin analogue) resemble the early phase of AP in humans.[14]

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There are still no therapies for acute pancreatitis. Medical treatment remains largely supportive such as the control of symptoms, and prevention of severe complications. Therefore, prevention of oxidative stress and acinar cell injury during the early phase of acute pancreatitis may stop the pathologic progression to severe pancreatitis.[1,2,4,8,15] The role of oxidative stress in the pathogenesis of AP and the benefits of antioxidants have been the subject of numerous studies.[14,16-19] Recent studies have focused on antioxidant and anti-inflammatory properties of phenolic compounds.[2,4,6,20] Quercetin (3,5,7,3',4' pentahydroxyflavone) is a plant-derived phenolic compound belonging to a class of substances known as flavonoids. Flavonoids are widely found in vegetables, such as black and green tea, red wine, apple, onion, bean etc. Biological effects of quercetin have been reported as follows: antioxidant, anti-inflammatory, antiviral, anti-ischemic, anticancer, antithrombotic, and antihistaminic etc.[2,21,22] Moreover, quercetin has been shown to inhibit amylase release induced by agonists such as cholecystokinin, carbachol, phorbol ester tetra decanoylphorbol-13--acetate.[23-25] A recent study has shown that one hour after the last dose of cerulein administration, quercetin treatment attenuates the development of AP in mice.[2]

The aim of the present study was to evaluate the protective and therapeutic effects of quercetin on pancreatic injury in cerulein-induced acute pancreatitis in rats.

MATERIALS AND METHODS

Chemicals and Drugs

Cerulein, quercetin, 3,3',5,5'- Tetra Methyl Benzydine (TMP), dimethyl sulfoxide (DMSO), formaldehyde, eosin and hematoxylin were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Malondialdehyde (MDA) and glutathione kits were purchased from Chromosystems Instruments & Chemicals (GmbH, Munich, Germany). ELISA kits including Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α) and ketamine were purchased from eBioscience (USA), Invitrogen Co. (Camarrillo, CA, USA), Alfason Int. B.V. (Voerden, Holland), respectively.

Animals

Animal procedures were performed according to the "Guide for the Care and Use of the Laboratory Animals" set by the Ethics Committee of Afyon Kocatepe University. Thirty-two female Sprague-Dawley rats (250-300 g) were housed in four cages at a temperature of 23±2°C with 12 h of light-dark cycle. Animals were fed with a standard rat chow (Aytekinler feed Industry, Konya, Turkey) and allowed to drink water ad libitum, but were deprived of food for 12 h before the experiments. All procedures were performed in sterilized conditions.

Experimental Procedures

Acute Pancreatitis (AP) was induced by intraperitoneal injection of cerulein, diluted in physiological saline (50 µg/kg body weight), four times at one hour intervals.[26] Quercetin was dissolved in DMSO (1%) and given intraperitoneally (100 mg/kg body weight).[22] Figure 1 illustrates the timeline of the procedures.

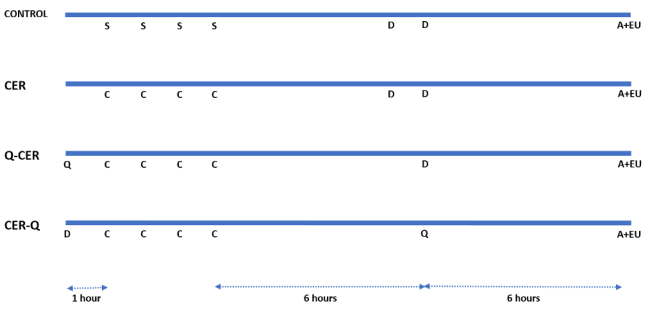

Figure 1. Timeline of the experimental procedure. Time markers shown for 1 and 6 hours. All injections given intraperitoneally. S: isotonic saline D: dimethyl sulfoxide (DMSO); C: Cerulein; Q: quercetin. A+EU: rats anesthetized and euthanized.

The thirty-two rats were randomly divided into four groups (eight in each group): rats in the CT group received intraperitoneally (i.p.) physiological saline four times and DMSO twice at 1-h intervals. Rats in the cerulein group (CER) received i.p. cerulein (50 µg/kg body weight in physiological saline), divided into four hourly doses and DMSO twice at 1-h intervals. Quercetin pre-treatment group (Q+CER) received i.p. quercetin as a single dose one hour before cerulein treatment applied as described and DMSO once, 6-h after cerulein treatment. Quercetin post--treatment group (CER+Q) received i.p. DMSO, once, one hour before cerulein treatment and quercetin, as a single dose, six hours after cerulein treatment.

The rats were anesthetized by an intramuscular injection of ketamine (50 mg/kg body wt.) 6-h after the last administration of DMSO or quercetin. Blood samples were drawn with a heparinized syringe by cardiac puncture and collected in heparinized tubes. Rats were euthanized by exsanguination with blood retained for serum harvest. Their pancreas tissues were taken for biochemical and histological analysis and rinsed with ice-cold saline and frozen at -20 °C until assay. A portion of pancreatic tissue from each rat was reserved for histological analysis. Plasma was obtained by centrifugation at 3000 rpm for 10 minutes at 4°C and stored at -20 °C until the analyses were performed. The pancreas tissues were homogenized in 0.1 M phosphate buffer (pH 7.4) with an Ultra Turrax homogenizer (T25, Janke and Kunkel). Homogenates were centrifuged at 5000 rpm, 4 ^{0}C for 10 minutes. Supernatants were removed and used for further analysis.

Plasma amylase and lipase activities were determined by an automated Cobas C-501 analyzer using Roche

Diagnostic kits (GmbH, Mannheim, Germany). Results are expressed as U/L.

Tissue malondialdehyde (MDA), reduced glutathione (GSH) and oxide glutathione (GSSG) concentrations were determined by high-pressure liquid chromatography (HPLC) in the isocratic phase in the Agilent 1100 series instrument with fluorescent detection (Ex:515, Em: 553 nm for MDA; Ex: 385, Em: 515 for GSH and GSSG) using a kit from Chromsystems Instruments & Chemicals GmbH (Munich, Germany). The results were evaluated as nmol/g protein for MDA and µmol/g protein for GSH and GSSG. Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6) levels as inflammatory cytokines were measured using commercial colorimetric kits. TNF-α and IL-6 levels were expressed as ng/g protein. Myeloperoxidase (MPO) activities as an indicator of polymorphonuclear leukocytes[27] and Carbonyl content as an indicator of protein oxidation[8] in pancreas tissue were measured according to previously described methods.

Histopathological examination

Pancreas tissue samples were fixed in 10% formaldehyde solution and embedded in paraffin using standard methods. Tissues were sectioned at 3-µm and stained with hematoxylin-eosin (H&E). Then, the stained sections were assessed under light microscopy and examined by a pathologist blinded to group division for grading of the histopathological alterations. Edema and neutrophil infiltration in pancreatic tissue were assessed using a scoring system from 0 to 3 as described by Schoenberg et al[29] and shown in Table 1.

Statistical Analysis

The data were analyzed using the SPSS Statistical Package (Version 20.0, Chicago, USA for Windows). The differences between groups were determined by the Kruskal-Wallis test. The Conover-Iman test was used to perform multiple comparisons between different treatment groups. The results are expressed as the Mean±SEM. The $p<0.05$ value was accepted as statistically significant.

Table 1. Histopathological grading system in experimental acute pancreatitis

Effect	Score	Edema/infiltration grade
Edema	0	No edema
	1	İnterlobular edema
	2	Moderate interlobular edema+intraacinar edema
	3	Maximum interlobular + intra-acinar edema
Neutrophil infiltration	0	No infiltration
	1	Intravascular margination of granulocytes
	2	Granulocytes present in the perivascular tissue
	3	Diffuse infiltration of entire pancreatic gland

RESULTS

Plasma amylase and lipase activities are shown in Table 2. Plasma amylase and lipase activities significantly increased in the cerulein-induced AP compared to the control group ($p<0.001$). Quercetin treatment (pre- and post-) significantly decreased amylase and lipase activities compared to the CER group ($p<0.001$) but the enzyme activities were higher than those of the controls.

The pancreatic levels of MDA, Carbonyl, MPO, TNF-α, and IL-6 levels in CER group increased significantly compared to the control group ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.01$, and $p<0.05$; respectively). Quercetin treatment before cerulein administration (Q+CER) decreased significantly MDA, Carbonyl, MPO, and TNF-α levels compared to the CER group ($p<0.05$, $p<0.05$, $p<0.001$, and $p<0.05$, respectively). As also shown in Table 2, Quercetin treatment after cerulein administration (CER+Q) also significantly decreased MDA, MPO, TNF-α, and IL-6 levels compared to the CER group ($p<0.001$, $p<0.001$, $p<0.05$, and $p<0.05$, respectively).

The pancreatic levels of reduced and oxidized gluthatione (GSH and GSSG) are shown in Figure 2. Reduced glutathione levels decreased significantly in the CER group compared to the control group ($p<0.01$); in contrast, oxidized gluthatione in the CER group increased significantly compared to the control group ($p<0.01$). In sharp contrast, pre- or post-quercetin treatment prevented the cerulein induced decrease of GSH and the increase of GSSG, both of which were not significantly different from their respective control levels. The GSH/GSSG ratio after cerulein induced pancreatitis decreased very sharply vs. controls ($p<0.001$); quercetin pre-treatment partially impeded the fall in of the GSH/GSSG ratio, whereas post-treatment impeded the fall of the GSH/GSSG ratio, which was significantly higher than that in the CER group and not significantly different from the controls ($p<0.05$ and $p<0.01$, respectively).

Table 3 shows that Cerulein induced intense pancreatic edema and inflammation, neither of which was countered by pre- or post-treatment with quercetin.

Figure 3 illustrates these findings. Panel A, collected from a control rat shows a typically normal pancreatic structure; in contrast, panels B and C, collected from cerulein administered rats revealed extensive tissue damage characterized by significant interlobular edema and neutrophil infiltration, respectively.

DISCUSSION

The present study showed that quercetin attenuated the severity of cerulein-induced acute pancreatitis

Table 2. Amylase, Lipase, MDA, Carbonyl, MPO, TNF-α and IL-6 levels in pancreatic tissue (Mean±SEM)

Parameters	Control	CER	Q+CER	CER+Q
Amylase (U/L)	848±34	3956±245[a]	2383±287[a,b]	1920±176[a,b]
Lipase (U/L)	8.51±0.17	136.40±15.59[a]	33.48±7.05[a,b]	23,37±12.01[a,c]
MDA (nmol/g protein)	58.91±9.27	195.33±27.24[a]	115.62±15.43[c]	94.34±13.16[b]
Carbonyl (µmol/g protein)	2.82±0.37	6.83±0.63[a]	4.08±0.66[c]	5.05±0.82
MPO (U/g protein)	0.38±0.07	1.15±0.12[a]	0.47±0.07[b]	0.59±0.13[b]
TNF-α (ng/g protein)	2.24±0.31	3.49±0.63[d]	2.03±0.40[c]	1.88±0.32[c]
IL-6 (ng/g protein)	62.94±1.86	84.10±5.31[e]	68.57±9.47	61.11±4.47[c]

[a] p < 0.001 vs. Control group; [b] p <0.05 vs. CER group; [c] p < 0.001 vs. CER group; [d] p < 0.01 vs. Control group; [e] p < 0.05 vs. Control group.

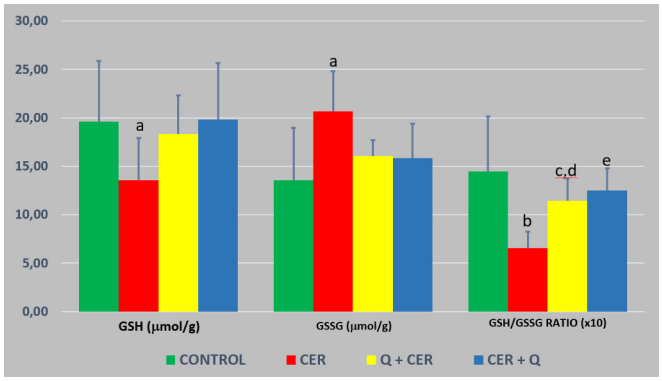

Figure 2. Pancreatic GSSG, GSH levels and GSH/GSSG ratios in control rats and rats with cerulein induced pancreatitis, untreated or treated with quercetin. [a] $p < 0.01$ *vs.* Control; [b] $p < 0.001$ *vs.* Control; [c] $p < 0.05$ vs group; [d] $p < 0.05$ *vs.* CER; [e] $p < 0.01$ *vs.* CER.

Table 3. Pancreas tissue edema and inflammation scores (Mean ± SEM)

Groups	Edema	Inflammation
Control group	0.12±0.12	0.12±0.12
CER group	1.00±0.00[a]	1.77±0.22[a]
Q+CER group	0.87±0.12[a]	1.75±0.25[a]
CER+Q group	0.87±0.12[a]	1.50±0.32[a]

[a] p < 0.001 vs Control group

(AP) in rats through anti-inflammatory and antioxidant mechanisms by reducing the inflammatory cytokines, lipid peroxidation and protein oxidation.

Pathophysiology of acute pancreatitis is a multifactorial process which involved the complex interaction of pro-inflammatory and anti-inflammatory pathways. Oxidative stress and cytokines have an important role in the formation of the pathways.[2] Cerulein-induced AP is one of the best–characterized rat models of experimental pancreatitis. There is much similarity between experimental and human pancreatitis with regard to morphological, biochemical and pathophysiological features.[2,30]

Cerulein, an analogue of cholecystokinin (CCK), overstimulates the acinar cells of pancreas by leading to pre-maturation to trypsin of trypsinogen; this leads to lysosomal degradation of intracellular organelles within autophagic vacuoles in acinar cells; this followed by interstitial edema and inflammation in the acinar cells. Inflammatory cells generate reactive oxygen species (ROS) which disrupt membranes via lipid peroxidation, protein oxidation, and trigger the inflammatory processes.[4,21] Pro-inflammatory cytokines such as TNF-α and IL-6 released by damaged pancreas cells play an important role in the pathogenesis of AP.[3,31]

There are still no specific therapies for AP. Treatment remains substantially supportive for symptoms. At present, all attention is focused on antioxidant and anti-inflammatory therapies.[2,3,4,6,18,20] Quercetin has been reported to exert multiple biological effects such as antioxidant, anti-inflammatory, and antihistaminic effects etc.[2,21,22]

The increased serum amylase activity which is at least three times higher than the upper limit of normal and lipase activity which remains high for up to 8 and 14 days; this fact allows its comparison to normal serum amylase activity and supports the diagnosis of acute pancreatitis;[32] however Bulut et al. report that this comparison does not always match the severity of AP.[33] In this study, plasma amylase (approximately fourfold above control) and lipase (approximately fifteen fold above control) activities in the CER group were significantly higher than the control group; quercetin pre- and post-treatment significantly decreased amylase and lipase activities compared to the CER group.

In the present study, the pancreas tissue MDA, Carbonyl, MPO, TNF-α and IL-6 levels in the CER group significantly increased compared to the control group. Quercetin pre-treatment significantly prevented increases of MDA, Carbonyl, MPO and TNF-α, but not of IL-6. Quercetin post-treatment significantly prevented increases of MDA, MPO, TNF-α and IL-6, not of carbonyl. Our previous studies[21,22] showed that quercetin was a more effective antioxidant and anti-inflammatory molecule and that the (3,5,7,4') positions of hydroxyl groups were associated with ROS inhibition. Therefore, the protective and therapeutic effect of quercetin could be attributed to its antioxidant and anti-inflammatory properties by various mechanisms.

It has been suggested that the mechanism of action of cerulein involves the production of large amounts of ROS

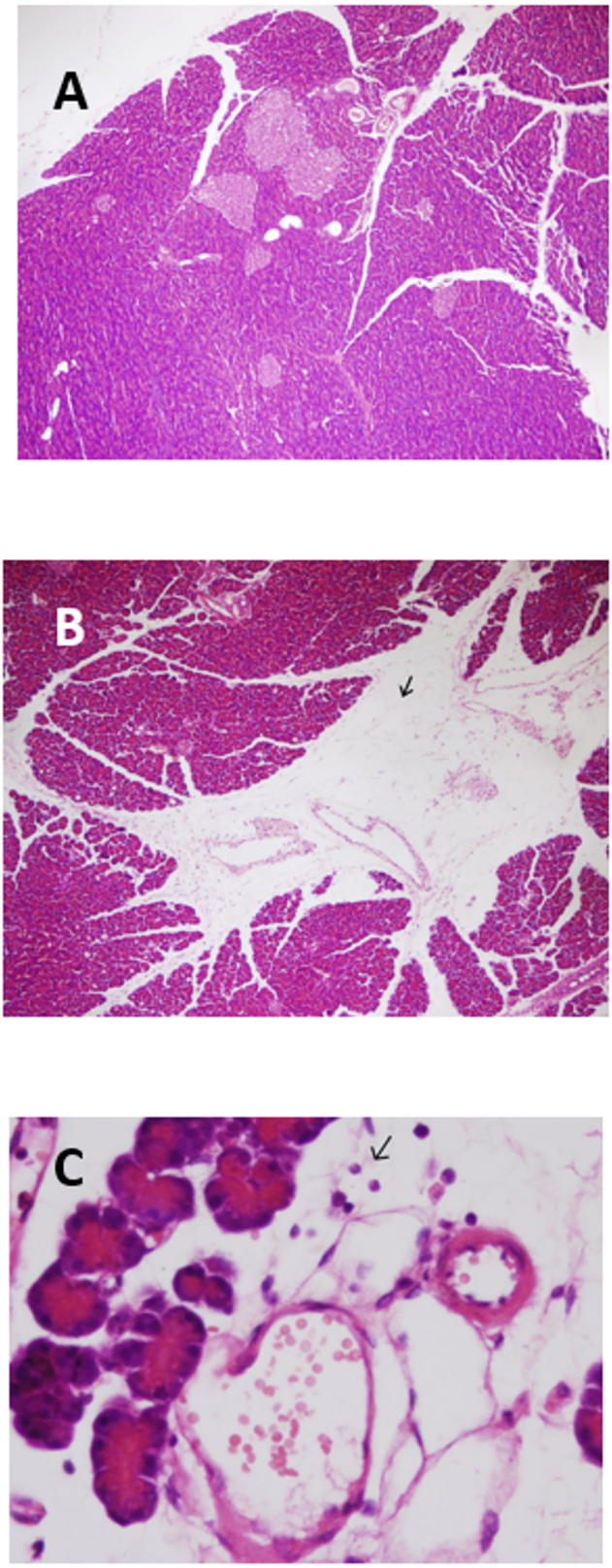

Figure 3. Histological features of pancreas tissue (HE x400): (A) normal architecture in a normal control rat; (B) interlobular edema (arrow) in a cerulein-treated rat; (C) perivascular neutrophil infiltration (arrow head), in a cerulein-treated rat.

and activation of the oxidant-sensitive transcription factor kB (NF-kB).[19] ROS can also activate the transcription of NF--kB.[19] NF-kB increases the transcription of inflammatory cytokines such as IL-6 and TNF-α which can initiate the pancreatic inflammatory process.[19,22] In the present study, quercetin potently suppressed neutrophil mediated MPO, TNF-α and IL-6, well established markers of inflammation, thereby inhibiting NF-kB activation.[2,34-36] Furthermore, it has been reported that quercetin decreased gene expression and production of the proinflammatory cytokines as TNF--alpha, interleukin (IL)-1β, IL-6, and IL-8 in mast cells.[22] Our results are compatible with such reports.[2,8,11]

Glutathione is the most important non-enzymatic antioxidant molecule in cells. It exists in a reduced (GSH) and in an oxidized form (GSSG): GSH is in equilibrium in GSSG, and the GSH/GSSG ratio is a measure of the redox--status of the cells: the ratio is a reliable indicator of oxidative stress and reflects the balance between antioxidant and oxidant status in cells.[10,14] However, GSH depletion and GSSG status in AP have not been well-established. Pancreatic GSH depletion has been shown in the initial phase of acute pancreatitis.[8,11,37,38] However, while some reports have shown increased pancreatic GSSG in AP,[13,14,37-39] others have found that pancreatic GSSG levels and the GSSG/GSH ratio remains essentially unchanged during the early course of AP.[10,12,14,39] Rau et al.[12] demonstrated a significant decrease of GSH levels parallel with an increased ratio of GSSG/Total glutathione. Gomez-Cambronero et al.[14] reported that the dose of cerulein affects GSSG levels and the ratio of GSH/GSSG in a dose dependent manner. The pancreatic ratio of GSH/GSSG did not change significantly in rats treated with low or moderate doses of cerulein (8-40 μg/kg), but it increased after a higher dose of cerulein (80 μg/kg). In this study, given alone, cerulein significantly decreased pancreatic GSH and increased GSSG, a sure sign of cellular oxidant stress. Quercetin treatment after and before cerulein partly reversed GSH decrease and GSSG increase: as an obvious consequence, the GSH/GSSG ratio significantly decreased after untreated pancreatitis induction, but this was effectively countered both by pre- and by post-quercetin treatment. ROS is the most probable inducer of this conversion of GSH to GSSG and we believe that quercetin reversed this process, mainly by scavenging ROS.

Our histopathological results showed that cerulein treatment caused edema and leukocyte infiltration of pancreatic acinar cells. Our previous study showed similar results.[9] Pre- and post- treatment of quercetin partly decreased edema and inflammation, but it did not prevent histologically detected pancreatic edema and inflammation induced by cerulein. However, cerulein-induced MPO activity as an indicator of leukocyte infiltration and the TNF-α and IL-6 levels as the indicators of inflammation significantly decreased by quercetin administration (Table 3). This confirmed the participation of ROS at early stage of acute

pancreatitis, independently of the underlying etiology. It is supposed that an imbalance between the production of free radicals and antioxidant systems of the organism would predispose to acute pancreatitis. Thereafter, premature activation of pancreatic enzymes, leukocyte infiltration, and cytokine production could aggravate local pancreatic injury and produce the spread of the inflammation to the rest of the organism.[11] For this reason, histological reflections of damage occur after biochemical changes and it also takes a certain period of time for the amelioration of the damage. The administration of quercetin at different points in time, to pre- and post-treatment groups can shed light on this issue.

CONCLUSION

Quercetin pre- and post-treatment attenuated the development of cerulein-induced AP and partly attenuated acute pancreatitis through antioxidant and anti-inflammatory mechanisms by minimizing inflammation, lipid peroxidation, and protein oxidation. In this regard, we believe that more studies are needed to exactly clarify the molecular mechanisms involved in this interaction, both in human and experimental models.

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CONFLICT OF INTEREST

Authors declare no conflict of interests regarding this study

AUTHOR PARTICIPATION

Kahraman A participated in the planning of the research, conduction of experiments, the acquisition of data, and the writing of the manuscript. Vurmaz A, Koca HB, and Çat K participated in the experimental procedure, and biochemical analysis. Tokyol Ç performed the histopathological examination. Polat C and Köken T participated in experimental procedure and conduction of biochemical analysis, respectively.

EFEITO DA QUERCETINA SOBRE A PANCREATITE INDUZIDA POR CERULEÍNA

OBJETIVO: O objetivo deste estudo foi avaliar os efeitos protetores e terapêuticos da quercetina na lesão pancreática da pancreatite aguda induzida por ceruleína.

MÉTODO: Trinta e dois ratos foram divididos aleatoriamente em quatro grupos, oito por grupo: (CT): controles não tratados (CER) tratados com ceruleína, 50 µg/kg de peso corporal; (Q+CER) pré-tratamento com quercetina, 100 mg / kg de peso corporal, seguido de ceruleína, 50 µg/kg; (CER+Q) pós-tratamento, ceruleína seguida de quercetina, mesmas doses. A ceruleína foi dividida em quatro doses, administradas a intervalos de 1 hora por injeção intraperitoneal. A quercetina foi administrada 1 hora antes (no grupo de pré-tratamento) ou 1 hora após (no pós-tratamento) a administração de ceruleína. Foram medidos o malondialdeído pancreático (MDA), carbonilo, mieloperoxidase (MPO), fator de necrose tumoral alfa (TNF-a), interleucina-6 (IL-6), glutationa reduzida e oxidada (GSH e GSSG, respetivamente). Foi estudada a histologia do pâncreas.

RESULTADOS: Os níveis de MDA, carbonila, MPO, TNF-a e IL-6 foram significativamente maiores nos ratos CER vs. CT. MDA, carbonila, MPO e TNF-α diminuíram significativamente em ratos pré-tratados versus CER. MDA, MPO, TNF-α, IL-6 também foram significativamente menores em ratos pós-tratados versus CER. A proporção reduzida de glutationa oxidada (GSH/GSSG) foi significativamente menor ratos CER vs. CT; pré e pós-tratamento com quercetina aumentaram significativamente esta proporção. A histologia pancreática mostrou que a quercetina não teve efeito morfológico significativo.

CONCLUSÃO: Estes resultados sugerem que a quercetina pode atenuar a gravidade da pancreatite aguda induzida por ceruleína, atuando como agente antioxidante e anti-inflamatório e combater o estresse oxidativo. Mais estudos são necessários para explicar claramente suas utilidades na pancreatite aguda.

PALAVRAS-CHAVE: pancreatite aguda, ceruleína, quercetina, estresse oxidativo.

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