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Original Article

Persimmon *(Diospyros Kaki L.)* Alleviates Ethanol-Induced Gastric Ulcer in Rats

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ABSTRACT

Objective: The worldwide incidence of a gastric ulcer is high, most often as a result of use of nonsteroidal anti-inflammatory drugs, excessive alcohol consumption, or *Helicobacter pylori* infection. An ethanol-based gastric ulcer model in rats was used to examine the effect of persimmon *(Diospyros kaki L.)* extract as a potential form of treatment.

Methods: Two dosages of persimmon extract were applied in a gastric ulcer model created with 5 mL/kg ethanol in Wistar albino rats. Histopathological and biochemical methods were used to assess any gastroprotective effects.

Results: Persimmon extract significantly decreased the level of the cytokines interleukin (IL)-10, IL-6, tumor necrosis factor alpha (TNF-α) and IL-1 beta. Caspase-3 and nuclear factor kappa B expression was also significantly reduced.

Conclusion: Persimmon fruit extract demonstrated a gastroprotective effect in an ethanol-based gastric ulcer model in rats.

INTRODUCTION

The etiology of a gastric ulcer can be complicated and the morbidity and mortality rate can be significant.[1] Although there have been many developments in gastric ulcer therapies, the prevalence worldwide continues to be substantial.[2] Exposure to stress, nonsteroidal anti-inflammatory drug use, the presence of *Helicobacter pylori (H. pylori)*, and excessive alcohol consumption may lead to the development of a gastric ulcer.[3,4] Ethanol damages the gastric mucosa through the vascular endothelia and increases the level of reactive oxygen radical species (ROS).[5]

Caspase 3 is a member of the cysteine protease family and plays a role in inflammation and apoptosis.[6,7] Nuclear factor-kappa B (NF-κB) regulates the expression of various genes related to inflammation.[8] Interleukin (IL)-1 beta (IL-1β) is a proinflammatory cytokine, and inflammation in-

duces IL-6 synthesis.[9,10] IL-10 has a role in suppressing the expression of proinflammatory cytokines.[11]

Ethanol consumption reduces the anti-inflammatory cytokine (IL-10) level and can lead to an overexpression of tumor necrosis factor alpha (TNF-α).[12] Antioxidant substances can provide a gastroprotective effect against ethanol-induced gastric ulcer.[13]

Persimmon *(Diospyros kaki L.)* has been shown to have various beneficial effects on human health.[14] Persimmon fruit has been reported to reduce ROS levels.[15] The chemical examination of persimmon fruit has revealed phenol compounds that act as antioxidants.[16,17]

In the current study, a gastric ulcer model was used to examine inflammatory parameters using persimmon fruit extract. Molecular and histopathological methods were also used to analyze apoptosis. These biochemical and histopathological parameters were studied to assess the potential protective effects of persimmon fruit extract on an ethanol-induced gastric ulcer.

MATERIALS AND METHODS

Preparation of persimmon fruit extract

The persimmon *(Diospyros kaki L.)* fruit used in the experiments was harvested from Mersin province in Turkey in the ninth month. The fruit was washed, cleaned, and cut into small pieces, and the seeds were removed. The fresh fruit was then homogenized as previously described to obtain the juice.[18] The pulpy juice (extract) was orally administered to the study groups at 4 mL/kg and 8 mL/kg doses (gavage) for 10 days in single doses.

Animals

The rats were acquired from the Atatürk University Experimental Animal Research Center. The subjects were housed in wire cages with appropriate laboratory conditions: 22±2°C temperature, 12-hour light/dark cycle, and 5±5% humidity. Standard rat feed (pellets) and tap water were available ad libitum.

Ethanol-induced gastric ulcer and treatment

A total of 32 Wistar Albino male rats weighing 250–300 g were used in the study. Four groups of 8 rats were randomly formed: Group 1 (control group): distilled water was administered by oral gavage for 10 days; Group 2 (ulcer): no treatment was performed until the ethanol administration phase; Group 3 (persimmon, 4 mL/kg); and Group 4 (persimmon, 8 mL/kg). Intragastric administration of the persimmon extract was performed for 10 days in both persimmon groups. All of the animals fasted for 1 day (24 hours) before the ethanol administration. In Groups 2, 3, and 4, 5 mL/kg absolute ethanol (99%) was administrated orally (gavage) on the 11th day. Euthanasia was performed 90 minutes after the ethanol application.

Ethical approval

The study design was approved by the Ataturk University Local Research Animal Ethics Committee on April 19, 2016 (no: 70).

Tissue collection

The gastric tissue was cut from the minor and major curvatures and washed with saline to remove the stomach contents. Images of the clean gastric tissue were recorded with a digital camera for macroscopic evaluation. The tissue was preserved with 10% formaldehyde at -80°C for histopathological and biochemical analyses.

Gastric tissue homogenization

Ice-cold saline was used to wash the tissue samples. Phosphate-buffered saline (PBS; 50 mM, pH 7.4) was used with an iced mammalian protease inhibitor cocktail as the tissue homogenate (10%). The homogenate preparation was centrifuged at 3000 x g for 15 minutes at 4°C. The supernatants were used to measure and analyze various biochemical markers.

High-performance liquid chromatography analysis

High-performance liquid chromatography (HPLC) paired with a photodiode array (HPLC-PDA) was used to generate mg/100 mL samples. Catechin, p-Coumaric acid, caffeic acid, syringic acid, gallic acid, 4-hydroxy benzoic acid, vanillic acid, chlorogenic acid, ferulic acid, delphinidin-3-glucosidase, and cyanidin-3-glucosidase were used to prepare standard calibration curves. An A 0.45-µm membrane filter was used and each filtered sample (1 mL) was placed in a vial and evaluated using HPLC (W600 system with 996 photodiode array detector; Waters Corp., Milford, MA, USA). A C18 column (Luna Omega; Phenomenex Inc., Torrance, CA, USA) was heated to 40°C.

The mobile phase was composed of solvent A (distilled water with 0.1% v/v trifluoroacetic acid [TFA]) and acetonitrile with 0.1% v/v TFA, and solvent B (acetonitrile with 0.1% v/v TFA). A linear gradient was used: at 0 minutes, 95% solvent A and 5% solvent B; at 45 minutes, 65% solvent A and 35% solvent B; at 47 minutes, 25% solvent A and 75% solvent B; and at 54 minutes a return to initial conditions. The rate of flow was 1 mL/minute. Chromatograms were recorded at 280, 312, 360, and 520 nm. Retention time determined the identification and quantification, using the standard ultraviolet spectra and external curves.[19]

Measurement of IL-10, TNF-α, IL-6, and IL-1β levels in gastric tissue

The IL-10, IL-1β, TNF-α, and IL-6 levels of the gastric tissue homogenates were gauged using rat immunoassay enzyme-linked immunosorbent assay kits (Elabscience, Wuhan, China).

Hematoxylin and eosin analyses

The gastric samples were preserved in 10% formaldehyde

for 48 hours. Next, they were dehydrated with alcohol and cleared with a xylene series. Following paraffin fixation, the samples were cut into 5-µm sections with a microtome (RM2235; Leica Microsystems, Wetzlar, Germany). Hematoxylin eosin staining was performed for histopathological examination using light microscopy.

Immunohistochemical analysis

Nuclear factor kappa B (NF-κB) (Abcam, Cambridge, UK) and caspase-3 (Novus Biologicals, Littleton, CO, USA) were used to evaluate the apoptotic and inflammatory properties immunohistopathologically. Following deparaffinization, the samples were rehydrated with water, ethanol, and phosphate-buffered saline (PBS). They were washed with distilled water and immersed in 3% hydrogen peroxide for 15 minutes. PBS and equilibration buffer were used for 20 minutes at room temperature. An anti-caspase-3 solution was used for the incubation of the sections at room temperature for 1 hour. The sections were incubated with PBS containing normal goat serum, without a primary antibody. Counterstaining with Mayer's hematoxylin was performed, and following that, the sections were examined under a light microscope (BH-40; Olympus Corp., Tokyo, Japan).

Table 1. Phenolic content of persimmon samples

Phenolic substances	Average (ppm)	SD
Gallic acid	57.62	8.85
Catechin	6.18	0.75
Procyanidin B1	2.39	0.60
Procyanidin B2	5.06	0.56
Epicatechin	1.61	0.24
P-Coumaric acid	0.18	0.03
Vanillic acid	0.71	0.02
Chlorogenic acid	0.23	0.06
Syringic acid	30.05	1.29
Cinnamic acid	5.61	0.16
Rutin	2.41	0.03
Cyanidin-3-glucosidase	3.70	3.01

High-performance liquid chromatography results; all experiments were conducted at least 3 times.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). All of the data were presented as mean±SD. The group differences were examined using one-way analysis of variance. P<0.05 was considered significant. All of the fruit extract experiments were performed at least 3 times.

RESULTS

The HPLC analysis of persimmon *(Diospyros kaki L.)* fruit extract

The phenolic compounds of the persimmon samples are shown in Table 1.

IL-10, IL-6, IL-1β, and TNF-α levels

It was determined that the proinflammatory and anti-inflammatory cytokine levels differed significantly between groups. The IL-1β, IL-10, IL-6, and TNF-α levels in the ulcer group were significantly higher than those of the control group (p<0.001). In the groups treated with persimmon, the IL-10, TNF-α, IL-6, and IL-1β levels were significantly lower than those seen in the ulcer group (p<0.001) (Fig. 1).

Hematoxylin and eosin analyses

The hematoxylin and eosin scores are presented in Table 2. The histopathological evaluation of the gastric mucosa can be seen in Figure 2.

In the control group, the mucosal cells were of normal shape and size, and the gastric pits were regular. In the ulcer group, the gastric pits were irregular, and no longer had a normal appearance. The mucosal cells were necrotized in the superficial and the deep mucosa, and the number of lymphocytes increased. In the group that received 4 mL/kg persimmon extract, the gastric pits were regular and had a normal appearance. Hypertrophic changes were seen in the surface mucosal cells. In the Persimmon 8 mL/kg group, the gastric pits were regular with an appearance similar to that of the control group.

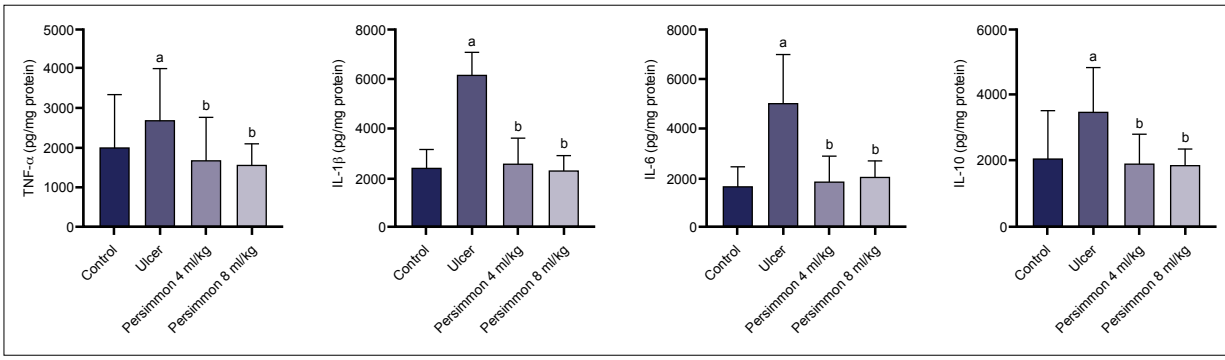

Figure 1. Effect of persimmon on some cytokine levels in a rat model of ethanol-induced gastric injury. IL: Interleukin; TNF-α: Tumor necrosis factor alpha.

Table 2. Hematoxylin and eosin staining scores, and NF-κB and caspase-3 expression of the study groups

Groups/parameters	H&E	NF-κB immunoreactivity	Caspase-3 immunoreactivity
Control	++	++	++
Ulcer	+++	+++	+++
Persimmon 4 mL/kg	++	++	++
Persimmon 8 mL/kg	++	++	++

+: Mild damage; ++: Medium damage; +++: Severe damage. H&E: Hematoxylin and eosin.

Immunohistochemical observation

The NF-κB and caspase-3 expression scores are presented in Table 2. The immunohistochemical evaluation of caspase-3 and NF-κB staining can be seen in Figure 2. The ulcer group demonstrated significant immunopositivity. The control group and both persimmon-treatment groups showed mild immunopositivity.

DISCUSSION

Gastric ulcer is a common digestive disorder.[1] Ethanol can directly injure the gastric mucosa, resulting in hemorrhagic lesions, edema, subepithelial hemorrhage, and cellular exfoliation with the rupture of the mucosa.[20] TNF-α not only induces IL-6 and IL-1β production, but

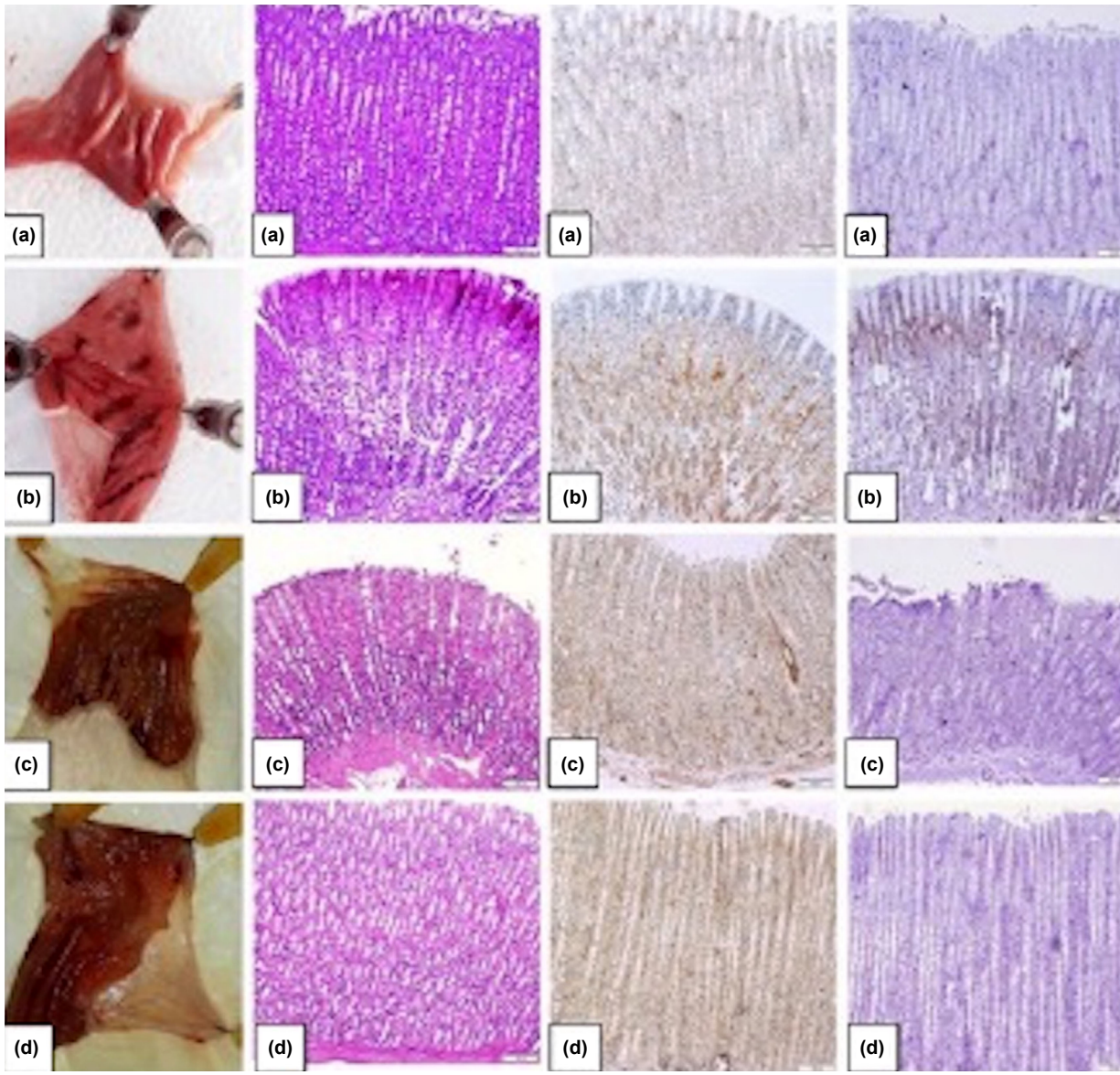

Figure 2. Histopathological studies of the study groups. **(a)** control group, **(b)** ulcer group, **(c)** persimmon 4mL/kg group, **(d)** persimmon 8 mL/kg group. H&E: Hematoxylin and eosin; NF-κB: Nuclear factor kappa B.

also enhances NF-κB activation via binding to the TNF-α receptor.[21,22]

Excessive proinflammatory gene expression, including IL-1β and TNF-α, have been determined in the gastric tissue following excessive intake of ethanol.[23,24] TNF-α plays a role in the activation of neutrophil infiltration and causes disturbance in gastric microcirculatory.[25] TNF-α is an important factor gastric ulcer formation as it initiates an acute inflammatory response.[26]

NF-κB expression, proinflammatory TNF-α, IL-1β, and anti-inflammatory IL-10 values have previously been shown to increase in a gastric ulcer model study of rats, as seen in our research.[27] In another gastric ulcer model, the TNF-α and caspase-3 levels were elevated in an ulcer group.[28] Aziz et al.[29] also observed high levels of TNF-α, NF-κB, and IL-6 expression in the ulcer group of another ethanol-induced gastric ulcer model.

Persimmon fruit has demonstrated antioxidant activity, and consumption is recommended for several health conditions, including stimulating the immune system, preventing cancer, and reducing inflammation and signs of aging.[30,31]

Persimmon has phenolic content, including p-Coumaric acid, gallic acid, syringic acid, vanillic acid, and catechin.[32] Nakano et al.[33] revealed that catechin derivatives downregulated inflammatory cytokine levels, including TNF-α and IL-1β. Vanillic acid compounds demonstrated anti-inflammatory, antioxidant effects, and inhibition of NF-κB-related proinflammatory cytokine production.[34] It has been reported that the potential antioxidant, antiapoptotic, and anti-inflammatory effects of Gallic acid and p-Coumaric acid may prevent hippocampal neurodegeneration.[35] It has also been demonstrated that gallic acid has a protective effect on cardiotoxicity associated with doxorubicin, and p-Coumaric acid therapy had a beneficial effect on the ototoxicity damage resulting from cisplatin-induced liver and kidney tissue injury.[36] Moreover, it has been reported that chlorogenic acid, p-Coumaric acid, and syringic acid had a positive effect in the treatment of various organ injuries caused by ischemia-reperfusion.[37–39] Another study demonstrated chlorogenic acid and cyanidin 3-glucoside antioxidant activity.[40] Avocado seeds *(Persea americana Mill.)*, which contain epicatechin, have been shown to prevent indomethacin-induced gastric ulcers.[41] Cinnamic acid has been reported to have gastroprotective effects.[42,43] The epicatechin and procyanidin in apple extract have been shown to protect against aspirin-related gastric mucosal injury in rats.[44]

In the present study, an ethanol-induced gastric ulcer led to increased IL-10, IL-1β, IL-6, and TNF-α levels, in addition to increased NF-κB and caspase-3 expression. All of these parameters demonstrate inflammation, but only IL-10 is an anti-inflammatory cytokine, which increases in a suppressive response to elevated proinflammatory cytokines. We found that the administration of persimmon fruit extract had a gastroprotective effect, demonstrating a decrease in all of the study parameters. IL-10 levels and proinflammatory cytokine levels decreased simultaneously. The polyphenolic content of persimmon fruit, which includes catechin, syringic acid, vanillic acid, gallic acid, and p-Coumaric acid, appears to have anti-inflammatory and antioxidant effects.

CONCLUSION

Persimmon fruit extract demonstrated a gastroprotective effect against an ethanol-induced gastric ulcer model in rats by suppressing proinflammatory parameters and inflammation-apoptosis-related expressions. It is believed that this was likely due to its various polyphenolic ingredients, which have potent anti-inflammatory and antioxidant properties.

A literature review revealed several studies examining the content of persimmon, but no study was found related a potential protective effect in a gastric ulcer model. Our research may provide new insight for gastric ulcer treatment.

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Approved by the local ethics committee.

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Concept: A.T., E.E., M.C.G., F.N.E.A.; Design: A.T., E.E., M.C.G., F.N.E.A.; Supervision: A.T., E.E., M.C.G., F.N.E.A.; Fundings: M.R.B., A.T., E.E., F.N.E.A.; Materials: M.R.B., E.T., N.K., E.Ç.G., G.Ö.; Data: M.R.B., E.T., N.K., E.Ç.G., G.Ö.; Analysis: A.T., E.E., M.C.G.; Literature search: M.R.B., E.T., N.K., E.Ç.G., G.Ö.; Writing: A.T., E.E., M.C.G.; Critical revision: A.T., E.E., M.C.G.

Conflict of Interest

None declared.

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Persimmon *(Diospyros Kaki L.)* Sıçanlarda Etanol ile İndüklenen Mide Ülserini Hafifletir

Amaç: Nonsteroid antiinflamatuvar ilaçlar, alkol tüketimi ve *Helicobacter pylori*, dünya çapında yüksek insidansla mide ülserinin en yaygın nedenleri arasındadır. Aşırı alkol tüketimi sonucu mide mukozasında hasar oluşumu artar. Alkol kaynaklı mide ülseri oluşumunu incelemek ve ülser tedavisi ile ilgili bileşikleri araştırmak için sıçanlarda etanol bazlı mide ülseri modeli kullanılmaktadır.

Gereç ve Yöntem: Persimmon (*Diospyros kaki L)*, Spraque Dawley sıçanlarında 5 ml/kg etanol ile oluşturulan mide ülseri modelinde uygulandı. Hurmanın mide ülseri üzerindeki olası gastroprotektif etkileri histopatolojik ve biyokimyasal yöntemlerle değerlendirildi.

Bulgular: Persimmon özü, IL-10, IL-6, TNF-α ve IL-1β gibi sitokin düzeylerini önemli ölçüde azalttı. Ayrıca kaspaz-3 ve NF-κB oluşumunu önemli ölçüde düşürdü.

Sonuç: Bu deneysel çalışmanın bir sonucu olarak persimmon, etanol ile oluşturulan mide ülseri modelinde mide koruyucu etki göstermiştir.

Anahtar Sözcükler: Etanol; mide ülseri; persimmon meyve ekstresi; sıçan; sitokin.