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Alpha-Mangostin Provides Protection from Mucosal Damage via Prostaglandin E2 in Indomethacin and Ethanol-Induced Gastric Ulcers

Alfa-Mangostin, İndometasin ve Etanol Kaynaklı Gastrik Ülserlerde Prostaglandin E2 Aracılığıyla Mukozal Hasara Karşı Koruma Sağlar

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ABSTRACT

Objective: Gastric ulcer is frequently observed among the gastrointestinal diseases and is induced by various factors. Alpha-mangostin (α-MG) has antioxidant and anti-inflammatory properties and may prevent gastric ulcers. This study was conducted to evaluate the healing effect of α-MG against gastric ulcer caused by indomethacin (Ind) and ethanol (Eth) in rats.

Methods: Wistar albino male rats were used to establish the experimental model. Seven groups were formed, as group I sham, group II (5 mL/kg Eth), group III (100 mg/kg Ind), group IV (Eth + Lansoprazole (Lans) 30 mg/kg), group V (Ind + Lans 30 mg/kg), group VI (Eth + α-MG 10 mg/kg), and group VII (Ind + α-MG 10 mg/kg) (n=10). Cytokines; VEGF-A; NOS2/iNOS; PGE2 levels were analyzed by the ELISA method. Besides, the general appearance of the gastric tissues was evaluated by hematoxylin-eosin staining, COX-1, COX-2, NF-κB, and caspase-3 levels were measured immunohistochemical (IHC).

Results: Cytokine levels decreased in the treatment groups compared to the ulcer groups. There was a decrease in VEGF-A and NOS2/iNOS levels in the α-MG administered groups. The reduction in PGE2 levels in the gastric ulcer groups was counteracted by an increase in both the Lans and α-MG administered groups. In the IHC results, while COX-1, COX-2, NF-κB, and caspase-3 levels were increased in gastric ulcer groups, significant decreases were observed in Lans and α-MG groups.

ÖZ

Amaç: Gastrik ülser, gastrointestinal hastalıklar arasında sıklıkla görülür ve çeşitli faktörler tarafından tetiklenir. Alfa-mangostin (α-MG), antioksidan ve anti-inflamatuar özelliklere sahiptir ve gastrik ülseri önleyebilir. Bu çalışma, sıçanlarda indometazin (Ind) ve etanol (Eth) kaynaklı gastrik ülsere karşı α-MG'nin iyileştirici etkisini değerlendirildi.

Yöntemler: Deneysel modeli oluşturmak için Wistar albino erkek sıçanlar kullanıldı. Grup I sham, grup II (5 mL/kg Eth), grup III (100 mg/kg Ind), grup IV (Eth+Lansoprazol (Lans) 30 mg/kg), grup V (Ind + Lans 30 mg/kg), grup VI (Eth + α-MG 10 mg/kg) ve grup VII (Ind + α-MG 10 mg/kg) olmak üzere yedi grup oluşturuldu (n=10). Sitokinler, VEGF-A, NOS2/iNOS, PGE2 düzeyleri ELISA yöntemi ile analiz edildi. Ayrıca, gastrik dokuların genel görünümü hematoksilen-eozin boyama ile değerlendirildi, COX-1, COX-2, NF-κB ve kaspaz-3 düzeyleri immünohistokimyasal olarak ölçüldü.

Bulgular: Sitokin düzeyleri, ülser gruplarına kıyasla tedavi gruplarında azaldı. α-MG uygulanan gruplarda VEGF-A ve NOS2/iNOS düzeylerinde azalma oldu. Gastrik ülser gruplarında PGE2 düzeyindeki azalma, hem Lans hem de α-MG uygulanan gruplarda artış gösterdi. İmmünohistokimyasal sonuçlarda, COX-1, COX-2, NF-κB ve kaspaz-3 düzeyleri gastrik ülser gruplarında artarken, Lans ve α-MG gruplarında önemli düşüşler görüldü.

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ABSTRACT

Conclusion: As a result, α-MG eased inflammation and increased PGE2 levels. It reduced the levels of COX-1, COX-2, NF-κB, and caspase-3. As a result of these data, α-MG may be a potential therapeutic agent against gastric ulcer.

Keywords: Gastric ulcer, indomethacin, ethanol, alpha-mangostin, rat

ÖZ

Sonuç: Sonuç olarak, α-MG inflamasyonu hafifletti ve PGE2 düzeylerini artırdı. COX-1, COX-2, NF-κB ve kaspaz-3 seviyelerini düşürdü. Bu veriler sonucunda α-MG, mide ülserine karşı potansiyel bir tedavi edici ajan olabilir.

Anahtar Sözcükler: Mide ülseri, indometasin, etanol, alfa-mangostin, sıçan

INTRODUCTION

Peptic ulcers, the most common disease of the gastrointestinal tract, negatively affect many people worldwide (1). Ulceration is observed if there is an imbalance between mucosal defense factors [enzymatic and non-enzymatic antioxidants, mucus secretion, bicarbonate secretion, blood flow, and prostaglandins (PGs)] and aggressive gastric factors [acid-pepsin, leukotrienes, and reactive oxygen species (ROS)] (2,3). Non-steroidal anti-inflammatory drugs (NSAIDs, e.g., indomethacin (Ind)), alcohol consumption, *Helicobacter pylori (H. pylori)* infections, smoking, and emotional stress are among factors leading to ulcer formation (4). ROS, neutrophil infiltration, inflammation, and lesions in the gastric mucosa are involved in the pathogenesis of experimental ulcer induced by ethanol (Eth) and NSAIDs, [e.g., (Ind)] (5-7). Proton pump inhibitors (e.g., lansoprazole, lans), histamine type 2 receptor blockers (e.g., ranitidine), or mucosal protective agents (e.g., misoprostol) are recommended for ulcer treatment. However, these treatments also have potential side effects. Therefore, it is essential to identify new agents with lower side effects (8,9).

Medicinal plant extracts are sources for new biologically active molecules, and have shown promising results in the treatment of various pathologies, including gastric ulcers (6). Mangosteen (garcinia mangostana L.) is a widely used medicinal plant in Thailand, India, Sri Lanka, and Myanmar. Studies reveal antioxidant, antiallergic, antibacterial, anti-inflammatory, antitumoral, and antiviral activities (10,11). The biological properties of mangosteen are related to the xanthones isolated from different parts. Studies have revealed important xanthones such as alpha beta gamma-mangostin, garcinone E, 8-deoxgartanine, and gartanin in phytochemical analysis (12). Alpha-mangostin (α-MG) is the most common polyphenolic xanthan in garcinia mangostana (10). α-MG shows potential antitumor effects in various types of cancer (12-15). It also has anti-inflammatory (16), antioxidant, hypoallergenic, and antifungal activities (17, 18). It has also been proven to have many pharmacological activities, including cardioprotective, anti-diabetic, and neuroprotective properties (19,20).

α-MG has been investigated in some ulcer models, and some protective effects have been reported. Current evidence cannot explain the protective role of this xanthone on a gastric ulcer. We performed several biochemical and histopathological analyses by creating an ulcer model in animals with Eth and Ind to evaluate the anti-ulcer activity of α-MG.

MATERIALS AND METHODS

Drug

α-MG (MedChemExpress, NJ, USA), ETH (99% absolute), IND (Sigma-Aldrich, MO, USA), and Lans (Cayman Chemical, Michigan, USA) were purchased. All drugs were dissolved in dimethyl sulfoxide (DMSO) and administered intragastrically (i.g.) to the animals.

Animals and Ethical Approval

Seventy male Wistar albino rats (body weight 250-300 g) were obtained from Atatürk University Medical Experimental Practice and Research Center, and the ulcer model was carried out at this center. All animals were housed under standard humidity, temperature (22±2 °C), and 12-hour light/dark cycle conditions. Animals were fed standard pellet feed and fasted for 12 hours before starting the study, but they were allowed free access to water. All experiments were carried out following the permission of Atatürk University Animal Experiments Local Ethics Committee (approval number: 175, date: 17.09.2018).

Creating an Ulcer Model with Eth and Ind

Seventy Wistar albino male rats were used to evaluate the effects of α-MG on the gastric ulcer. Seven groups of 10 rats each were randomly formed. Experimental groups are as follows. After the gastric ulcer model was created, drugs (Lans and α-MG) were administered. After 90 minutes, the rats were sacrificed under anesthesia, and their stomachs were excised. Gastric tissues were incised along the small curvature and washed with saline to clear blood clots. Stomach tissues were kept in suitable storage conditions for biochemical and histopathological analysis.

Sham group; 750 µL/250 g b.w., DMSO, i.g. (21).

Eth group; 5 mL/kg, i.g. (22).

Ind group; 100 mg/kg, i.g. (21)

Eth + Lans group; respectively, 5 mL/kg+30 mg/kg, i.g. (23)

Ind + Lans group; respectively, 100 mg/kg+30 mg/kg, i.g. (24)

Eth + α-MG group; respectively, 5 mL/kg+10 mg/kg, i.g.

Ind + α-MG group; respectively, 100 mg/kg+10 mg/kg, i.g.

Biochemical Analysis

Gastric tissues were homogenized for 15 minutes, using phosphate buffer solution (PBS) in the cooled area. Homogenates were filtered and centrifuged at 4 °C. Supernatants were used for analysis. All experiments were carried out at room temperature. Tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and IL-10, vascular endothelial growth factor A (VEGF-A), nitric oxide synthase 2 (NOS2)/ inducible NOS (iNOS), and PG E2 (PGE2) levels were measured from gastric tissue by enzyme-linked immunosorbent test (ELISA). The parameters measured in the study were performed using rat TNF-α, IL-1β, IL-10, VEGF-A, NOS2/iNOS, and PGE2 ELISA test kits (Wuhan, China) according to the manufacturer's instructions.

Histopathological Method

Necropsy of the rats was performed, and the gastric tissues were fixed in 10% neutral formalin solution. Tissues were embedded in paraffin blocks after routine alcohol-xylol follow-up procedures. Sections of 5 µm, taken on poly-lysine slides, were stained with hematoxylin-eosin and evaluated as none (0), mild (1), moderate (2), and severe (3) for degenerative and ulcerative changes.

Immunohistochemical Method

Gastric tissues were fixed in 10% neutral formalin solution. Tissues were embedded in paraffin blocks after routine alcohol-xylol processing. After washing with PBS, 5 µm sections taken on poly-lysine slides were passed through xylene and alcohol-series. Then, endogenous peroxidase inactivation was achieved by keeping them in 3% H_2O_2 for 10 minutes. The antigen was treated with retrieval solution at 500 watts for two 5-minute intervals. Subsequently washed tissues with PBS Cyclooxygenase-1 (COX-1) (Santa Cruz, Catalog No, sc-19998 1/200 dilution ratio), COX-2 (Abcam, Catalog No ab15191, 1/200 dilution rate), nuclear factor kappa B (NF-κB) (Abcam, Catalog No ab7971, 1/200 dilution ratio), caspase 3 (Biorbyt, Catalog No Orb382909, 1/200 dilution ratio) with primary antibodies at room temperature for 20 minutes. Mouse and Rabbit Specific HRP/DAB immunohistochemical (IHC) Detection Kit-Micro-polymer Kit (Abcam, Catalog No. ab236466) was used as the secondary antibody, as recommended by the manufacturer. DAB (3,3'-Diaminobenzidine) was used as the chromogen. After counterstaining with Mayer's Hematoxylin, it was covered with entellan and examined under a light microscope. Immune positivity in gastric tissues was examined as no (0 point), mild (1 point), moderate (2 point), and severe (3 point).

Statistical Analysis

SPSS v.20 (Chicago, USA) was used for all statistical analyses. The distribution of the data was evaluated using the Shapiro-Wilk test. One-way ANOVA was used for biochemical analysis. In histopathological findings, the Kruskal-Wallis test and Mann-Whitney U test were used to find differences between groups. A p-value less than 0.05 (<0.05) was considered statistically significant. Data were presented as mean ± SD. All graphs were drawn using GraphPad Prism v.8 (San Diego, USA).

RESULTS

Gastric Cytokine Levels

Cytokine levels of TNF-α, IL-1, and IL-10 in all groups are presented in Figure 1. In the experimental models created with Eth and Ind, TNF-α

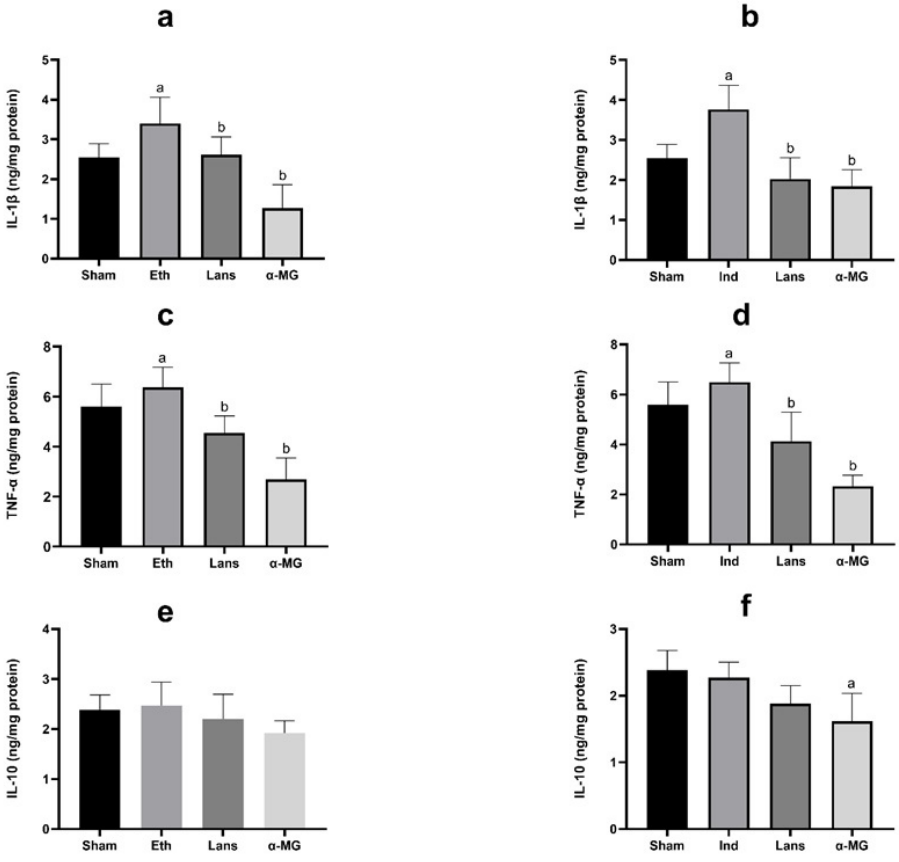

Figure 1. Cytokine levels were measured in the homogenized gastric tissues in the experimental groups. (a) IL-1β levels in the Eth group, (b) IL-1β levels in the Ind group, (c) TNF-α levels in the Eth group, (d) TNF-α levels in the Ind group, (e) IL-10 levels in the Eth group (f), IL-10 levels in the Ind group. Data are presented as mean ± SD. ap<0.05 compared to the control group, bp<0.05 compared to the Eth and Ind groups.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG; Alpha mangostin, TNF-α; Tumor necrosis factor-alpha, IL-1ß, Interleukin-1 beta, IL-10: Interleukin 10

levels increased without significant difference compared to the sham group (p>0.05), while IL-1 levels increased significantly (p<0.05). The Lans and α-MG treatments decreased both proinflammatory cytokine levels (p<0.05). IL-10 levels did not change significantly in both ulcer models (p>0.05), but the decrease in IL-10 levels was significant in the Ind+α-MG group (p<0.05).

Gastric VEGF-A Levels

VEGF-A levels in all groups were determined in gastric tissues (Figure 2). There was no change in VEGF-A levels in ulcer groups created with Eth and Ind (p>0.05). However, in the Eth group, the α-MG treatment decreased VEGF-A levels (p<0.05). In the Ind group, the VEGF-A level decreased in both the model group and the group receiving α-MG treatment (p<0.05).

Gastric NOS2/iNOS Levels

NOS2/iNOS levels in all groups were determined in gastric tissue (Figure 3). No change was observed in NOS2/iNOS levels in the Eth group (p>0.05). However, we found significant reductions in the Lans-treated and α-MG-treated groups (p<0.05). NOS2/iNOS levels decreased in ulcer models with Ind (p<0.05), and a similar decrease was observed in Lans and α-MG groups (p<0.05).

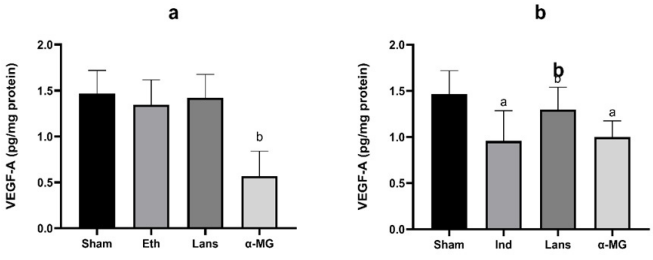

Figure 2. VEGF-A levels were measured in the gastric tissues homogenized from the experimental groups. (a) VEGF-A levels in Eth group (b) VEGF-A levels in Ind group. Data are presented as mean ± SD. ap<0.05 compared to the control group, bp<0.05 compared to Eth and Ind groups.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin, VEGF-A: vascular endothelial growth factor-A

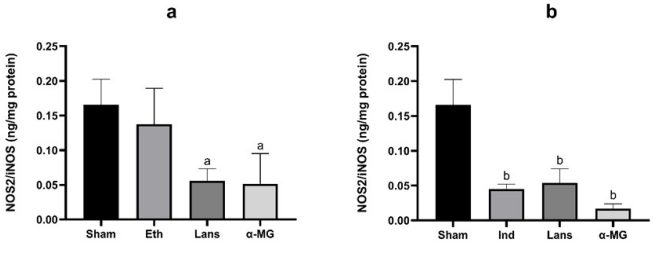

Figure 3. NOS2/iNOS levels were measured in the homogenized gastric tissues in the experimental groups. (a) NOS2/iNOS levels in the Eth model (b) NOS2/iNOS levels in the Ind model. Data are presented as mean ± SD. ap<0.05 compared to the control group, bp<0.05 compared to Eth and Ind groups.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin, NOS2/iNOS: Nitric oxide synthase 2/inducible NOS

Gastric PGE2 Levels

PGE2 levels in all groups were determined in gastric tissue (Figure 4). PGE2 levels decreased in both ulcer groups (p<0.05). The ulcer model created with Eth, Lans, and α-MG applications caused significant increases in PGE2 levels (p<0.05). In the Ind-induced ulcer model, while PGE2 level increased in the Lans-treated group (p<0.05), a slight increase was found in the α-MG-treated group (p>0.05).

Histopathological Staining

A statistically significant difference was found between the groups regarding degenerative and ulcerative changes in the gastric mucosa glands (Figure 5 and Figure 6). No degenerative or ulcerative findings were present in the epithelium and glands of the gastric mucosa of the animals in the sham group. While severe ulcerative changes were observed in the gastric mucosa in the Eth and Ind groups, it was found that ulcerative and degenerative changes decreased in the Eth + Lans, Ind + Lans, E + α-MG, and Ind + α-MG groups, and the gastric mucosa glands especially had a more regular structure (Figure 7).

Immunohistochemical Staining

There was a significant difference between the groups in terms of COX-1, COX-2, NF-κB, and Caspase-3 immunopositivity in gastric tissues. COX-1, COX-2, NF-κB, and Caspase-3 immunopositivity were not determined at a significant level in the gastric tissues of rats in the sham group. It was determined that COX-1, COX-2, NF-κB, and Caspase-3 immunopositivity were severe in the gastric tissues of the animals in the Eth and Ind groups. Besides, the immunopositivity of COX-1, COX-2, NF-κB, and Caspase-3 were moderately in the Eth + Lans, Ind + Lans, Eth + α-MG, and Ind+αMG groups (Figure 7). Evaluation of immunopositivity is presented in Figure 5 and Figure 6.

DISCUSSION

Ulcer, a common disease of the gastrointestinal tract, is characterized by inflammatory lesions or mucosal injuries due to an imbalance between aggressive factors such as acid, *H. pylori*, pepsin, and defense factors, including bicarbonate ions, PGs, and gastric mucus (25). Gastric ulcers and gastritis are often seen in people who use NSAIDs, smoke, or drink alcohol (26). Gastric ulcers caused by Eth administration, occur due to its direct necrotizing effect on the

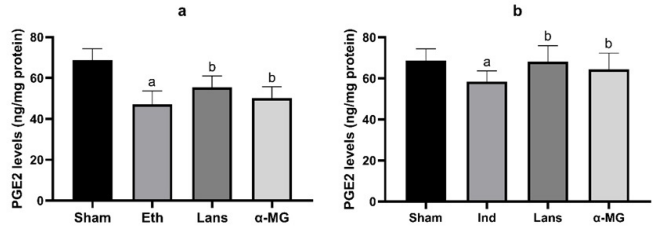

Figure 4. PGE2 levels were measured in the homogenized gastric tissues in the experimental groups. (a) PGE2 levels in the Eth group, (b) PGE2 levels in the Ind group. Data are presented as mean ± SD. ap<0.05 compared to the control group, bp<0.05 compared to Eth and Ind groups.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin; PGE2: Prostaglandin

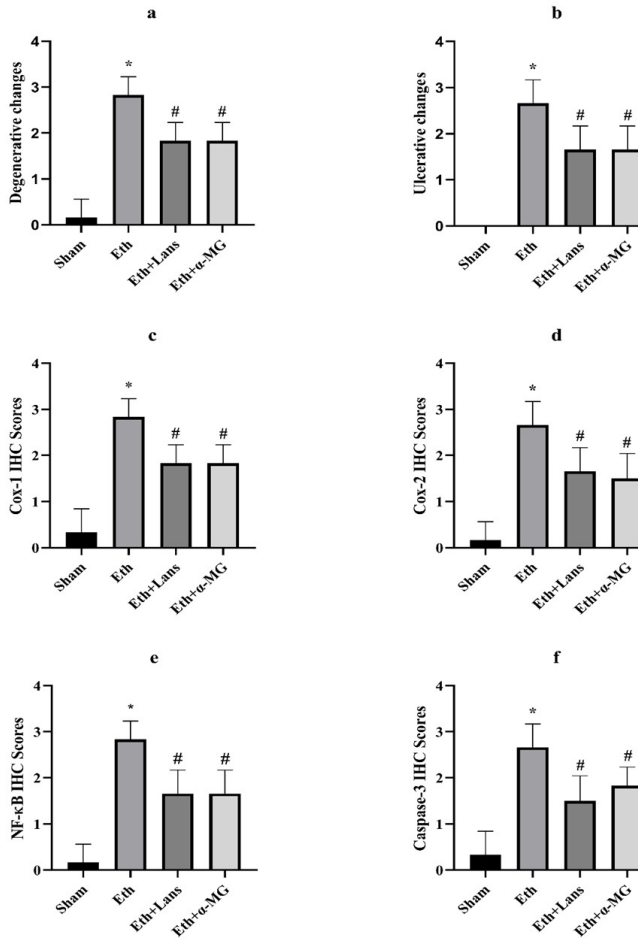

Figure 5. Scoring of immune staining in Eth-induced gastric ulcer model. (a) Degenerative changes and (b) ulcerative changes, (c) COX-1 and (d) COX-2, (e) NF-kB and (f) Caspase-3 IHC scores. Data are presented as mean±SD.

*p<0.05 compared to the sham group, #p<0.05 compared to the Eth group.

Eth: Ethanol, Lans: Lansaprazole; α-MG: Alpha mangostin, α-MG; COX-1: Cyclooxygenase-1, COX-2: Cyclooxygenase-2, NF-kB: Nuclear factor kappa B

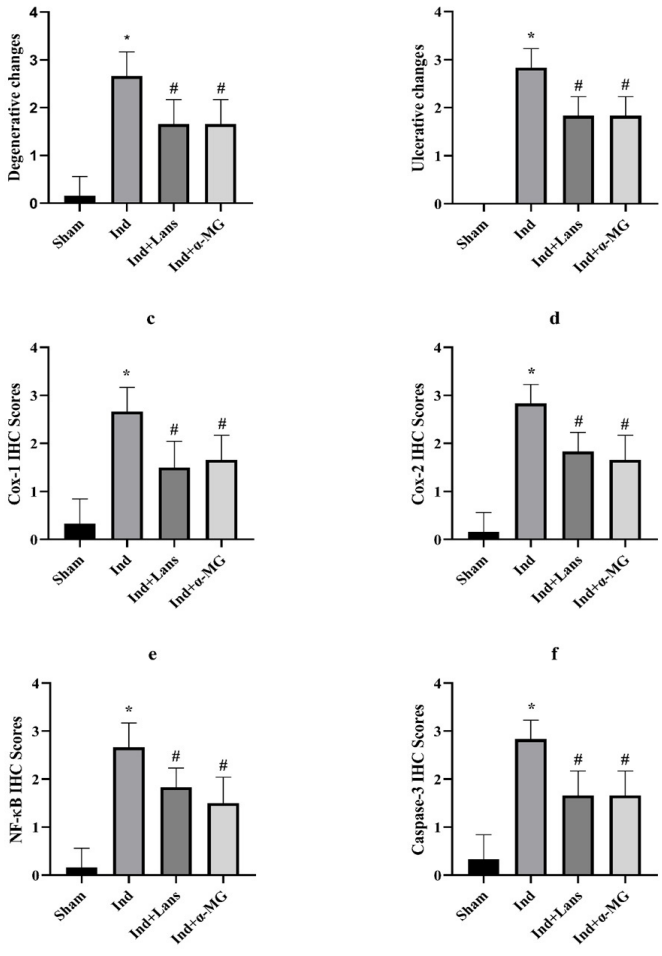

Figure 6. Scoring of immunostaining in the Ind-induced gastric ulcer model. (a) Degenerative changes and (b) ulcerative changes, (c) COX-1, (d) COX-2, (e) NF-kB, and (f) Caspase-3 IHC scores. Data are presented as mean ± SD.

*p<0.05 compared to the sham group, # p <0.05 compared to the Ind group.

Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin, COX-1: Cyclooxygenase-1, COX-2: Cyclooxygenase-2, NF-kB: Nuclear factor kappa B

gastric mucosa. Moreover, Eth causes gastric lesions by disrupting the protective mucus/bicarbonate barrier and subsequent microcirculatory disorders, ischemia, and generation of free radicals, which damage the vascular endothelium (27). Regarding Ind, NSAIDs act by inhibiting COX-1 and COX-2 to promote a decrease in PG levels. Therefore, inhibition of PG synthesis results in the weakening of the mucosal defense (28).

Eth and Ind cause ulcerative lesions including deterioration in the structure of mucosal cells, hemorrhage, and edema by reducing the defensive factors that protect the gastric mucosa. α-MG reduces the ulcerative and degenerative effects that occur in the stomach in both gastric ulcer models. To explain α-MG's mechanism of actionα-MG, we focused on the PGE2 pathway inhibited by Eth and Ind. PGs, especially PGE2, protect the gastric mucosa through the activation of different EP receptors, increasing mucus and bicarbonate secretion, increasing blood flow, and reducing acid secretion. Moreover, PGE2 deficiency causes neutrophil infiltration and activation of inflammatory pathways (29,30). Gastric PGE2 level decreases in Eth and Ind-induced gastric ulcers (31,32). The NF-κB signaling pathway contributes to gene expression control of multiple factors and plays an important role in cell stress response, apoptosis, immune response, inflammation, and cancer development (33). NF-κB contributes to the expression of inflammatory genes. Activation of neutrophils leads to increased expression of the proinflammatory cytokines TNF-α, IL-1β, and IL-6 (34). It has been shown that inhibition of NF-κB can contribute to ulcer healing in both ulcer models created with Eth and Ind (35,36). Besides cytokine regulation, NF-κB is also associated with iNOS expression and NO release (37). NO is

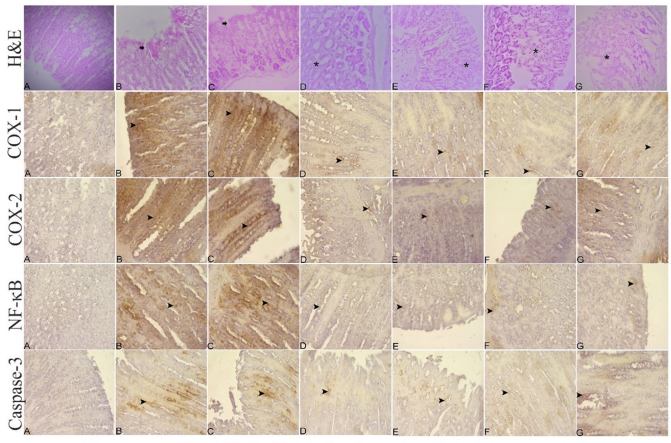

Figure 7. Evaluation of H&E staining and COX-1, COX-2, NF-kB and Caspase-3 immune positivity in gastric ulcer induced by Eth and Ind. (A) Sham group, (B) Eth group, (C) Ind group, (D) Eth + Lans group, (E) Ind + Lans group, (F) Eth + α-MG group, (G) Ind + α-MG group. Gastric mucous glands and immunopositivity respectively was indicated by star and arrowhead.

Eth: Ethanol, Ind: Indomethacin, Lans: Lansaprazole, α-MG: Alpha mangostin, COX-1: Cyclooxygenase-1, COX-2: Cyclooxygenase-2, NF-kB: Nuclear factor kappa B

part of the gastrointestinal mucosal defense but also contributes to mucosal damage (38). Overexpression of NO can cause cell damage by interacting with other radicals and injure the gastric mucosa. High NOS2 levels may lead to secretion of large amounts of NO and severe damage to many tissue types (39,40). In previous studies, α-MG significantly inhibited the production of NO, TNF-α, PGE2, and iNOS in some cell lines stimulated with lipopolysaccharide (17). In our study, NOS2 levels in the gastric mucosa decreased in both model groups, and a similar decrease was observed in the α-MG treated groups. The healing effect of α-MG was also accompanied by anti-inflammatory activity. α-MG decreased TNF-α, IL-1β, and NOS2/iNOS levels in gastric tissues of ulcerated animals. This is in line with previous studies showing that α-MG can modulate the inflammatory cytokine and mediator production under inflammatory conditions (41-43).

Gastric mucosa damage also brings vascular damage to ulcerated areas. At this point, angiogenesis facilitates ulcer healing by playing an important role in accelerating ulcer healing because nutrient delivery to the healing tissue is maintained (44). The main trigger of this change is tissue hypoxia, which stimulates genes encoding angiogenic growth factors such as VEGF. As a result, endothelial cells from micro vessels preserved at the injury site migrate, proliferate, and ultimately form a microvascular network (45). VEGF-A from the VEGF family plays a key role in blood vessel growth (46). VEGF-A levels were slightly decreased in both ulcer models we used in this study. A significant decrease in VEGF-A levels was also detected in the α-MG treatment groups. In another study, it has been shown that α-MG can increase the VEGF level depending on time, and this situation can occur in a time-dependent manner (47). In the same study, it was reported that α-MG can bind superoxide radicals, remove them from the environment, and increase the VEGF level by increasing NO levels (47).

Caspase-3 activation contributes to the disruption of mucosal integrity due to pathological events that occur during epithelial cell damage, cell cytotoxicity, or mitochondrial damage caused by both NSAIDs and Eth (48,49). Caspases, a family of cysteine proteases, play a critical role in the execution of apoptosis. Caspase-3 is not only a promoter but also a marker for apoptosis. It has been demonstrated that α-MG suppresses the IHC expression of caspase-3 in ulcer models. α-MG could reduce cell damage by inhibiting several enzymes involved in the apoptotic cascade. As a result, α-MG can reduce the gastric injuries induced by Ind and Eth. α-MG is a natural polyphenolic xanthone and affects NO release and inhibits COX-1 and COX-2. Based on the evidence obtained, α-MG can be expressed as a protective and healing agent for gastric ulcers through different mechanisms. However, a series of molecular analyses is needed for clearer results.

Ethics

Ethics Committee Approval: All experiments were carried out following the permission of Atatürk University Animal Experiments Local Ethics Committee (approval number: 175, date: 17.09.2018).

Informed Consent: Since it is an animal study, ethical approval is not required.

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Footnotes

Authorship Contributions

Concept: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Design: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Supervision: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Resources: E.E., A.T., M.C.G., Material: E.E., B.B., A.T., M.C.G., Data Collection or Processing: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Analysis or Interpretation: E.E., B.B., A.T., M.C.G., Y.B., S.Ç., Literature Search: E.E., B.B., A.T., M.C.G., Writing: E.E., B.B., M.C.G., Critical Review: E.E., B.B., A.T., M.C.G., Y.B., S.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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