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Evaluation of the Gastroprotective Effects of Hazelnut Oil Against Ethanol-Induced Gastric Mucosal Injury in Rats

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Abstract

Objective: This study aimed to investigate the gastroprotective effects of hazelnut oil against ethanol-induced gastric mucosal injury in rats by macroscopic and histopathological evaluations.
Material and Method: Thirty-five male Wistar rats (180–220 g) were randomly divided into five groups (n=7): Control (saline), Ethanol (75% ethanol, 5 mL/kg), Hazelnut Oil-Low Dose (HO-L, 2.5 mL/kg hazelnut oil + ethanol), Hazelnut Oil-High Dose (HO-H, 5 mL/kg hazelnut oil + ethanol), and Ranitidine (50 mg/kg + ethanol). Treatments were administered orally for 7 days, followed by ethanol. Ulcer area, inhibition rate, and histopathological scores (inflammation, edema, epithelial damage, hemorrhage) were evaluated. Statistical analysis was performed using one-way ANOVA and Kruskal-Wallis tests.
Results: Ethanol induced significant gastric injury, while HO-L, HO-H, and Ranitidine groups showed significantly reduced ulcer areas ($P < 0.001$) and histopathological scores ($P < 0.005$). The highest inhibition was observed in the Ranitidine group (95%), followed by HO-H (78%) and HO-L (39%).
Conclusion: Hazelnut oil exerts a dose-dependent protective effect against ethanol-induced gastric damage, likely due to its oleic acid and vitamin E content. These findings suggest hazelnut oil may serve as a natural alternative in the prevention of gastric ulcers.
Key Words: Hazelnut oil, gastric mucosal injury, ethanol, gastroprotection, ulcer area, histopathology

Fındık Yağının Etanol Kaynaklı Mide Mukozal Hasarına Karşı Gastroprotektif Etkilerinin Değerlendirilmesi

Özet

Amaç: Bu çalışmada, fındık yağının etanol ile oluşturulan mide mukozal hasarına karşı gastroprotektif etkileri makroskopik ve histopatolojik olarak değerlendirilmiştir.
Materyal ve Metot: Otuz beş erkek Wistar sıçanı (180–220 g) rastgele beş gruba ayrıldı (n=7): Kontrol (salin), Etanol (%75 etanol, 5 mL/kg), Fındık Yağı-Düşük Doz (HO-L, 2.5 mL/kg fındık yağı + etanol), Fındık Yağı-Yüksek Doz (HO-H, 5 mL/kg fındık yağı + etanol) ve Ranitidin (50 mg/kg + etanol). Tedaviler 7 gün boyunca oral olarak uygulandı, ardından etanol verildi. Ülser alanı, inhibisyon oranı ve histopatolojik skorlar (inflamasyon, ödem, epitel hasarı, hemoraji) değerlendirildi. İstatistiksel analiz tek yönlü ANOVA ve Kruskal-Wallis testleriyle yapıldı.
Bulgular: Etanol ciddi mide hasarı oluştururken, HO-L, HO-H ve Ranitidin grupları anlamlı derecede düşük ülser alanları ($P < 0.001$) ve histopatolojik skorlar ($P < 0.005$) gösterdi. En yüksek inhibisyon oranı Ranitidin grubunda (%95), ardından HO-H (%78) ve HO-L (%39) ile gözlendi.
Sonuç: Fındık yağı, etanol kaynaklı mide hasarına karşı doza bağlı koruyucu etki göstermektedir. Bu etkinin oleik asit ve E vitamini içeriğinden kaynaklandığı düşünülmektedir. Elde edilen bulgular, fındık yağının mide ülserlerinin önlenmesinde doğal bir alternatif olabileceğini göstermektedir.
Anahtar kelimeler: Fındık yağı, mide mukozal hasarı, etanol, gastroproteksiyon, ülser alanı, histopatoloji

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INTRODUCTION

Gastric mucosal injury, a key pathological process underlying gastritis and peptic ulcer disease, remains a prevalent global health issue that affects millions annually and imposes significant healthcare burdens (1). These injuries typically result from an imbalance between mucosal defensive mechanisms (e.g., mucus, bicarbonate secretion, prostaglandins) and damaging agents, such as Helicobacter pylori infection, non-steroidal anti-inflammatory drugs (NSAIDs), excessive alcohol intake, and stress (1,2). Among these, ethanol is commonly used in experimental models due to its reproducible ability to disrupt the gastric mucosal barrier via oxidative stress, inflammation, epithelial apoptosis, and microcirculatory impairment, ultimately leading to ulcer formation (2,3).

Pharmacological interventions such as proton pump inhibitors (PPIs) and histamine H2 receptor antagonists (e.g., Ranitidine) are standard treatments that alleviate symptoms and promote mucosal healing by suppressing gastric acid secretion (4). However, long-term use of these agents may cause adverse effects, including hypomagnesemia, vitamin B12 deficiency, alterations in gut microbiota, an increased risk of enteric infections, and renal complications (4,5). This has stimulated interest in alternative, naturally derived compounds that provide mucosal protection with fewer side effects. Among these alternatives, plant-based oils rich in bioactive lipids have emerged as promising gastroprotective agents. Olive oil, characterized by its high oleic acid content (~70–80%) and vitamin E content, has demonstrated anti-inflammatory and antioxidant effects that strengthen the mucosal barrier and reduce ulcer formation in various experimental settings (6,7). Oleic acid has been shown to modulate inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). At the same time, vitamin E mitigates oxidative mucosal damage by scavenging reactive oxygen species (ROS) (8–12). Hazelnut oil (Corylus avellana L.) is nutritionally and chemically similar to olive oil, containing high levels of monounsaturated fatty acids—particularly oleic acid—as well as tocopherols, phytosterols, and polyphenols (8). Despite these favourable properties, its gastroprotective potential remains poorly understood, and, to our knowledge, no prior study has directly examined the protective effects of hazelnut oil in ethanol-induced gastric injury models.

Therefore, this study aimed to evaluate the gastroprotective potential of hazelnut oil against ethanol-induced gastric mucosal injury in rats. Using macroscopic and histopathological assessments, its efficacy was compared to a standard antiulcer agent. We hypothesized that hazelnut oil would offer significant mucosal protection due to its antioxidant and anti-inflammatory properties.

MATERIALS AND METHODS

Animals and Ethical Approval

Thirty-five male Wistar rats (weighing 180–220 g) were obtained from the Experimental Research and Application Centre of Ordu University. Animals were maintained under standard laboratory conditions (22 ± 2°C, 12-h light/dark cycle, 50–60% humidity) with free access to standard rodent chow and tap water. All procedures were performed in accordance with the European Directive 2010/63/EU for the protection of animals used for scientific purposes. Ethical approval was granted by the Ordu University Animal Experiments Local Ethics Committee (HADYEK) under protocol number 2020/14.

Experimental Groups and Protocol

The rats were randomly allocated into five groups (n = 7 per group):

Control Group: received 0.9% saline (5 mL/kg/day, orally) for 7 consecutive days; no ethanol was administered.

Ethanol Group: received saline (5 mL/kg/day, orally) for 7 days; on day 7, 75% ethanol (5 mL/kg, orally) was administered to induce gastric injury (3).

Hazelnut Oil–Low Dose (HO-L) Group: received hazelnut oil (2.5 mL/kg/day, orally) for 7 days; on day 7, ethanol was administered.

Hazelnut Oil–High Dose (HO-H) Group: received hazelnut oil (5 mL/kg/day, orally) for 7 days; on day 7, ethanol was administered.

Ranitidine Group: received Ranitidine (50 mg/kg/day, orally) for 7 days; on day 7, ethanol was administered.

Hazelnut oil was obtained through the cold-pressing of Corylus avellana L. harvested from the Black Sea region and stored in dark-glass bottles at room temperature. The doses were selected based on similar studies using plant-based oils for gastrointestinal protection (13). Ranitidine (50 mg/kg) was freshly prepared in saline prior to administration.

On the seventh day, one hour after the final treatment, rats in all groups (except the control group) were administered 75% ethanol (5 mL/kg, orally) to induce acute gastric mucosal injury. One hour later, rats were anaesthetized with

intraperitoneal ketamine (75 mg/kg) and xylazine (10 mg/kg), and euthanized via cervical dislocation.

Macroscopic Evaluation of Gastric Lesions

The stomachs were removed through midline laparotomy, opened along the greater curvature, rinsed gently with saline, and photographed. Macroscopic ulcerations on the glandular portion were examined using a stereomicroscope (×10 magnification). The ulcerated areas were measured in square millimetres (mm^2) using ImageJ software (National Institutes of Health, USA). The ulcer inhibition rate (%) was calculated for each treatment group using the formula described by Nguelefack et al. (2005) (14):

Anti-ulcerative effect (%) = ((Ulcer area of control group - Ulcer area of treatment group) / Ulcer area of control group) × 100

Histopathological Analysis

Gastric tissues were fixed in 10% neutral-buffered formalin, dehydrated through graded ethanol, embedded in paraffin, and sectioned at 6 µm thickness. Sections were stained with hematoxylin and eosin (H&E) and evaluated under a light microscope by a blinded pathologist at the Department of Pathology, Ordu University Faculty of Medicine. Histopathological changes were scored semi-quantitatively as follows:

Inflammation and epithelial damage were graded on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Oedema and haemorrhage were graded on a 5-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe).

A total histopathological score was obtained by summing the scores of all four parameters for each specimen.

Statistical Analysis

Data were analyzed using SPSS software version 21.0 (IBM Corp., Armonk, NY, USA). Macroscopic ulcer areas were presented as mean ± standard deviation (SD) and analyzed using one-way ANOVA followed by Tukey's post hoc test. Histological scores, being non-parametric, were analyzed using the Kruskal-Wallis test, followed by Bonferroni-adjusted Mann–Whitney U tests for intergroup comparisons. A P value of < 0.05 was considered statistically significant.

RESULTS

Macroscopic Analysis

Macroscopic evaluation revealed significant differences in ulcer area among groups (Table 1, Figure 1). The Control group showed no mucosal damage (Median = 0.00, IQR = 0.00 mm^2), confirming the absence of injury in the absence of ethanol exposure.

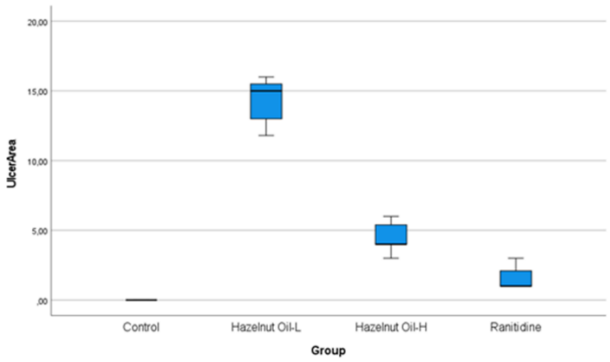

Figure 1. Box-Plot of Ulcer Area Across Experimental Groups

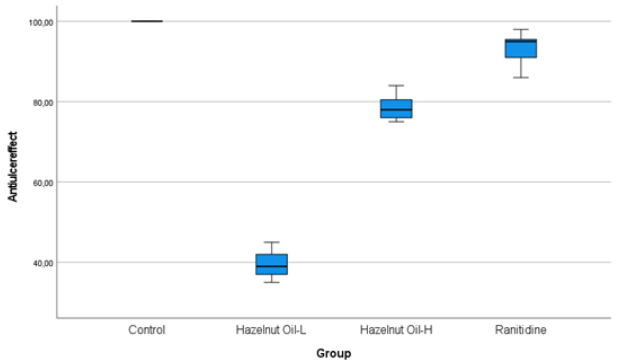

Figure 2. Box-Plot of Inhibition Rate Across Experimental Groups

In contrast, the Ethanol group exhibited extensive ulceration (Median = 19.00, IQR = 17.36–21.23 mm²), consistent with ethanol's known erosive effects (13). The Hazelnut Oil-Low Dose (HO-L), Hazelnut Oil-High Dose (HO-H), and Ranitidine groups demonstrated significantly reduced ulcer areas compared to the Ethanol group ($P < 0.001$ for all). Specifically, HO-L reduced the ulcer area to a median of 15.00 mm² (IQR = 13.25–17.25 mm²), HO-H to 4.00 mm² (IQR = 3.60–5.40 mm²), and Ranitidine to 1.00 mm² (IQR = 1.00–2.20 mm²). The inhibition rates, reflecting the percentage reduction in ulcer area relative to the Ethanol group, were 39.57 ± 3.78% (Median = 39.00%, IQR = 36.00–44.00%) for HO-L, 78.57 ± 3.36% (Median = 78.00%, IQR = 76.00–82.00%) for HO-H, and 93.14 ± 4.41% (Median = 95.00%, IQR = 90.00–98.00%) for Ranitidine (Figure 2). One-way ANOVA confirmed significant differences in ulcer area across groups ($F(4,30) = 154.461$, $P < 0.001$).

Post-hoc Tukey tests indicated that all treatment groups (Control, HO-L, HO-H, Ranitidine) had significantly lower ulcer areas than the Ethanol group ($P < 0.001$). Ranitidine outperformed HO-H ($P = 0.032$), and HO-H outperformed HO-L ($P < 0.001$), suggesting a dose-dependent effect of hazelnut oil. The Control and Ranitidine groups showed no significant difference ($P = 0.458$). For inhibition rates, one-way ANOVA revealed significant differences among treatment groups ($F(2,18) = 357.650$, $P < 0.001$), with post-hoc tests confirming higher inhibition rates for HO-L, HO-H, and Ranitidine compared to Ethanol ($P < 0.001$). Ranitidine's inhibition rate was significantly higher than HO-H ($P < 0.001$), and HO-H's was higher than HO-L ($P < 0.001$).

Histopathological Analysis

Histopathological examination of H&E-stained gastric tissue sections (100x magnification, 100 µm scale bar) revealed marked differences among groups (Table 2, Figures 3 and 4).

Table 1. Ulcer Area and Inhibition Rate Across Experimental Groups

Groups	Treatments	Ulcer area (mm^2)	p	Inhibition (%)	p
1	Control	0.00±0.00	<0.001	100±0.00	<0.001
2	Ethanol	19.00 (17.36–21.23)		0 (0–0)	
3	Hazelnut Oil-L	15.00(13.25–17.25)			
4	Hazelnut Oil-H	4.00 (3.60–5.40)		39.0(36.00–44.00)	
5	Ranitidine	1.00 (1.00–2.20)			

Ulcer area data are presented as median (interquartile range, IQR). Inhibition rate data are presented as mean ± standard deviation (SD) and median (IQR), analysed using one-way ANOVA followed by Tukey's post-hoc test. P-values indicate comparisons with the ethanol group. The control group inhibition rate is not applicable, as no ethanol was administered.

The Control group displayed intact gastric mucosa with standard glandular architecture and no signs of inflammation, oedema, epithelial damage, or haemorrhage (Median = 0, IQR = 0–0 for all parameters). The Ethanol group exhibited severe mucosal damage, characterized by extensive neutrophil infiltration, submucosal edema, epithelial erosion, and multifocal hemorrhage (Median [IQR]: inflammation 2 [1.5–2.5], edema 3 [2.5–3.5], epithelial damage 2 [2–2.5], hemorrhage 3 [2.5–3.5], total score 10 [9–11]). In contrast, the HO-L, HO-H, and Ranitidine groups showed reduced damage. HO-L exhibited mild-to-moderate damage (Median [IQR]: inflammation 0.5 [0–1], oedema 1 [1–1.5], epithelial damage 1 [1–1.5], haemorrhage 1 [0.5–1.5], total score 4 [3.5–5]). HO-H showed minimal damage (Median [IQR]: inflammation 0 [0–0.5], oedema 1 [0.5–1], epithelial damage 0.5 [0–1], haemorrhage 1 [0–1], total score 2.5 [23]).

Ranitidine exhibited the least damage (Median [IQR]: inflammation 0 [0–0.5], oedema 0.5[0–1], epithelial damage 0.5 [0–1], haemorrhage 0.5 [0–1], total score 1.5 [1–2]).

The Kruskal-Wallis test indicated significant differences in total histopathological scores ($H(4) = 27.560$, $P < 0.001$). Bonferroni-corrected Mann-Whitney U tests (adjusted $\alpha = 0.005$) confirmed that Control ($U = 0.000$, $P = 0.001$), HO-L ($U = 0.500$, $P = 0.001$), HO-H ($U = 0.000$, $P = 0.001$), and Ranitidine ($U = 0.000$, $P = 0.001$) groups had significantly lower scores than the Ethanol group. The Control group outperformed HO-L ($U = 0.000$, $P = 0.001$) and HO-H ($U = 3.500$, $P = 0.004$) but was not significantly different from Ranitidine ($U = 10.500$, $P = 0.073$). HO-L had higher scores than Ranitidine ($U = 4.500$, $P = 0.007$), but no significant differences were observed between HO-H and Ranitidine ($U = 14.000$, $P = 0.209$) or HO-L and HO-H ($U = 10.000$, $P = 0.073$).

Table 2. Histopathological Scores Across Experimental Groups

Groups	Treatments	Inflammation	Edema	Epithelial Damage	Hemorrhage	Total Score
1	Control	0	0	0	0	0
2	Ethanol	2 (1.5–2.5)	3 (2.5–3.5)	2 (2–2.5)	3 (2.5–3.5)	10 (9–11)
3	Hazelnut	0.5 (0–1)	1 (1–1.5)	1 (1–1.5)	1 (0.5–1.5)	4 (3.5–5)
4	Hazelnut	0 (0–0.5)	1 (0.5–1)	0.5 (0–1)	1 (0–1)	2.5 (2–3)
5	Ranitidine	0 (0–0.5)	0.5 (0–1)	0.5 (0–1)	0.5 (0–1)	1.5 (1–2)

Histopathological scores (0–3 for inflammation and epithelial damage; 0–4 for oedema and haemorrhage) are presented as median (interquartile range, IQR). Data were analysed using the Kruskal-Wallis test followed by Bonferroni-corrected Mann-Whitney U tests (adjusted $\alpha = 0.05/10 = 0.005$ for 5 groups).

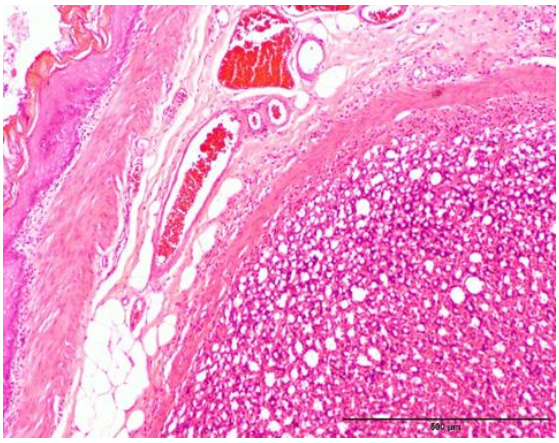

Figure 3. Hazelnut Oil-Low Dose group: Moderate mucosal damage with reduced inflammation, oedema, epithelial erosion, and haemorrhage (Scale bar: 100 µm. Magnification: 100x)

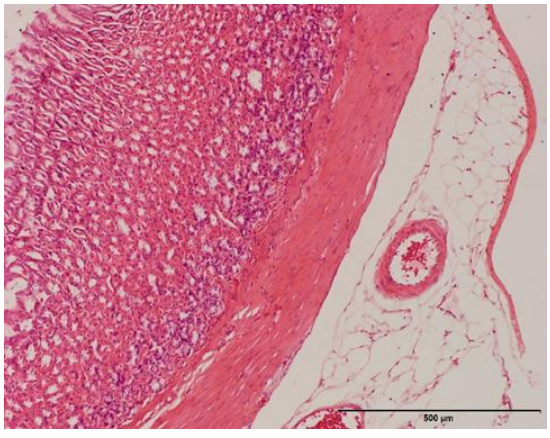

Figure 4. Hazelnut Oil-High Dose group: Minimal mucosal damage with mild inflammation, oedema, epithelial erosion, and haemorrhage (Scale bar: 100 µm. Magnification: 100x)

DISCUSSION

This study provides the first evidence that hazelnut oil (Corylus avellana L.) exerts significant, dose-dependent gastroprotective effects against 75% ethanol-induced gastric mucosal injury in rats, as demonstrated by reduced ulcer areas and histopathological damage. The Ethanol group's extensive ulceration (Median = 19.00 mm²) and severe histopathological scores (Median = 10) confirm the robustness of the model, mirroring ethanol's well-established erosive effects via oxidative stress, inflammation, and epithelial disruption (3). In contrast, the Hazelnut Oil-Low Dose (HO-L, 2.5 mL/kg) and Hazelnut Oil-High Dose (HO-H, 5 mL/kg) groups exhibited significant reductions in ulcer area (15.00 mm² and 4.00 mm², respectively, $P < 0.001$) and histopathological scores (4 and 2.5, respectively, $P < 0.005$), with HO-H approaching the efficacy

of Ranitidine (1.00 mm², 1.5). These findings support the hypothesis that hazelnut oil's bioactive components—oleic acid (~78%) and vitamin E—confer gastroprotective benefits, likely through anti-inflammatory and antioxidant mechanisms (6,7,10,12).

The selection of hazelnut oil doses (2.5 mL/kg and 5 mL/kg) and the 7-day treatment duration followed by a 1-hour waiting period before ethanol administration were based on previous studies investigating plant-based oils for gastrointestinal protection (13). These doses were chosen to align with studies on oils with similar fatty acid profiles, such as apricot kernel oil, which demonstrated gastroprotective effects at comparable doses (13). The lower dose (2.5 mL/kg) was selected to evaluate a minimal effective dose, while the higher dose (5 mL/kg) aimed to maximize the delivery of bioactive components like oleic acid and vitamin E to the gastric mucosa. The 7-day pretreatment period was employed to allow sufficient time for the potential upregulation of mucosal defensive mechanisms, such as mucus production and antioxidant enzyme activity, as reported in prior studies with olive oil and other monounsaturated fatty acid-rich oils (6,14). The 1-hour interval between the final treatment and ethanol administration was chosen to ensure adequate absorption and distribution of hazelnut oil in the gastrointestinal tract, consistent with the pharmacokinetics of dietary lipids in rodent models (13,15)

The dose-dependent effects of hazelnut oil are particularly noteworthy. The HO-H group's 78% inhibition rate (IQR = 76.00–82.00%) significantly outperformed HO-L's 39% ($P < 0.001$), suggesting that higher doses enhance the delivery of protective components to the gastric mucosa. Oleic acid, a monounsaturated fatty acid, is known to stimulate mucus production, which forms a physical barrier against acid and ethanol-induced damage (10,11). It also modulates inflammatory pathways, such as those involving TNF-α and IL-6, which are critical in ethanol-induced injury (9,16). Vitamin E, a potent antioxidant, likely mitigates oxidative stress by neutralizing reactive oxygen species (ROS), which are generated by ethanol metabolism and contribute to mucosal damage (9,12).

These mechanisms align with those observed in other oils rich in oleic acid. For instance, apricot kernel oil (~56% oleic acid) reduced ethanol-induced gastric injury in rats by decreasing inflammation and oxidative stress (13), while olive oil (~70–80% oleic acid) attenuated gastrointestinal inflammation in models of inflammatory bowel disease (15). Hazelnut oil's higher oleic acid content may explain its robust effects, potentially surpassing those of apricot kernel oil. Compared to Ranitidine, a histamine

H2 receptor antagonist that inhibits gastric acid secretion (4), hazelnut oil's efficacy, particularly at 5 mL/kg, was impressive. Ranitidine's 95% inhibition rate and near-normal histopathological scores (Median = 1.5) reflect its established role in ulcer prevention (4). However, the lack of significant difference between HO-H and Ranitidine in histopathological scores (P = 0.209) suggests that hazelnut oil may offer comparable protection through distinct mechanisms, such as mucus enhancement and antioxidant activity, rather than acid suppression. This is particularly relevant given the side effects of long-term use of H2 receptor antagonists and PPIs, including nutrient deficiencies and an increased risk of infection (4,5). Hazelnut oil, as a natural, food-grade product, may provide a safer alternative for patients seeking to avoid pharmacological interventions. The gastroprotective effects of hazelnut oil observed in this study likely stem from the synergistic actions of its bioactive components, particularly oleic acid and vitamin E, which target multiple pathways involved in ethanol-induced gastric injury. Oleic acid enhances mucus production, which strengthens the gastric mucosal barrier, and downregulates pro-inflammatory cytokines such as TNF-α and IL-6, as demonstrated in models of gastrointestinal inflammation (8,10,11). Vitamin E, a lipid-soluble antioxidant, scavenges reactive oxygen species (ROS) generated by ethanol metabolism, thereby reducing oxidative stress and lipid peroxidation in gastric tissues (9,12). Additionally, hazelnut oil's phytosterols and polyphenols may contribute to its anti-inflammatory and cytoprotective effects, as reported for similar plant-based oils (6,14). These multifaceted mechanisms distinguish hazelnut oil from pharmacological agents like Ranitidine, which primarily act via acid suppression. The comparable efficacy of high-dose hazelnut oil (5 mL/kg) to Ranitidine in histopathological outcomes suggests its potential as a complementary or alternative therapy, particularly for patients with concerns about the long-term side effects of proton pump inhibitors or H2 receptor antagonists, such as nutrient deficiencies or increased infection risk (4,5). The food-grade nature of hazelnut oil further supports its potential for dietary incorporation in populations at risk of gastric mucosal injury, such as those with chronic alcohol consumption or NSAID use.

The strengths of this study include the use of a well-established and reproducible ethanol-induced gastric injury model (3), the inclusion of appropriate control and comparison groups (including a standard antiulcer drug), and comprehensive outcome assessment through both macroscopic and blinded histopathological evaluations. Moreover, the dose-response design

enabled the assessment of efficacy at two clinically relevant concentrations of hazelnut oil, highlighting the enhanced protective effects at higher doses.

However, the study has several limitations. First, only two doses were tested, which limited the ability to construct a complete dose-response curve. Second, the investigation was restricted to an acute injury model; chronic ulceration models (e.g., NSAID- or H. pylori-induced) may offer additional insights into long-term mucosal protection. Third, no molecular or biochemical analyses (e.g., malondialdehyde, glutathione, TNF-α, IL-6) were performed to confirm oxidative stress or inflammatory pathways, which limits mechanistic interpretation. Additionally, although the pathologist was blinded, the randomisation methodology and allocation concealment were not explicitly implemented, which could introduce bias (16,17).

Future studies should explore the protective mechanisms of hazelnut oil in more detail by incorporating biochemical assays and gene expression analyses. Comparative studies with other plant-based oils (e.g., olive, sesame, and apricot kernel) could elucidate relative efficacy and synergistic effects. Chronic administration models, particularly those involving NSAIDs or Helicobacter pylori, may help to determine long-term protective potential. Ultimately, clinical trials evaluating the safety, tolerability, and efficacy of dietary hazelnut oil in human populations are warranted, particularly in individuals at risk of gastric mucosal injury.

CONCLUSION

Hazelnut oil demonstrated an apparent, dose-dependent gastroprotective effect against ethanol-induced gastric mucosal injury in rats. At higher doses, its efficacy approached that of Ranitidine, with significant improvements observed in both macroscopic ulcer area and histopathological damage scores. These findings highlight the potential of hazelnut oil as a natural, well-tolerated alternative to conventional pharmacological agents for gastric mucosal protection. Further studies in chronic models and clinical settings are needed to validate its long-term safety and therapeutic value.

Ethics Committee Approval: Prior to the study, the approval of Ordu University Clinical Research Ethics Committee' numbered ODÜ-HADYEK-2020/13 was obtained.

Author Contributions: Conception - Çağrı Akalın, Özlem Özdemir, Mürüvvet Akçay Çelik; Design - Çağrı Akalın, Onur Olgaç Karagülle; Supervision - Tevfik Noyan; Data Collection and/or Processing - Çağrı Akalın, Onur Olgaç Karagülle; Analysis and/or Interpretation - Özlem Özdemir, Tevfik Noyan; Literature

Search - Mürüvvet Akçay Çelik, Özlem Özdemir; Writing - Çağrı Akalın, Onur Olgaç Karagülle; Critical Review - Özlem Özdemir, Tevfik Noyan

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could affect the work reported in this article.

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Ethical Statement: The authors declare that they comply with research and publication ethics.

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