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The Protective Effects of Idebenone and Chrysin on Ethanol-Induced Gastric Ulcer Model in Rats

Sıçanlarda Etanol ile İndüklenen Gastrik Ülser Modelinde Idebenon ve Krisinin Koruyucu Etkileri

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ABSTRACT

In this study, the protective effects of idebenone and chrysin against ethanol-induced gastric ulcers in rats were investigated. Twenty-eight *Sprague-Dawley* male rats were categorized into four groups: a control group receiving 1 ml saline, an ethanol (ET) group receiving ET (5 ml/kg) to induce gastric ulcers, and two treatment groups, one receiving ET followed by idebenone (200 mg/kg) and the other receiving ET followed by chrysin (100 mg/kg). Treatments were administered orally via gavage. Histopathological examinations and immunohistochemical analyses focusing on somatostatin and aquaporin-1 levels were performed to evaluate gastric mucosal damage and the protective mechanism of the treatments. In histopathological examinations, severe degenerative and necrotic changes were observed in the ET treated group. The results showed that gastric mucosal damage was significantly reduced in the treatment groups compared to the ET group and there was a significant reduction in the severity of necrotic lesions. Quantitative analysis revealed a significant increase in somatostatin and aquaporin-1 expression in the treatment groups ($p < .05$), indicating increased gastric mucosal defense. Idebenone and chrysin were found to significantly mitigate histopathological damage and increase the expression of somatostatin and aquaporin-1 in ET-induced gastric ulcers. The reduction in necrotic lesions and enhancement of gastric mucosal defense mechanisms suggest that idebenone and chrysin may offer therapeutic potential for the prevention and treatment of gastric ulcers.

Keywords: Chrysin, Ethyl alcohol, Gastric ulcer, Idebenone.

ÖZ

Bu çalışmada, sıçanlarda etanol ile indüklenen gastrik ülsere karşı idebenon ve krisinin koruyucu etkileri araştırıldı. Yirmi sekiz *Sprague-Dawley* erkek sıçan dört gruba ayrılmıştır: 1 ml serum fizyolojik alan kontrol grubu, gastrik ülser indüklemek için etanol (ET) (5 ml/kg) alan ET grubu ve iki tedavi grubu; biri ET'yi takiben idebenon (200 mg/kg), diğeri ET'yi takiben krisin (100 mg/kg) alan gruplar. Tedaviler oral gavaj yoluyla uygulandı. Gastrik mukozal hasarı ve tedavilerin koruyucu mekanizmasını değerlendirmek için, somatostatin ve aquaporin-1 düzeylerine odaklanan histopatolojik incelemeler ve immünohistokimyasal analizler gerçekleştirildi. Histopatolojik incelemelerde, ET ile muamele edilen grupta şiddetli dejeneratif ve nekrotik değişiklikler gözlendi. Sonuçlar, tedavi gruplarında gastrik mukozal hasarın ET grubuna kıyasla önemli ölçüde azaldığını ve nekrotik lezyonların şiddetinde anlamlı bir azalma olduğunu gösterdi. Kantitatif analiz, tedavi gruplarında somatostatin ve aquaporin-1 ekspresyonunda anlamlı bir artış olduğunu ortaya koydu ($p < .05$), bu da artmış gastrik mukozal savunmayı göstermektedir. İdebenon ve krisinin, ET ile indüklenen gastrik ülserlerde histopatolojik hasarı önemli ölçüde azalttığı ve somatostatin ile aquaporin-1 ekspresyonunu artırdığı bulundu. Nekrotik lezyonlardaki azalma ve gastrik mukozal savunma mekanizmalarının güçlenmesi, idebenon ve krisinin gastrik ülserlerin önlenmesi ve tedavisi için terapötik potansiyel sunabileceğini düşündürmektedir.

Anahtar kelimeler: Etil alkol, Gastrik ülser, İdebenon, Krisin.

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Introduction

Peptic ulcer disease is a substantial global health concern, characterized by lesions due to the disruption of the gastric mucosa (Yaghoobi & Armstrong, 2022). Despite various treatment options, current medications often show limited efficacy and are associated with adverse side effects, prompting growing interest in alternative therapeutic approaches (Serafim et al., 2020). This disorder, particularly among the younger population, affects millions worldwide, underscoring the need for more effective and safer treatments (Kaya, 2022).

The pathogenesis of peptic ulcers is closely linked to the breakdown of mucosal integrity, compromised defense mechanisms, and the influence of several aggressive factors (Küçükler et al., 2022). Ethanol (ET) consumption is a notable risk factor, inducing necrotic lesions in the gastric mucosa due to its direct toxic effects. Ethanol (ET) reduces bicarbonate secretion, inhibits mucus production, and causes membrane damage, leading to increased ion permeability. Moreover, the intracellular accumulation of Ca2+ plays a crucial role in mucosal damage, resulting in cell death and sloughing of the surface epithelium, which can quickly lead to hemorrhagic erosions and ulcer formation (Zhou et al., 2020).

Idebenone (IDE), a synthetic analogue of coenzyme Q10 (CoQ10), contains a benzoquinone ring and is recognized for its potent antioxidant properties. It inhibits lipid peroxidation and protects cells from oxidative harm (Suárez-Rivero et al., 2021). The benzoquinone ring in idebenone participates in redox reactions, intercepting reactive oxygen species (ROS) such as superoxide and peroxyl radicals, helping maintain redox balance (Cores et al., 2023). Research has demonstrated that idebenone protects against oxidative stress and reduces levels of various pro-inflammatory cytokines (Akpinar et al., 2022).

Chrysin (CHR), a natural flavonoid, enhances antioxidant defenses and facilitates the removal of free radicals (Naz et al., 2019). It also decreases lipid peroxidation levels and exhibits anti-inflammatory effects by inhibiting cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and nitric oxide (NO) in both in vitro and in vivo settings (Baykalir et al., 2020). (Şimşek et al., 2023).

Given these considerations, this study aimed to investigate and evaluate the gastroprotective effects of idebenone and chrysin on ethanol-induced gastric ulcers in rats. The research focuses on assessing histopathological changes, somatostatin, and aquaporin-1 levels in the gastric mucosa, and quantifying the therapeutic efficacy of these compounds in alleviating gastric mucosal damage.

Methods

Materials

Ethical approval was obtained from the Atatürk University Animal Experiments Local Ethics Committee under the decision dated February 26, 2024, and approval number 2024/43. Twenty-eight male *Sprague-Dawley* rats, weighing 250 ± 25 g and aged three months, were procured from the Atatürk University Medical Experimental Application and Research Center Directorate. The animals were housed under standard care conditions (room temperature: 20 ± 2°C) with a 12-hour light/12-hour dark cycle and were fed ad libitum. The rats were randomized into four groups:

Control group (n=7): This group consisted of healthy rats. These rats were orally administered 1 ml of saline solution.

Ethanol (ET) group (n=7): Rats in this group were administered absolute ethanol (5 ml/kg) by gavage following a 24-hour fasting period (İpek et al., 2022).

Ethanol + Idebenone (ET+IDE) group (n=7): Following a 24-hour fasting period, rats in this group were administered absolute ethanol (5 ml/kg) by gavage, followed by 200 mg/kg idebenone administered by gavage 30 minutes later (Kaya, 2022).

Ethanol + Chrysin (ET+CHR) group (n=7): Following a 24-hour fasting period, rats in this group were administered absolute ethanol (5 ml/kg) by gavage, followed by 100 mg/kg chrysin administered 30 minutes later (Küçükler et al., 2022).

Following the conclusion of the experiment, rats were deeply sedated using sevoflurane (Sevorane®, Abbott Lab. Istanbul, Türkiye), cervical dislocation was then performed, and stomach tissue samples were collected. Some of the obtained stomach tissues were stored at -80°C for ELISA.

Stomach tissue specimens were immersed in a 10% buffered neutral formalin solution, and following standard histological processes, they were embedded in paraffin wax.

Methods

Histopathological Examination

Stomach tissue samples obtained from the rats' necropsies were fixed in 10% neutral buffered formalin solution. The tissues were then processed through routine alcohol-xylene sequences and embedded in paraffin blocks. Sections of 5 µm thickness were cut from the blocks and stained with hematoxylin and eosin (H&E). The slides were evaluated under a light microscope for necrotic and degenerative changes on a semi-quantitative scale: none (normal mucosal surface, -), mild (20%< of the mucosal surface, +), moderate (20- 40% of the mucosal surface, ++), and severe (40%> of the mucosal surface, +++) (Gezer & Sari, 2023).

Immunohistochemical Examination

Sections of 4 µm thickness, obtained on poly-L-lysine slides, underwent processing through xylene and alcohol series, followed by PBS washing. Subsequently, endogenous peroxidase activity was quenched by incubating in 3% H_2O_2 for 10 minutes. Antigen retrieval was performed with antigen retrieval solution at 500 watts for 2x5 minutes to expose the tissue antigens. Subsequently, the sections were incubated overnight with primary antibodies against Somatostatin (Catalog no: ab183855, Abcam) and Aquaporin-1 (Catalog no: ab9566, Abcam) at a dilution of 1/200. The Large Volume Detection System: anti-Polyvalent, HRP (Catalog no: TP-125-HL, Thermofischer) was administered as instructed by the manufacturer, serving as the secondary antibody. DAB (3,3'-Diaminobenzidine) was employed as the chromogen. After counterstaining with Mayer's Hematoxylin and mounting with Entellan, the slides were examined under a light microscope. Immunoreactivity was scored as none (0), mild (1), moderate (2), and severe (3) (Gezer et al., 2023).

Statistical Analysis

The data obtained were analyzed using the SPSS 20.00 software. Differences between groups were assessed utilizing the Kruskal-Wallis test, and the groups showing difference were pinpointed using the Mann-Whitney U test (p< .05).

Results

Histopathological Findings

Statistically notable variances were noted among the groups in histopathological examinations (Table 1).

Table 1. Comparison of groups in terms of gastric mucosal injuries.
Tablo 1. Gastrik mukozal yaralanmalar açısından grupların karşılaştırılması.

Groups	Gastric Mucosa Injury
Control	0.16 ±0.41[a]
ET	2.84 ±0.41[c]
ET+IDE	0.39 ±0.51[b]
ET+CHR	0.39 ±0.51[b]

ET: ethanol, IDE: idebenone, CHR: chrysin; Values are expressed as mean ± SD; Different superscript letters indicate significant differences between groups, a, b, c Indicates a difference between groups (p< .05).

The control group displayed a normal histological appearance. In the ET group, severe levels of degenerative and necrotic changes were observed in the mucosa epithelium. In contrast, groups administered with idebenone and chrysin alongside ET showed only mild levels of degenerative and necrotic changes (Figure 1).

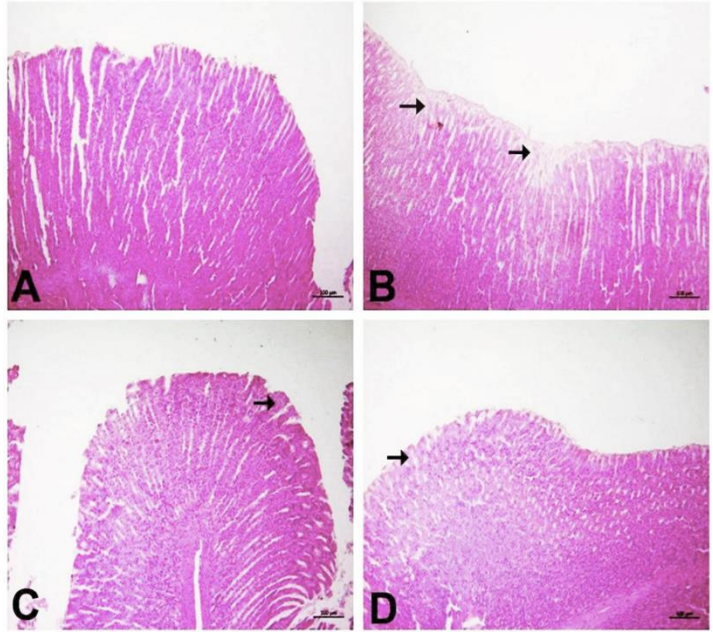

Figure 1. Histological changes in rat stomach. A) Control group; in normal histologic appearance, B) ET group; severe degenerative areas in the mucosal epithelium (arrows), C) ET+İDE group; mild degenerative areas in the mucosal epithelium (arrows), D) ET+CHR group; mild degenerative areas in the mucosal epithelium (arrows). Bar: X100, H&E.

Şekil 1. Sıçan midesinde histolojik değişiklikler. A) Kontrol grubu; normal histolojik görünümde, B) ET grubu; mukozal epitelde şiddetli dejeneratif alanlar (oklar), C) ET+İDE grubu; mukozal epitelde hafif dejeneratif alanlar (oklar), D) ET+CHR grubu; mukozal epitelde hafif dejeneratif alanlar (oklar). Bar: X100, H&E.

Immunohistochemical Findings

Immunohistochemical analyses revealed statistically noteworthy variances among the groups (Table 2, $p < .05$).

Table 2. Immunohistochemical findings of Somatostatin and Aquaporin-1.

Tablo 2. Somatostatin ve Aquaporin-1'in immünohistokimyasal bulguları.

Groups	Somatostatin	Aquaporin-1
Control	2.84 ±0.40[a]	2.01 ±0.00[a]
ET	2.01 ±0.00[b]	1.18 ±0.41[b]
ET+IDE	2.68 ±0.51[a]	2.17 ±0.40[a]
ET+CHR	2.82 ±0.40[a]	1.84 ±0.41[a]

ET: ethanol, IDE: idebenone, CHR: chrysin; Values are expressed as mean ± SD; Different superscript letters indicate significant differences between groups, a, b Indicates a difference between groups ($p< .05$).

In immunohistochemical staining for somatostatin, immunopositivity was severe in the control, ET+IDE, and ET+CHR groups, while it was moderate in the group treated with ET alone. Aquaporin immunopositivity showed a similar pattern to somatostatin, with medium levels in the control, ET+IDE, and ET+CHR groups, and mild levels in the ET group (Figures 2, 3).

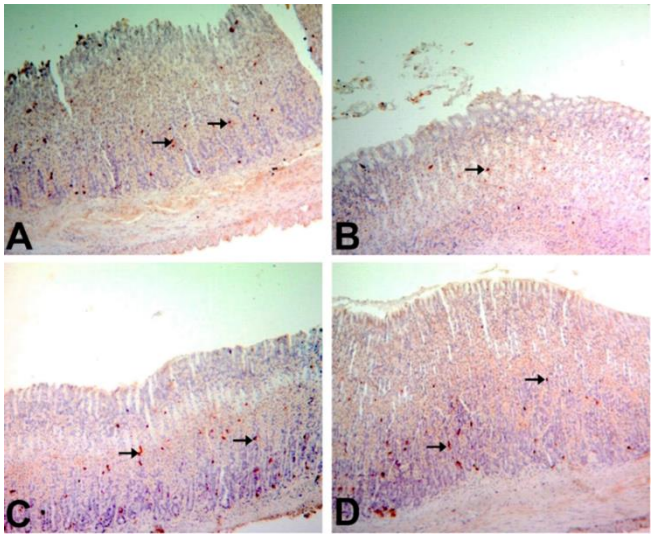

Figure 2. Immunohistochemical findings of Somatostatin. A) Control group; severe level, B) ET group; mild level, C) ET+İDE group; severe level, D) ET+CHR group; severe level Somatostatin immunopositivity (arrows). Bar: X100, IHC.

Şekil 2. Somatostatin'in immünohistokimyasal bulguları. A) Kontrol grubu; şiddetli seviye, B) ET grubu; hafif seviye, C) ET+İDE grubu; şiddetli seviye, D) ET+CHR grubu; şiddetli düzeyde Somatostatin immünopozitifliği (oklar). Bar: X100, IHC.

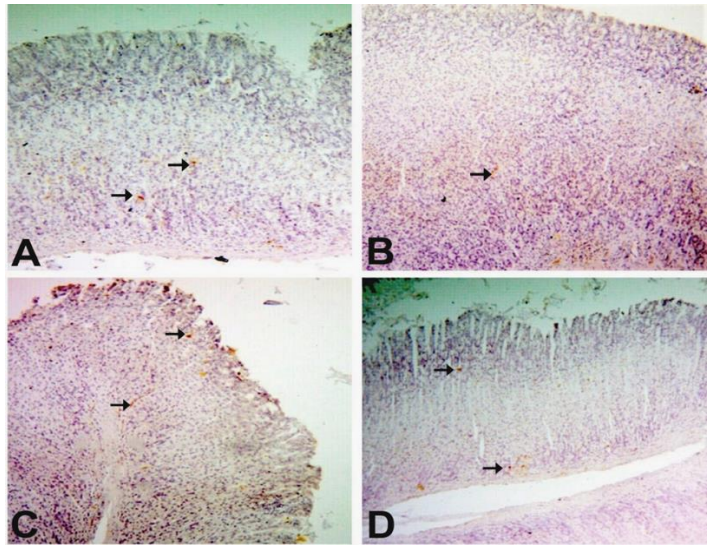

Figure 3. Immunohistochemical findings of Aquaporin-1. A) Control group; moderate level, B) ET group; mild level, C) ET+IDE group; mild level, D) ET+CHR group; mild level, Aquaporin immunopositivity (arrows). Bar: X100, IHC.

Şekil 3. Aquaporin'in immünohistokimyasal bulguları. A) Kontrol grubu; orta seviye, B) ET grubu; hafif seviye, C) ET+IDE grubu; hafif seviye, D) ET+CHR grubu; hafif seviye, Aquaporin immünopozitifliği (oklar). Bar: X100, IHC.

Discussion

Peptic ulcer disease, a significant global health challenge marked by gastric mucosal lesions due to compromised mucosal integrity and weakened defense mechanisms against aggressive factors, impacts 5-10% of the global population, particularly affecting the younger demographic (Toktay & Selli, 2022; Yaghoobi & Armstrong, 2022). In this study, we explored the protective effects of idebenon and chrysin against ET-induced gastric ulcers, focusing on histological changes, somatostatin and aquaporin-1 levels, and the underlying mechanisms of action.

The pathogenesis of ethanol-induced gastric ulcers involves direct toxic effects on the gastric mucosa, leading to necrosis and disruption of the epithelial integrity (Kim et

al., 2011). Our histopathological results corroborate these mechanisms, as the ET group exhibited severe degenerative and necrotic changes in the gastric mucosa. Remarkably, our findings demonstrated that treatment with idebenon and chrysin significantly mitigated these histological alterations.

Idebenone, a synthetic analog of coenzyme Q10, is known for its potent antioxidant properties. It inhibits lipid peroxidation and protects against oxidative damage by reducing the formation of ROS (Shastri et al., 2020b). Idebenone's benzoquinone ring participates in redox reactions, intercepting ROS such as superoxide and peroxyl radicals, thus maintaining redox balance. This aligns with previous findings by Shastri et al., who demonstrated idebenone's effectiveness in reducing oxidative stress markers and enhancing intestinal barrier proteins in models of ulcerative colitis (Shastri et al., 2020a; Shastri, et al., 2020b). Shastri et al. showed that idebenone improves disease markers such as body weight loss, disease activity index, and histopathological scores through the modulation of oxidative stress markers and enhancement of intestinal barrier proteins (Shastri et al., 2020b). Similarly, Inatsu et al. highlighted idebenone's capacity to inhibit *Helicobacter pylori (H. pylori)* growth by impeding respiration and reducing cellular ATP levels, indicating a unique dual-action approach that extends beyond conventional antioxidative therapy (Inatsu et al., 2006). This mechanism suggests a novel pathway for managing *H. pylori*-associated ulcers, indicating that idebenone may offer both antioxidative and antimicrobial benefits.

Chrysin, a natural flavonoid, exhibits anti-inflammatory and antioxidative effects that play a crucial role in minimizing tissue damage and facilitating mucosal healing. Several studies have validated the gastroprotective effects of chrysin. Küçükler et al. demonstrated chrysin's ability to modulate oxidative stress, inflammation, and apoptosis markers in indomethacin-induced gastric ulcers (Küçükler et al., 2022). Their study showed increased antioxidant enzyme activities and decreased pro-inflammatory cytokines, underscoring chrysin's efficacy in mitigating gastric mucosal injury through antioxidative and anti-inflammatory pathways. Fagundes et al. further emphasized chrysin's role in inhibiting inflammatory remodeling and promoting mucosal healing in different gastric ulcer models (Fagundes et al., 2020). Researchers' findings highlight chrysin's comprehensive protective mechanism, mirroring our findings of enhanced mucosal defense and reduced inflammation. George et al. presented evidence of chrysin's protective effects against indomethacin-induced gastric ulcers, focusing on its antioxidative, anti-inflammatory, and angiogenic activities (George et al., 2018). The activation of anti-inflammatory macrophages and promotion of angiogenesis by chrysin suggest an integrated approach to ulcer healing, which complements our study's emphasis on chrysin's capacity to improve mucosal integrity and reduce inflammatory and oxidative stress.

Our study identified an upregulation of somatostatin and aquaporin-1 expression in the groups treated with idebenone and chrysin. Gastric delta cells, or D-cells, play a pivotal role in gastric mucosal defense by secreting somatostatin, a key inhibitor of acid secretion and promoter of mucosal blood flow, thus serving as the principal paracrine agent in suppressing gastric acid production (Kim et al., 2023). Somatostatin regulates gastric acid secretion by inhibiting the release of histamine from enterochromaffin-like cells, gastrin from G cells, and directly inhibiting parietal cells. The elevation of somatostatin levels suggests that idebenone and/or chrysin may enhance these natural defense mechanisms, providing a protective buffer against ethanol-induced gastric acid damage (Bogdanov, 2012; Kaya, 2022). This observation aligns with previous research by George et al., who highlighted the role of somatostatin in maintaining gastric mucosal integrity under stress conditions (Mazzoni et al., 2021; Oncel & Basson, 2022). In our study, the increase in somatostatin levels within the treatment groups indicates a potential mechanism through which idebenone and chrysin exert their protective effects. By enhancing somatostatin secretion, these compounds may contribute to the regulation of gastric acid secretion and mucosal protection.

Aquaporin-1 is a water channel protein involved in maintaining cellular water homeostasis and has been implicated in mucosal protection and repair. Aquaporin-1 facilitates water movement through the gastric epithelium, essential for preserving a moist and protective mucosal barrier (Liao et al., 2021; Ye et al., 2023). The increased expression of aquaporin-1 in the treatment groups indicates improved mucosal hydration and integrity, crucial components of the mucosal defense system against ethanol-induced damage. This enhancement of barrier function likely plays a significant role in the observed protective effects, further underscoring the multifaceted mechanism of action of these compounds. Aquaporin-1 also plays a role in fat digestion, saliva production, and is

linked to the development of esophageal and gastric cancers. The increased expression of aquaporin-1 suggests that idebenone and chrysin contribute to the maintenance of mucosal hydration, a vital component of the mucosal defense system against ethanol-induced damage. The role of aquaporins in mucosal integrity is further supported by studies such as those by Hardin et al., which showed that the expression of AQP4 and AQP8 decreases in a mice model of dextran sodium sulfate-induced colitis. Similarly, human studies revealed that the expressions of AQP7 and AQP8 significantly decrease in the colon of patients with moderate to severe ulcerative colitis, moderate to severe Crohn's disease, and infectious colitis (Hardin et al., 2004). These findings suggest that aquaporins are crucial in maintaining mucosal integrity in various gastrointestinal conditions, reinforcing the importance of our observations of increased aquaporin-1 expression in enhancing gastric mucosal defense against ethanol-induced damage. Additionally, Bodis et al. conducted studies on aquaporins in chemically induced gastric mucosal lesions. They found that in ethanol-treated rat stomachs, the levels of AQP1 and AQP4 initially increased, contributing to the formation of gastric mucosal edema, followed by a decrease over time (Bodis et al., 2001). This suggests that aquaporins play a significant role in the initial response to mucosal injury and the subsequent maintenance of mucosal integrity. Our findings of increased aquaporin-1 expression in the treatment groups align with these results, indicating that idebenone and chrysin may enhance mucosal hydration and barrier function, thus protecting against ethanol-induced gastric damage.

Comparatively, our findings contribute to the existing literature by further elucidating the gastroprotective mechanisms of idebenon and chrysin in ET-induced gastric ulcer models. The significant reduction in histological damage, coupled with the modulation of key markers such as somatostatin and aquaporin-1, underscores the therapeutic potential of these compounds. Our study aligns with previous research in demonstrating the importance of antioxidative and anti-inflammatory pathways in ulcer protection and highlights additional mechanisms such as enhanced mucosal defense and barrier function.

Conclusion

In conclusion, our study contributes to the comprehension of the gastroprotective effects of idebenon and chrysin against ET-induced gastric ulcers. By demonstrating the ability of these compounds to mitigate histological damage and enhance the expression of somatostatin and aquaporin-1, we provided evidence of their therapeutic potential. Ultimately, while idebenon and chrysin have demonstrated potential as alternative treatments for gastric ulcers, further detailed research is required. This includes investigations into their long-term effects, optimal dosages, and possible side effects. The promising findings suggest that these compounds could offer new avenues for ulcer therapy, yet the need for more comprehensive studies remains to fully establish their therapeutic utility and safety profile in the treatment of gastric ulcers.

Ethics Committee Approval: Ethics committee approval was received for this study from the ''Local Ethics Committee of Atatürk University University Animal Experiments'' (Protocol date: 26.02.2024-Protocol Number: 2024/43).

Author Contributions: AG, ASM, GB and HÜ experiment design, experiment application, samples collection. AG, ASM and GB histopathological and immunohistochemical, investigation. All the authors contributed to the writing and editing, and they read and approved the manuscript.

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