Original Article

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Effects of *Momordica Charantia* on Gastritis

Momordica Charantia'nın Gastrit Üzerine Etkisi

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ABSTRACT

Objective: Gastritis is a significant global health concern caused by various factors and associated with considerable morbidity if not properly managed. Oxidative stress and proinflammatory cytokines are known to play critical roles in gastric mucosal injury and disease progression. Although *Momordica charantia (M. charantia)* is recognized for its antioxidant, anti-inflammatory, and gastroprotective properties, its therapeutic role in experimental gastritis models has not been comprehensively investigated. This study aimed to evaluate the efficacy of appropriately formulated *M. charantia* in ethanol-induced gastritis in rats, using detailed biochemical and histopathological assessments. **Methods:** Experimental gastritis was induced in male Sprague-Dawley rats via intragastric administration of 80% ethanol (5 mL/kg). Rats were randomized into control and treatment groups receiving *M. charantia* extract, proton pump inhibitors (PPI), or a multi-herbal capsule compound for 14 days. Biochemical analyses measured total antioxidant status, total oxidant status, oxidative stress index, and proinflammatory cytokines [interleukin (IL)-1β, IL-6, tumor necrosis factor-α, transforming growth factor-β] in serum and gastric tissues. Histopathological examinations assessed mucosal damage, inflammatory cell infiltration, ulceration, and the presence of *Helicobacter pylori*. **Results:** *M. charantia*-treated rats demonstrated significantly reduced oxidative stress markers and lower levels of inflammatory cytokines compared to the ethanol-only group ($p<0.05$). Histopathological analyses revealed reduced mucosal damage, less edema, and decreased inflammatory infiltration in the *M. charantia* group. The therapeutic efficacy of *M. charantia* was comparable to

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Amaç: Gastrit, multifaktöriyel etiyolojisi ve tedavi edilmediğinde yol açtığı ciddi komplikasyonlarla, dünya genelinde önemli bir sağlık sorunu olmaya devam etmektedir. Son yıllarda oksidatif stresin ve proenflamatuvar sitokinlerin, gastrik mukoza bütünlüğünün bozulmasında ve hastalığın ilerleyişinde merkezi roller üstlendiği gösterilmiştir. *Momordica charantia (M. charantia)*, antioksidan, anti-enflamatuvar ve gastroprotektif özellikleriyle dikkat çekmektedir. Ancak, bu bitkinin deneysel gastrit modellerindeki terapötik etkinliği, detaylı biçimde araştırılmamıştır. Yaptığımız bu çalışmada, uygun şekilde formüle edilmiş *M. charantia*'nın etanol ile indüklenen rat gastriti üzerindeki etkinliğini, detaylı biyokimyasal ve histopatolojik değerlendirmelerle incelemeyi amaçlamıştır. **Yöntemler:** Deneysel gastrit, erkek Sprague-Dawley ratlarına intragastrik yolla %80 etanol (5 mL/kg) uygulanarak indüklenmiştir. Ratlar, kontrol ve tedavi gruplarına rastgele dağıtılmış ve 14 gün boyunca *M. charantia* ekstresi, proton pompa inhibitörleri (PPI) veya çoklu bitkisel kapsül bileşimi ile tedavi edilmiştir. Biyokimyasal analizlerde serum ve gastrik dokularda toplam antioksidan düzeyi, toplam oksidan düzeyi, oksidatif stres indeksi ve proenflamatuvar sitokinler [interlökin (IL)-1β, IL-6, tümör nekroz faktörü-α, transforme edici büyüme faktörü-β] ölçülmüştür. Histopatolojik incelemelerde mukozal hasar, enflamatuvar hücre infiltrasyonu, ülserasyon ve Helicobacter pylori varlığı değerlendirilmiştir. **Bulgular:** *M. charantia* ile tedavi edilen ratlarda, yalnızca etanol uygulanan grupla karşılaştırıldığında, oksidatif stres belirteçleri ve enflamatuvar sitokin düzeyleri anlamlı derecede düşük bulunmuştur ($p<0,05$). Histopatolojik analizlerde *M. charantia* grubunda mukozal hasarın, ödemin ve enflamatuvar

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ABSTRACT

PPI in most histological outcomes, although prevention of intestinal metaplasia was less pronounced in groups without PPI treatment. **Conclusion:** This study indicates that *M. charantia* effectively mitigates gastric mucosal injury by enhancing mucosal defenses and reducing oxidative stress and inflammation. To our knowledge, such detailed evaluation of *M. charantia* in gastritis has not been previously reported, highlighting the novelty of these findings. Phytotherapeutic agents like *M. charantia* may offer safe and effective adjuncts or alternatives to standard therapies, contributing to improved management of gastritis and gastric ulcers.

Keywords: Gastritis, *Momordica charantia*, ethanol, oxidative stress, rat model

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infiltrasyonun azaldığı gözlenmiştir. *M. charantia*'nın terapötik etkinliği, histolojik parametrelerin çoğunda PPI ile karşılaştırılabilir bulunmuş, ancak intestinal metaplazi önlenmesi, PPI uygulanmayan gruplarda daha az belirgin olmuştur. **Sonuç:** Yapılan bu çalışma, *M. charantia*'nın gastrik mukoza hasarını azaltmada, mukozal savunmayı güçlendirerek ve oksidatif stres ile enflamasyonu düşürerek etkili olduğunu göstermektedir. Bilindiği kadarı ile gastritte *M. charantia*'nın detaylı değerlendirmesi literatürde daha önce raporlanmamıştır ve bulguların değerini ortaya koymaktadır. *M. charantia* gibi fitoterapötik ajanlar, gastrit ve gastrik ülserlerin tedavisinde standart tedavilere güvenli ve etkili bir yardımcı veya alternatif seçenek sunabilir ve hastalık yönetimine katkı sağlayabiliceği düşünülmektedir.

Anahtar Kelimeler: Gastrit, *Momordica charantia*, ethanol, oksidatif stress, sıçan modeli

Introduction

Gastritis is a chronic, global health issue associated with various etiologies, leading to serious complications in the long term. It can develop due to various etiologies and, if left untreated, can be associated with serious long-term complications (1). Based on the pathology and course of the disease, different classification definitions exist, but it is commonly classified as acute and chronic gastritis. Acute gastritis is typically triggered by factors such as irritating foods, medications, chemical corrosive substances, bacterial infections, and stress reactions. On the other hand, chronic gastritis has a much more complex etiology and mechanisms and is often multifactorial (2). The gastric mucosa is remarkably resistant to self-digestion by hydrochloric acid and pepsin due to protective barrier mechanisms; however, disruption of these defenses can lead to gastritis and ulcer formation. Some important elements of gastric barrier mechanisms are listed in Table 1. When this defense mechanism is compromised, gastritis and gastric ulcer formation occur (3).

Among the principal factors contributing to gastric mucosal damage are reactive oxygen species (ROS) and proinflammatory cytokines, which play pivotal roles in the initiation and progression of gastritis. Excessive ROS production, triggered by infections such as *Helicobacter pylori* (*H. pylori)* or various stressors, can overwhelm endogenous antioxidant systems, leading to lipid peroxidation, protein oxidation, and DNA damage within gastric epithelial cells. Elevated levels of ROS, coupled with the release of inflammatory cytokines—including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β1—sustain chronic inflammation and disrupt mucosal integrity, thereby increasing susceptibility to further injury and contributing to disease progression and potential neoplastic transformations (4-6). Despite the availability of pharmacological treatments, the high rates of recurrence and adverse effects associated with long-term conventional therapy highlight the urgent need for alternative therapeutic strategies.

Table 1. Factors associated with gastric barrier function and cell protection (3)

Components	Mediators
Mucosal barrier	Prostaglandins
Bicarbonate secretion	Nitric oxide
Epithelial barrier Hydrophobic phospholipids Tight junctions Repair	Epidermal growth factor Calcitonin gene-related peptide Hepatocyte growth factor Histamine gastrin-releasing peptide
Microcirculation (reactive hyperemia)	
Afferent sensory neurons	

In recent years, phytotherapeutic agents derived from medicinal plants have attracted considerable interest as potential alternatives for managing gastritis due to their natural origin, lower toxicity profiles, and diverse bioactive compounds. *Momordica charantia (M. charantia)*, widely used in traditional medicine systems, is known for its antioxidant, anti-inflammatory, antidiabetic, and gastroprotective properties. Phytochemical analyses have revealed that *M. charantia* contains bioactive compounds such as flavonoids, triterpenes, and saponins, which exhibit significant free radical scavenging activity and modulate inflammatory pathways (7). *M. charantia* has attracted considerable scientific interest due to its diverse pharmacological properties, including immunostimulatory, anti-inflammatory, antioxidant, cardioprotective, and hypoglycemic effects. Previous studies have demonstrated that *M. charantia* effectively scavenges hydroxyl radicals and superoxide anions, contributing to its significant antioxidant activity. Furthermore, it has been shown to inhibit proinflammatory cytokines such as TNF-α and IL-6, reduce intracellular oxidative stress, enhance endogenous antioxidant enzyme activity, and promote mucosal healing, thereby exhibiting potential therapeutic benefits in various inflammatory and oxidative stress-related conditions.

These properties suggest that *M. charantia* may offer protective effects against gastric mucosal injury by attenuating oxidative stress and inflammatory responses. Experimental studies suggest that *M. charantia* exerts significant anti-gastritis effects by strengthening the gastroprotective barrier through anti-inflammatory, antioxidative, and mucosal protective mechanisms, while olive oil-based formulations may enhance its bioavailability. However, despite its recognized pharmacological activities, there is a paucity of research specifically investigating the efficacy of appropriately formulated *M. charantia* preparations in experimental models of gastritis, leaving a significant gap in the current understanding of its therapeutic potential in this context (8,9).

Therefore, this study aimed to evaluate the effects of appropriately formulated *M. charantia* treatment on experimental gastritis in rats by assessing various biochemical markers of oxidative stress and inflammation parameters, as well as conducting detailed histopathological analyses. This research aims to provide new insights into the potential role of *M. charantia* as a natural therapeutic agent for the prevention and management of gastritis, an area for which limited research currently exists in the literature.

Methods

Experimental Procedure

Ethical approval for animal experimentation was obtained from the Local Ethics Committee for Animal Experiments for the Gastritis Model Animal Experimental Study at Bezmialem Vakıf University (decision no: 2022/06, date: 24.01.2022). Detailed experimental procedures are presented in Figure 1. Prior to the study, approximately 25 male Sprague-Dawley rats of similar age were acclimatized to the laboratory environment for two weeks. During this acclimatization period, the rats were housed in standard cages under a 12-hour light / dark cycle at a controlled room temperature of 22-25 °C. They were provided with a pellet diet and ad libitum access to water. Before the experiments commenced, the body weights of all animals were recorded, and the rats were randomly assigned to control and experimental groups. All groups were fasted for 24 hours prior to the start of the experimental procedures, while water remained available without restriction. All experimental protocols and animal care practices complied with current standards for the ethical treatment of laboratory animals.

Eighty percent ethanol (C2H5OH) was administered to rats at a dose of 5 mL/kg via intragastric route using oral gavage and 4 hours later, a gastritis-gastric ulcer model was established in accordance with the literature (10). Group 1 was exposed to similar stress by administering the same volume of distilled water via oral gavage. In Group 3, olive oil-based extracts of *M. charantia*, known for their high bioavailability, were preferred for treatment (11). The treatment duration was set at 14 days, consistent with previous studies, and each treatment administered to the groups was given orally via gavage in a similar manner (12). After creating the models in rats and treating them with different methods according to their groups for 14 days, the rats were sacrificed by using 90 mg/kg of ketamine (Ketalar®, Pfizer Pharma GMBH, Germany) and 10 mg/kg of xylazine hydrochloride (Alfazyne®, 2%, Alfasan International, 3440 AB, Woerden, Holland) anesthesia. Bloods were collected and then midline incision was made between the sternum and anus to reach the gastric region. Total gastrectomy was performed. Tissue sections were then separated for histopathological and biochemical evaluation. Samples of blood, serum, and gastric tissue were stored under laboratory conditions at -80 degrees Celsius.

The following parameters were recorded in the blood samples among the groups: white blood cells (2.1-19.5×10^9 cells/uL),

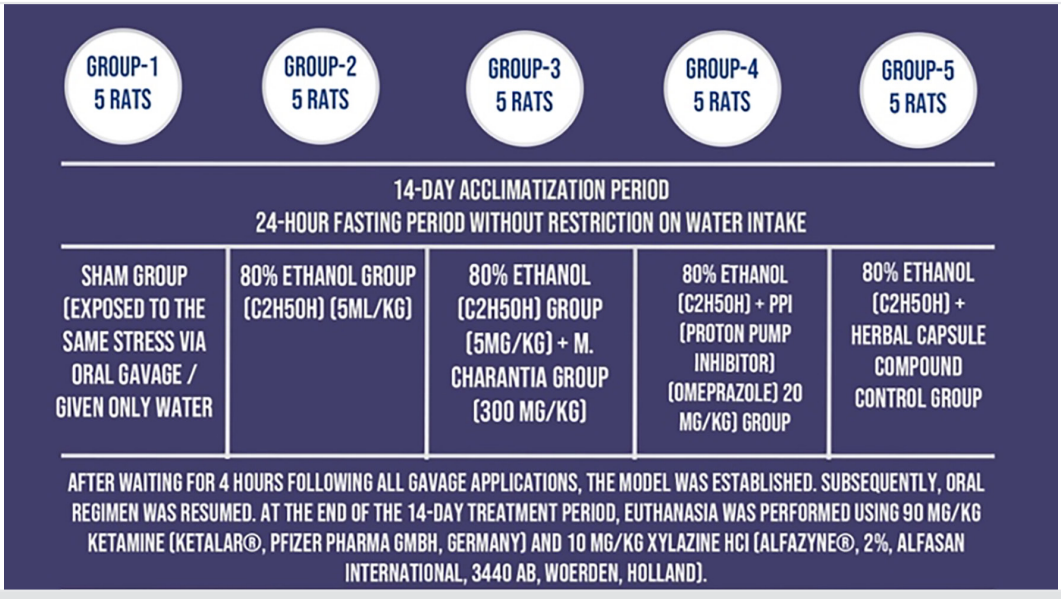

Figure 1. Graphical abstract of experimental procedure & 8195

M. Charantia: Momordica Charantia

lymphocytes (2-14.1×10^9 cells/uL), monocytes (MONO) (0-0.098×10^9 cells/uL), granulocytes (GRA) (0.1-5.4×10^9 cells/uL), red blood cells (5.3-10×10^12 cells/uL), hemoglobin (HGB) (14-18 g/dL), hematocrit (35-52%), mean corpuscular volume (50-62 fl), mean corpuscular hemoglobin (MCH) (16-23 pg), MCH concentration (MCHC) (31-40 g/dL), red cell distribution width %, platelet (500-1370×10^9 cells/uL), plateletcrit %, mean platelet volume (fl), platelet distribution width %, hemoglobin A1c %, total antioxidant status (AU), total oxidant status (AU), IL-1β, TNF-α (pg/mL), oxidative stress index (AU), IL-6, and TGF-β. Similarly, biochemical analyses were performed on stomach tissue samples obtained from the rats, and the results were recorded. The excised stomach tissue from the sacrificed rats was dissected along the greater curvature for macroscopic evaluation. It was then sent for light microscopic examination at our pathology department. Tissue samples were fixed in 10% neutral buffered formaldehyde prepared in phosphate-buffered saline for 1 day. After washing the stomach samples with 0.9% isotonic sodium chloride (Polyflex, Polifarma,Tekirdağ, Türkiye), examinations were conducted to determine macroscopic gastric damage and, if present, ulceration areas. Sections of tissues prepared using the hematoxylin and eosin staining method were examined under a light microscope. Various parameters such as edema, chronic inflammation, presence of lymphoid follicles, prevalence of gastritis, erosion extent, ischemic necrosis, inflammation activity, and bleeding were evaluated among the groups. The sections were compared between groups, and the results were recorded. Histopathological presence of *H. pylori* was investigated using the Giemsa staining technique. Additionally, the presence of intestinal metaplasia in tissues was evaluated using the periodic acid-Schiff staining technique. All evaluations were repeated at least two times. Experimental models of gastritis were established in rats using various protocols, including non-steroidal anti-inflammatory drugs (NSAIDs)-induced, stress-related, alcohol-associated, and congestive gastropathy models, each reflecting distinct pathophysiological mechanisms and enabling the investigation of gastric mucosal injury (13).

Statistical Analysis

Due to the sample size (n<30) in each group, the normal distribution of variables was not assessed. Continuous variables were expressed as median (interquartile range) [Q2(Q1:Q3)], while categorical variables were expressed as n (%). Kruskal-Wallis H test was used for comparisons between more than two groups of variables. Fisher-Freeman-Halton test was employed for comparing categorical variables. Bonferroni correction was applied for comparisons showing significant differences between groups. Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA), and p<0.05 was considered statistically significant.

Herbal capsule compound - (G-Two® PolyPhyto Polymer Health E.M.T, İstanbul, Türkiye - olive leaf extract 250 mg, *M. charantia* extract 200 mg, *Garcinia cambogia* extract 150 mg, cinnamon 100 mg, L-carnitine 50 mg, chromium 100 μg) and its effects on gastritis

Olive leaf extract is known to contain bioactive phenolic compounds, while *Garcinia cambogia*, cinnamon, L-carnitine, and chromium are included for their various biological properties. In this study, the effects of *M. charantia* on gastritis were investigated through biochemical assessments of oxidative stress and inflammatory cytokines, along with histopathological analyses (14,15).

Results

Statistical analysis of hemogram results among groups is presented in Table 2. Statistically significant differences were observed between groups in MONO-count (×10^9 cells/μL), GRA count (×10^9 cells/μL), MONO percentage (%), HGB (g/dL), and MCHC (g/dL) values [p<0.05 (p<0.05)]. Upon examination of Table 3 statistically significant differences were observed between groups in terms of biochemical parameters in blood values and enzyme-linked immunosorbent assay (ELISA) Analyses (p<0.05). Similarly, significant differences were found between groups in the statistical evaluations of biochemical parameters in tissue examinations and ELISA analyses (p<0.05) (Table 4).

Table 2. Analysis of hemogram results among groups

Variables	Group 1 sham group	Group 2 80% ethanol (C2H5OH)	Group 3 80% ethanol (C2H5OH) + *Momordica charantia*	Group 4 80% ethanol (C2H5OH) + PPI	Group 5 80% ethanol (C2H5OH) + herbal capsule compound	p[a] value
Weight (gr)	340 [317.5:360]	325 [317.5:352]	325 [312.5:337.5]	325 [312.5:337.5]	325 [315:337.5]	0.757
WBC	6.53 [4.67:7.95]	8.6 [7.41:9.91]	6 [5.22:9.53]	6.34 [5.37:17.66]	7.97 [5.27:9.57]	0.497
LYM (2-14.1 10*9 uL)	4.64 [3.81:6.88]	5.40 [4.49:6.82]	4.59 [3.43:8.03]	4.96 [3.56:8.86]	6.35 [4.21:8.19]	0.905
MONO (0-0.098 10*9 uL)	0.07 [0.05:0.71]	0.06 [0.05:0.62]	0.17 [0.13:0.54]	0.50 [0.24:1.24]	0.16 [0.14:0.28]	**0.046**
GRA (0.1-5.4 10*9 uL)	1.80 [1.20:1.91]	1.92 [1.77:2.05]	1.30 [1.14:1.45]	1.57 [1.15:7.45]	1 [0.79:1.46]	**0.024**
LYM (55-97%)	76.4 [72:78.1]	72 [65.3:74.3]	76.6 [65.9:84.5]	74.4 [48.6:78.6]	83.4 [74.5:86.2]	0.161
MONO (0-5%)	1.1 [0.7:1.35]	7 [5:7]	1.8 [1.65:10.15]	7.4 [3.1:9.7]	1.9 [1.7:5.3]	**0.014**
GR (2-31%)	23 [19.7:26.5]	23 [20.5:29.5]	21.7 [13.9:24]	20.7 [16.9:41.8]	14.9 [11.15:21.05]	0.204
RBC (5.3-10 10* 12 uL)	8.26 [7.58:8.38]	8.2 [7.68:8.59]	8.05 [4.08:8.37]	7.82 [7.67:7.90]	8.48 [8.29:8.63]	0.110

Table 2. Continued

Variables	Group 1 sham group	Group 2 80% ethanol (C2H5OH)	Group 3 80% ethanol (C2H5OH) + *Momordica charantia*	Group 4 80% ethanol (C2H5OH) + PPI	Group 5 80% ethanol (C2H5OH) + herbal capsule compound	p[a] value
HGB (14-18 g/dL)	14.5 [14.2:14.8]	14.4 [14.2:14.6]	14.8 [13.85:15.05]	13.4 [12.8:13.85]	14.4 [14.1:14.95]	**0.026**
HCT (35-52%)	40 [37.8:41.25]	40 [38.5:40.7]	41.07 [38.26:42.27]	38.3 [36.2:39.15]	39.4 [39.05:42.1]	0.241
MCV (50-62 fl)	49 [48:54]	50 [41.5:51.5]	49 [48:50.5]	49 [47:50]	47 [46.5:49]	0.441
MCH (16-23 pg)	17.8 [17.6:18.35]	18.2 [17.2:18.85]	17.8 [17.35:18.1]	17.2 [16.55:17.65]	17 [16.9:17.4]	0.052
MCHC (31-40 g/dL)	36.7 [35.05:36.75]	36.5 [36.2:36.25]	36.2 [35.5:36.25]	35 [34.75:35.9]	36 [35.5:36.35]	**0.043**
RDW c %	16.8 [16:17.15]	16.9 [16.55:17.2]	16.2 [16.2:16.65]	17.1 [17.05:17.5]	16.5 [16.5:17.45]	0.049
PLT (500-1370 10*9 uL)	917 [879:1186]	934 [891:991]	943 [865:1025]	846 [838.5:912]	867 [628.5:956]	0.287
PCT %	0.67 [0.55:0.88]	0.65 [0.53:0.73]	0.64 [0.58:0.69]	0.59 [0.59:0.62]	0.60 [0.45:0.66]	0.528
MPV (fl)	7.3 [6.3:7.4]	7.1 [6.95:7.55]	6.8 [6.6:6.85]	7 [6.65:7.1]	6.9 [6.7:7.25]	0.257
PDWc %	34.8 [33.45:35.8]	34.5 [33.2:36.05]	33.8 [33.05:34]	35 [33.95:35.35]	34.8 [34.15:36.3]	0.231

The significance level was set at p<0.05
Q2 [Q1:Q3] was used for defining the variables
[a]: Kruskal-Wallis test, WBC: White blood cells, LYM: Lymphocytes, MONO: Monocytes, GRA: Granulocytes, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, PLT: Platelet, PCT: Plateletcrit, MPV: Mean platelet volume, PDWc: Platelet distribution width

Table 3. Biochemical parameters in blood values and ELISA analyses among groups

Variables	Group 1 sham group	Group 2 %80 ethanol (C2H5OH)	Group 3 %80 ethanol (C2H5OH) + *Momordica charantia*	Group 4 %80 ethanol (C2H5OH) + PPI	Group 5 %80 ethanol (C2H5OH) + herbal capsule compound	p[a] value
TAS	0.33 [0.32:0.37]	0.17 [0.15:0.18]	0.27 [0.24:0.28]	0.31 [0.27:0.33]	0.22 [0.20:0.25]	**<0.001**
TOS	1.78 [1.59:1.88]	2.82 [2.52:2.99]	2.36 [2.2:2.45]	2.02 [1.99:2.16]	2.5 [2.44:2.63]	**<0.001**
IL1β	96.06 [91.21:102.36]	265.6 [260.3:274.6]	195.4 [179.9:205.5]	144.7 [12.3:158.4]	217.2[213.7:239.7]	**<0.001**
OSI	5.12 [4.64:5.59]	16.51 [14.56:19.22]	8.83 [8.46:9.31]	6.98 [6.31:7.32]	11.06 [9.69:12.96]	**<0,001**
IL-6	49.11 [48.08:52.73]	163.9 [123.6:175.4]	113.7 [101.6:115.6]	79.57 [74.04:85.24]	127.6 [123.3:147,6]	**<0.001**
TNF-α (pg/mL)	87.01 [83.3:97.3]	214.2 [183.5:227.4]	129.5 [121.1:140.7]	109.1 [101.8:119.9]	172.3 [154.2:183.6]	**<0.001**
TGF-β	52.2 [50.04:55.79]	106.5 [101.5:118.02]	76.8 [70.4:82.6]	69.03 [56.12:73.89]	80.65 [76.65:86.8]	**0.001**

Variables were defined using Q2[Q1:Q3]
[a]: Kruskal-Wallis test, ELISA: Enzyme-linked immunosorbent assay, PPI: Proton pump inhibitor, TAS: Total antioxidant status, TOS: Total oxidant status, IL: Interleukin, OSI: Oxidative stress index, TNF-α: Tumor necrosis factor alpha, TGF-β: Transforming growth factor beta

Table 4. Biochemical parameters in tissue examinations and ELISA analyses among groups

Variables	Group 1 sham group	Group 2 %80 ethanol (C2H5OH)	Group 3 %80 ethanol (C2H5OH) + *Momordica charantia*	Group 4 %80 ethanol (C2H5OH) + PPI	Group 5 %80 ethanol (C2H5OH) + herbal capsule compound	p[a] value
TAS	0.42 [0.39:0.43]	0.14 [0.11:0.16]	0.25 [0.23:0.29]	0.31 [0.29:0.33]	0.19 [0.17:0.23]	**<0.001**
TOS	0.31 [0.28:0.34]	0.72 [0.71:0.78]	0.49 [0.46:0.52]	0.46 [0.39:0.48]	0.60 [0.55:0.64]	**<0.001**
IL-1β	207.8 [204.7:22.3]	370.9 [356.9:382.3]	302.1 [300.8:315.9]	279.01 [269.7:287.05]	324.5 [312.9:359.7]	**<0.001**
OSI	0.79 [0.67:0.82]	5.88 [4.57:6.43]	1.86 [1.7:2.14]	1.42 [1.23:1.63]	3.18 [2.46:3.64]	**<0.001**
IL-6	102.7 [50.12:107.5]	234.7 [227.6:253.9]	175.1 [166.7:183.1]	143.9 [130.2:152.8]	198.6 [190.8:207.8]	**<0.001**
TNF-α (pg/mL)	191.4 [170.3:205.8]	270.8 [257.2:280.8]	224.9 [215.4:243.3]	219.3 [198.9:230.4]	247.1 [225.1:262.6]	**0.001**
TGF-β	171.4 [147.5:184.6]	275.6 [256.1:297.1]	223.9 [217.8:227.2]	203.4 [199.7:210.2]	229.2 [217.2:261.6]	**<0.001**

Variables were defined using Q2 [Q1:Q3]
[a]: Kruskal-Wallis test, ELISA: Enzyme-linked immunosorbent assay, PPI: Proton pump inhibitor, TAS: Total antioxidant status, TOS: Total oxidant status, IL: Interleukin, OSI: Oxidative stress index, TNF-α: Tumor necrosis factor alpha, TGF-β: Transforming growth factor beta

Upon examination of Table 5, when histopathological response findings to treatments were evaluated, it was observed that there was a significant difference in terms of frequencies in all comparisons made (p<0.05).

In Table 6, when the histopathological results of tissue examinations between Group 3 and Group 4 groups were compared in pairwise statistical analysis, no statistically significant difference was found between the groups in terms of treatment methods. Upon examination of Table 7, when pairwise statistical analysis of histopathological results of tissue examinations between Group 4 and Group 5 were conducted, it was observed that in Group 5 herbal capsule compound control, the presence of chronic inflammation/lymphoid follicles and gastritis-gastric ulcer was 80%, while it was not observed in Group 4, and this difference was found to be statistically significant (p=0.048). Additionally, a statistically significant difference was observed between the groups in terms of the presence of *H. pylori* (p=0.048) Histopathological examinations showing responses of different groups to gastritis treatment are depicted in the images (Figures 2-8).

Table 5. Statistical analysis of histopathological results in tissue examinations among groups

Variables	Group 1 sham group	Group 2 %80 ethanol (C2H5OH)	Group 3 %80 ethanol (C2H5OH) + *Momordica charantia*	Group 4 %80 ethanol (C2H5OH) + PPI	Group 5 %80 ethanol (C2H5OH) + herbal capsule compound	P[b] value
Edema						
Present	0	4 (80%)	1 (20%)	0	4 (80%)	**0.005**
Absent	5 (100%)	1 (20%)	4 (80%)	5 (100%)	1 (20%)	
Chronic inflammation lymphoid follicle						
Present	0	5 (100%)	1 (20%)	0	4 (80%)	**<0.001**
Absent	5 (100%)	0	4 (80%)	5 (100%)	1 (20%)	
Gastritis and gastric ulcer						
Present	0	5 (100%)	1 (20%)	0	4 (80%)	**<0.001**
Absent	5 (100%)	0	4 (80%)	5 (100%)	1 (20%)	
Prevalence of gastritis						
1-10%	0	2 (40%)	1 (20%)	1 (20%)	2 (40%)	**0.009**
11-20%	0	3 (60%)	0	0	2 (40%)	
None	5 (100%)	0	4 (80%)	4 (80%)	1 (20%)	
Erosion and ischemic necrosis						
Present	0	5 (100%)	1 (20%)	0	3 (60%)	**0.002**
Absent	5 (100%)	0	4 (80%)	5 (100%)	2 (40%)	
Activity of gastritis						
Present	0	5 (100%)	1 (20%)	0	3 (60%)	**0.002**
Absent	5 (100%)	0	4 (80%)	5 (100%)	2 (40%)	
Gastric bleeding						
Present	0	5 (100%)	1 (20%)	0	3 (60%)	**0.002**
Absent	5 (100%)	0	4 (80%)	5 (100%)	2 (40%)	
Intestinal metaplasia						
Present	0	4 (80%)	5 (100%)	4 (80%)	5 (100%)	
Absent	5 (100%)	1 (20%)	0	1 (20%)	0	**0.002**
Helicobacter pylori						
Present	4 (80%)	1 (20%)	1 (20%)	0	4 (80%)	
Absent	1 (20%)	4 (80%)	4 (80%)	5 (100%)	1 (20%)	**0.020**

The significance level was set at p<0.05
Variables were defined using n (%)
[b]: Fisher-Freeman-Halton test

Table 6. Pairwise statistical analysis of histopathological results of tissue examinations between Group 3 *Momordica charantia* and Group 4 PPI groups

Variables	Group 3 %80 ethanol (C2H5OH) + *M. charantia*	Group 4 %80 ethanol (C2H5OH) + PPI	P[b] value
Edema			
Present	1 (20%)	0	0.500
Absent	4 (80%)	5 (100%)	
Chronic inflammation lymphoid follicle			
Present	1 (20%)	0	0.500
Absent	4 (80%)	5 (100%)	
Gastritis and gastric ulcer			
Present	1 (20%)	0	0.500
Absent	4 (80%)	5 (100%)	
Prevalence of gastritis			
1-10%	1 (20%)	1 (20%)	
11-20%	0	0	0.778
None	4 (80%)	4 (80%)	
Erosion and ischemic necrosis			
Present	1 (20%)	0	0.500
Absent	4 (80%)	5 (100%)	
Activity of gastritis			
Present	1 (20%)	0	0.500
Absent	4 (80%)	5 (100%)	
Gastric bleeding			
Present	1 (20%)	1 (20%)	0.778
Absent	4 (80%)	4 (80%)	
Intestinal metaplasia			
Present	5 (100%)	4 (80%)	0.500
Absent	0	1 (20%)	
Helicobacter pylori			
Present	1 (20%)	0	0.500
Absent	4 (80%)	5 (100%)	

The significance level was set at p<0.05
Variables were defined using n (%)
[b]: Fisher-Freeman-Halton test, PPI: Proton pump inhibitor

Table 7. Pairwise statistical analysis of histopathological results of tissue examinations between Group 4 proton pump inhibitor and Group 5 herbal capsule compound control

Variables	Group 4 %80 ethanol (C2H5OH) + PPI	Group 5 %80 ethanol (C2H5OH) + herbal capsule compound	P[b] value
Edema			
Present	0	4 (80%)	**0.048**
Absent	5 (100%)	1 (20%)	
Chronic inflammation lymphoid follicle			
Present	0	4 (80%)	**0.048**
Absent	5 (100%)	1 (20%)	
Gastritis and gastric ulcer			
Present	0	4 (80%)	**0.048**
Absent	5 (100%)	1 (20%)	
Prevalence of gastritis			
1-10%	1 (20%)	2 (40%)	
11-20%	0	2 (40%)	0.524
None	4 (80%)	1 (20%)	
Erosion and ischemic necrosis			
Present	0	3 (60%)	0.167
Absent	5 (100%)	2 (40%)	
Activity of gastritis			
Present	0	3 (60%)	0.167
Absent	5 (100%)	2 (40%)	
Gastric bleeding			
Present	1 (20%)	3 (60%)	0.286
Absent	4 (80%)	2 (40%)	
Intestinal metaplasia			
Present	4 (80%)	5 (100%)	0.500
Absent	1 (20%)	0	
Helicobacter pylori			
Present	0	4 (80%)	**0.048**
Absent	5 (100%)	1 (20%)	

The significance level was set at p<0.05
Variables were defined using n (%)
[b]: Fisher-Freeman-Halton test, PPI: Proton pump inhibitors

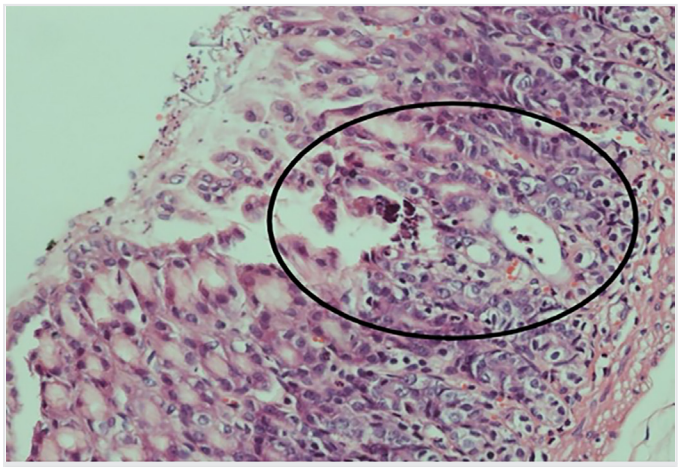

Figure 2. Mild active inflammation in gastric mucosa (H&E staining, 100x magnification)

H&E: Hematoxylin & eosin

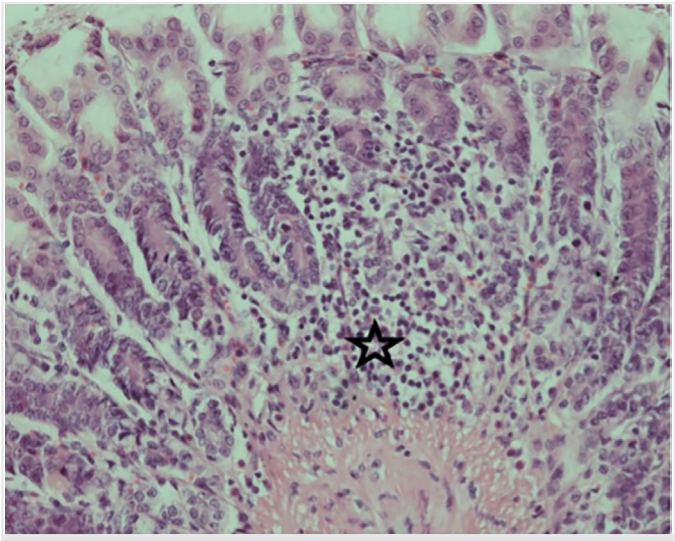

Figure 3. Chronic active inflammation in gastric mucosa (H&E staining, 100x magnification)

H&E: Hematoxylin & eosin

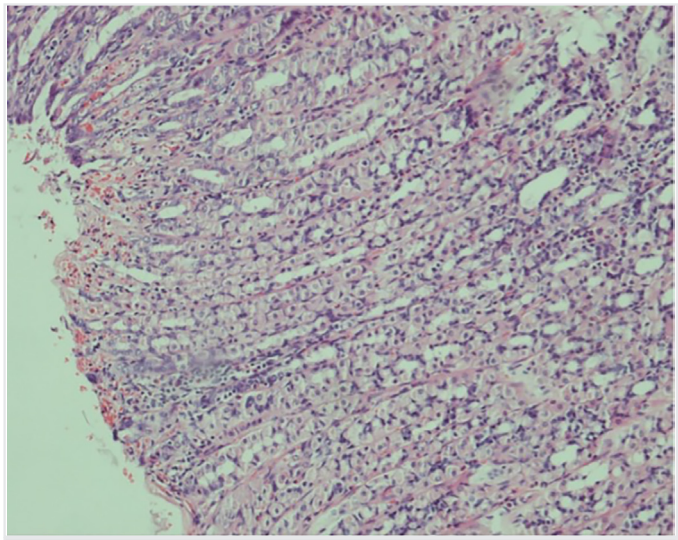

Figure 4. Chronic active inflammation and focal erosion in gastric mucosa (H&E staining, 100x magnification)

H&E: Hematoxylin & eosin

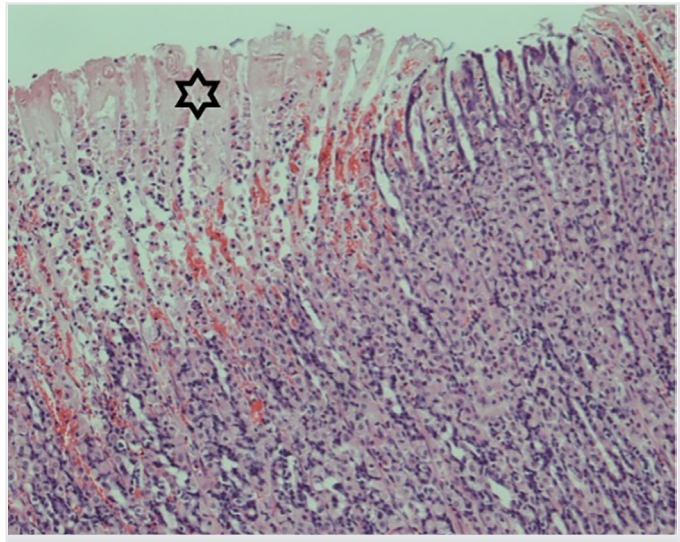

Figure 5. Erosion and infarction in gastric mucosa (H&E staining, 100x magnification)

H&E: Hematoxylin & eosin

Discussion

Gastritis ranks among the lifelong diseases, and it is estimated that half of the world's population will encounter or has encountered a condition related to gastritis throughout their lives. Looking at the long-term outcomes, it poses significant economic burdens on the healthcare systems of countries and is associated with progressive complications if left untreated (gastric ulcer, gastric perforation, iron deficiency anemia, chronic atrophic gastritis, gastric metaplasia-dysplasia/cancer, mucosa-associated lymphoid tissue lymphoma, neuroendocrine tumors, etc.) Early diagnosis, treatment, and management are crucial, and ongoing research by scientists in this field explores alternative treatments alongside existing standard therapies (2). Gastritis pathophysiology fundamentally involves the development of cell damage because of the release of free oxygen radicals by various mechanisms and mediators, initiated by an aggressive factor attacking the gastric mucosa. For instance, in *H. pylori*-associated gastritis, this damage occurs through different mechanisms mediated by various virulence factors (cell adhesion - BabA-sabA-OipA, urease A/B) (16). NSAIDs have been emphasized to trigger gastritis through the inhibition of prostaglandin synthesis (prostaglandins play a protective role in the gastric mucosa against damage caused by hydrochloric acid). In a study conducted by deFoneska et al. (17), similar mechanisms were highlighted in accordance with guideline recommendations.

The gastric mucosa damaged by the generated free oxygen radicals further exacerbates the damage to the mucosa through

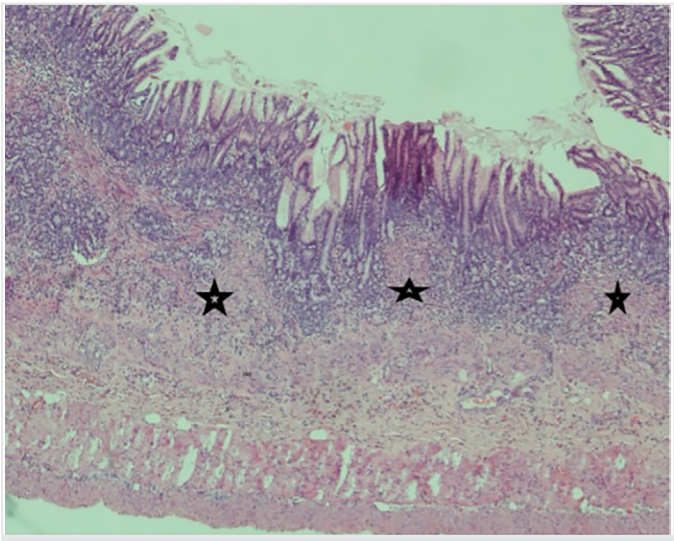

Figure 6. Chronic inflammation and atrophy in gastric mucosa (H&E staining, 40x magnification)

H&E: Hematoxylin & eosin

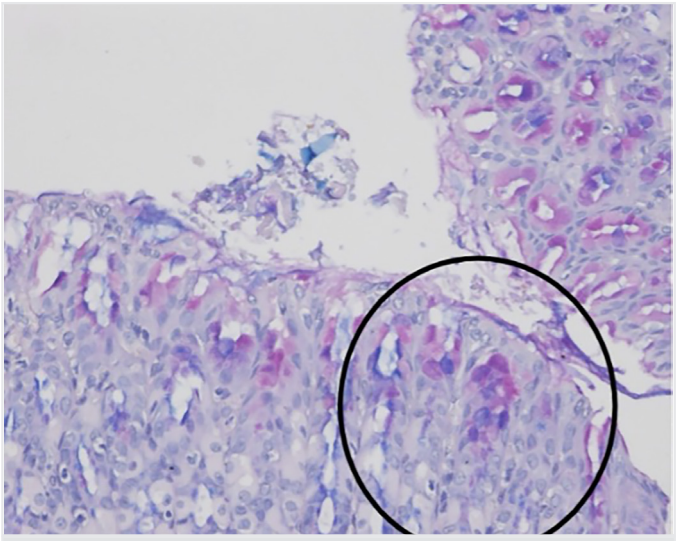

Figure 7. Positivity for intestinal metaplasia in gastric epithelium showing PAS-AB histochemistry (PAS-AB staining, 200x magnification)

PAS: Periodic acid-Schiff, AB: Alcian blue

lipid peroxidation and covalent binding, triggering the activation of antioxidant barriers in the body by the cells' perception. It is believed that determining total oxidative stress and total antioxidant levels biochemically and histopathologically may be beneficial in assessing the degree of damage and inflammation, aiding in current inflammation treatment. Total antioxidant levels are crucial for preventing advanced damage and can lead to a better understanding of homeostatic mechanisms. In previous studies, it has been reported that in cases where total antioxidant capacity decreases or reactive oxygen radicals cannot be neutralized, irreversible damage may occur in the cell nucleus (18).

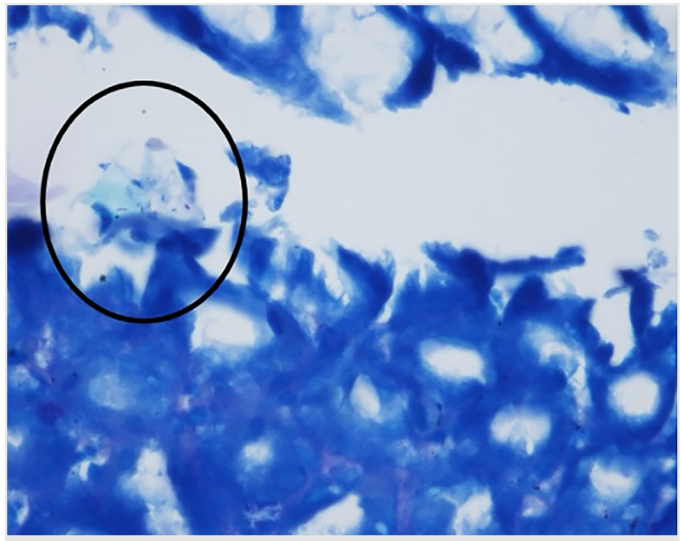

Figure 8. Spiral-shaped suspicious bacteria suggestive of *Helicobacter pylori* in giemsa histochemistry

In a study conducted by Jia et al. (8) in 2017, it was reported that extracts derived from *M. Charantia* could form a gel structure with pectin polysaccharides, exhibiting mucoprotective effects, and acting as potent anti-gastritis and anti-ulcerogenic agents. Similarly, Raish et al. (19) reported in their study that *M.charantia* inhibited inflammatory cytokines (such as TNF-α and IL-6) in isoproterenol-induced myocardial cells apoptosis. This effect was emphasized to occur through a decrease in intracellular free oxygen radicals level, restoration of endogenous antioxidant enzymes, and reduction in the formation of pro-apoptotic proteins. Furthermore, in another study, it was observed that treatment with *M. charantia* in mice led to a significant reduction in ethanol-induced TNF-α levels, thereby alleviating inflammation in the stomach. The reduction in gastric mucosal inflammation, characterized by a decrease in mucosal damage, edema, and leukocyte infiltration, was histopathologically demonstrated and supported by the presence of visibly reduced inflammatory cell infiltration and edema (11). Considering these effects, *M. Charantia* is thought to be effective in the treatment of gastritis.

In our study, to enhance the reliability of acute inflammatory parameter analyses, investigations were conducted in both blood and tissue samples among the groups. Significant differences were found in total oxidative stress and total antioxidant levels, oxidative stress index, IL-1β, IL-6, TNF α, TGF-β values. The median values of stress and inflammation parameters were observed to be highest in Group 2, as expected. Similarly, histopathological examinations revealed findings indicative of gastritis inflammation in Group 2, confirming the significance of the model.

As mentioned above, when examining the median values of biochemical parameters indicating acute inflammatory findings in Group 2, it was observed that they were higher in Group 3. When evaluated together with histopathological examinations,

the presence of edema, chronic inflammation/lymphoid follicles, gastritis, gastritis prevalence, erosion/ischemic necrosis, bleeding was not observed in most of Group 3. Therefore, it can be concluded that the administered *M. charantia* treatment is effective.

When comparing the results of histopathological tissue examinations among the groups, a statistically significant difference was found among all groups. In Group 1 and Group 4, no edema, chronic inflammation/lymphoid follicle presence, gastritis, gastritis prevalence, erosion, ischemic necrosis, and gastritis activity were observed. In advanced pairwise analyses, no significant difference was found between Group 3 and Group 4 groups in terms of gastritis treatment superiority. When evaluating the histopathological treatment responses of both groups, it is observed that both treatment alternative is effective.

Group 4 and Group 5 herbal capsule compound groups, a statistically significant difference was found in the parameters of edema presence, chronic inflammation / lymphoid follicle, and gastritis severity. It is observed that Group 4 is superior in these aspects. When examining the acute inflammatory biochemical parameters for Group 3, it was observed that the median values of total oxidative stress and oxidative stress index, IL-1β, IL-6, TNF α, and TGF-β were lower in the Group 5 while the median value of total antioxidant level in Group 3 was higher than that of the Group 5 control. Based on this, it could be said that Group 5 control was more effective in gastritis treatment when examined in histopathological data. Among all groups, the lowest acute inflammatory parameter median values were found in the gold standard Group 4. Histopathologically, when intestinal metaplasia was evaluated, the most effective treatment method appeared to be Group 4. It seemed that the mucoprotective effect of Group 3 was insufficient here, and similarly, Group 5 also failed to prevent intestinal metaplasia. This situation may be related to the different mechanisms of action they use in their treatment efficacy.

H. pylori can exhibit a spectrum of effects ranging from mild gastritis to cancer; therefore, it should be considered in cases of gastritis resistant to medical treatment. In our study group, *H. pylori* was not detected in Group 4, but it was found in 20% of Group 3. In Group 5, *H. pylori* presence was observed in a significant portion (80%). After determining the etiology of gastritis, eradication treatment for *H. pylori* should be added in addition to the current treatment. In addition to the existing *H. pylori* eradication therapy, *M. charantia* may be effective through mucoprotective and antioxidant mechanisms.

Study Limitations

This study has several limitations. The relatively small sample size and the use of an ethanol-induced rat gastritis model may limit the generalizability of the findings to human clinical settings. Moreover, while the study provides detailed biochemical and histopathological data, it does not address long-term treatment outcomes or potential side effects. Finally, the effects of the tested compounds were evaluated only in acute gastritis; further studies are needed to explore their efficacy in chronic gastritis and in combination with standard therapies such as *H. pylori* eradication.

Conclusion

This study demonstrated that *M. charantia* reduced mucosal damage in gastritis, mainly by strengthening mucoprotective defenses and by suppressing inflammation and oxidative stress through its antioxidant effects. To our knowledge, the effects of appropriately formulated *M. charantia* on gastritis have not been previously investigated in detail, highlighting the novelty of our findings. Phytotherapeutic agents specifically selected for the disease may exert synergistic effects alone or with conventional therapies, offering fewer side effects and lower recurrence rates. Such treatments could serve as adjuncts or alternatives to proton pump inhibitors in managing or preventing gastritis and gastric ulcers and may be considered alongside eradication therapy in *H. pylori* infections. These results lay the groundwork for future research and suggest that *M. charantia* may represent a promising natural therapeutic option.

Ethics

Ethics Committee Approval: Ethical approval for animal experimentation was obtained from the Local Ethics Committee for Animal Experiments for the Gastritis Model Animal Experimental Study at Bezmialem Vakıf University (decision no: 2022/06, date: 24.01.2022).

Informed Consent: This study involved experimental animals only.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.İ., A.A., N.Ş., E.M.G., Concept: Y.İ., A.A., C.G., Design: Y.İ., A.A., Data Collection or Processing: Y.İ., A.A., C.G., N.Ş., E.M.G., Analysis or Interpretation: Y.İ., A.A., C.G., N.Ş., E.M.G., Literature Search: Y.İ., A.A., C.G., E.M.G., Writing: Y.İ., C.G., E.M.G.

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