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Research Article

Anti-inflammatory and Gastroprotective Effects of Saroglitazar in a Rat Model of Ethanol-Induced Gastric Ulcer

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Abstract

Background: Gastric ulcer is a prevalent gastrointestinal disorder characterized by several recurrences; each year, a million patients are diagnosed with gastric ulcers. Different groups of medications, using various strategies, participate in the prevention and treatment of gastric ulcers and in preventing ulcer relapses after treatment, but their negative effects limit their utility. ***Objective***: To evaluate the possible anti-inflammatory and gastroprotective effects of saroglitazar in ethanol-induced gastric ulcers. ***Methods***: Thirty-five male Wistar albino rats were randomly distributed into five groups, each group with 7 rats, as follows: negative control, positive control, Vonoprazan group, saroglitazar 4 mg/kg group, and saroglitazar 2 mg/kg group. All the medications were administered orally daily, and a single dose of ethanol (1 ml) was administered on day 15 for all except the negative control. After scarification, blood samples were gathered, and the stomachs were excised for gross evaluation. ***Results***: TNF-α serum level reduced and gastric pH significantly Increased with Saroglitazar pretreatment groups; mucosal and vascular structure preservation, collagen restoration, and inflammation control were markedly recorded with the Saroglitazar 4 mg/kg group and to some extent with the vonoprazan and Saroglitazar 2 mg/kg groups. Gross examination of stomach images indicated marked protection in the pretreatment groups in different ranges. ***Conclusions***: Saroglitazar shows gastroprotective effects on gastric ulcers induced with ethanol through anti-inflammatory properties, stomach content regulation, mucosal and vascular change protection, collagen restoration, and fibroblast activity stimulation.

Keywords: Anti-inflammatory activity; Gastric ulcer; Gastroprotective effects; Saroglitazar; TNF-α; Vonoprazan.

التأثيرات المضادة للالتهابات والحماية المعوية لساروغليتزار في نموذج الجرذان لقرحة المعدة الناتجة عن الإيثانول

الخلاصة

الخلفية: قرحة المعدة اضطراب شائع في الجهاز الهضمي يتميز بعودة متكررة؛ يتم تشخيص مليون مريض سنويا بقرحة المعدة. تشارك مجموعات مختلفة من الأدوية، باستخدام استراتيجيات متنوعة، في الوقاية من قرحة المعدة وعلاجها ومنع انتكاسها بعد العلاج، لكن آثارها السلبية تحد من فوائدها. **الهدف**: تقييم التأثيرات المضادة للالتهابات والواقية للمعدة المحتملة للساروغليتازار في تقرحات المعدة الناتجة عن الإيثانول. **الطرائق**: تم توزيع خمسة وثلاثين ذكرا من جرذان ويستار الأمهق عشوائيا إلى خمس مجموعات، كل مجموعة تضم 7 جرذان: مجموعة تحكم سلبي، مجموعة ضابطة إيجابية، مجموعة فونوبرازان، مجموعة ساروجليتازار 4 ملغ/كغ، ومجموعة ساروغليتزار 2 ملغ/كغ. تم إعطاء جميع الأدوية عن طريق الفم يوميا، وتم إعطاء جرعة واحدة من الإيثانول (1 مل) في اليوم الخامس عشر لجميع الأدوية باستثناء العوامل المضايقة السلبية. بعد حصول التقرحات، تم جمع عينات دم، واستئصال المعدة لتقييم شامل. **النتائج**: انخفض مستوى مصل TNF-α وارتفع الرقم الهيدروجيني في المعدة بشكل ملحوظ مع مجموعات العلاج المسبق في ساروجليتزار؛ تم تسجيل الحفاظ على البنية المخاطية والأوعية الدموية، واستعادة الكولاجين، والتحكم في الالتهاب بشكل ملحوظ مع مجموعة ساروغليتزار 4 ملغ/كجم وإلى حد ما مع مجموعات فونوبرازان وساروغليتزار 2 ملغ/كغ. أظهر الفحص العام لصور المعدة وجود حماية واضحة في مجموعات ما قبل العلاج في نطاقات مختلفة. **الاستنتاجات**: يظهر ساروغليتزار تأثيرات حماية معوية ضد تقرحات المعدة الناتجة عن الإيثانول من خلال خصائصه المضادة للالتهابات، وتنظيم محتوى المعدة، وحماية التغيرات المخاطية والأوعية الدموية، واستعادة الكولاجين، وتحفيز نشاط الأروى الليفية.

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INTRODUCTION

Gastric ulcers are one of the prevalent gastrointestinal disorders, characterized by recurrence during patients' lives, impacting a significant number of people globally each year. A stomach ulcer is a disruption in the gastric mucosal lining, generally exceeding 5 millimeters in diameter and penetrating more than 3 millimeters into the mucosa of the muscularis layer [1, 2]. This results in an anticipated mortality rate of 15 deaths per 15,000 complications annually [2]. Around 8.6% of individuals with hemorrhages are associated with peptic ulcers, and 23.5% of patients with perforated peptic ulcers passed away after thirty days [3]. Patients with a history of gastric ulcers have a higher risk of malignancy than patients diagnosed with ulcers in the upper part of the intestine; after two years from the diagnosis of gastric ulcers, the risk of developing stomach cancer increases 10-fold compared to healthy individuals [3]. A gastric ulcer is a condition in which there is deep damage in the stomach lining that extends through the muscular layer, caused by the harmful effects of gastric acid and pepsin [1]. The pathology of gastric ulcers is characterized by disruption of protective factors. Moreover, harmful factors significantly contribute to

the development of gastric ulcers. Lifestyle behaviors such as smoking, drinking alcohol, and stress contribute to negative factors. Furthermore, infection with Helicobacter pylori and medications including nonsteroidal drugs and steroids have a major role in developing gastric ulcers [4]. Excessive consumption of alcohol can impact the entire digestive system, leading to an inflammatory pathogenic process or directly causing alterations that result in diverse clinical characteristics [5]. Alcohol adversely impacts the stomach, impairing digestion and the gut's absorption ability. Vascular injury is an initial pathogenic factor in the development of stomach hemorrhagic erosions induced with ethanol [6]. One of the common gastric ulcer models in experimental animals is the ethanol-induced gastric ulcer [7]. In gastric ulcer treatment Different groups of treatments with different mechanisms of action and targeting several aspects in the pathophysiology of gastric ulcers are used, including antibiotics for H. pylori eradication; acid secretion suppression, including proton pump inhibitors and H2 receptor antagonists; and acid neutralizing agents [8]. From their development in medical care in the late 1980s, proton pump inhibitors (PPIs) have significantly transformed the treatment of peptic ulcer disease [9]. There are different concerns about the chronic safety profile of PPI use, and these concerns have induced alterations in prescription behaviors and patient delays in seeking medical therapy [10]. Up to 13% of patients administered lansoprazole continue to meet ulcer relapse; researchers try to identify alternative treatment groups [11]. Preventing ulcer recurrence is the most important long-term goal for reducing morbidity and mortality [9]. Saroglitazar is a peroxisome proliferator-activated receptor (PPAR) activator that works on both alpha/gamma (α/γ) receptor subtypes, authorized in India by a general official agency for the management of elevated serum triglycerides and dyslipidemia in patients with type 2 diabetes mellitus inadequately controlled by statin treatment. Saroglitazar is the earliest medicine in the new category of dual PPAR α/γ agonists (glitazars) to receive approval and clinical application globally [12]. The U.S. Food and Drug Administration (FDA) has designated Saroglitazar as an orphan drug and fast-track drug for its possible use in primary biliary cholangitis [13]. In addition to its advantages in diabetes, current studies indicate that saroglitazar can mitigate non-alcoholic steatohepatitis (NASH) [14]. It obtained Indian marketing authorization for a specific stage of non-alcoholic steatohepatitis [15]. Various studies demonstrate anti-inflammatory, antioxidant, and wound-healing effects [16-18]. The PPAR transcription regulator controls genes that are responsible for the production of proteins that regulate metabolic balance and function in different parts of the body, including the heart, muscles, liver, and intestine [19]. Research in animals has shown different impacts of agents on stomach secretion and cell protection, such as ciprofibrate and bezafibrate, through activation of PPAR-α [20]. Numerous studies demonstrate the gastroprotective and therapeutic effects of pioglitazone in various animal models [21]. Moreover, stimulation of PPAR-γ with cilostazole enhances the healing effects of stomach ulcers [22]. Numerous PPAR agonists have previously exhibited gastroprotective benefits via various mechanisms. For instance, bezafibrate, whether administered alone or in conjunction with Ginkgo biloba extract, along with pioglitazone and ciglitazone, has demonstrated protective effects against experimental stomach damage [2,23-25]. Saroglitazar, a dual PPAR-α/γ agonist, has attracted interest as a potential candidate for several disorders. However, despite these therapeutic benefits, research about its gastroprotective effect has not been previously investigated. This study examined the anti-inflammatory and gastroprotective effects of saroglitazar in a rat model of ethanol-induced gastric ulcer by assessing gastric ulcer severity, inflammatory biomarkers, hematological parameters, and histological changes.

METHODS

Study design and animal selection

Thirty-five male Wistar rats, weighing (220 ± 60 g), were obtained from the animal house of the University of Sulaimani/College of Pharmacy. The rats were kept in plastic containers with adequate ventilation and a temperature of 25 ± 2°C. The animals were housed for two weeks to acclimate before the trial began. The typical scientific feed was given to the rats along with unlimited water. The Hawler Medical University College of Medicine's ethical committee approved the procedure with the ethical approval number (4-35-9/4/2026). The Canadian Council on Animal Care (CCAC) recommendations, 1998, were used to conduct the study. Prior to the commencement of the investigation, ethanol dosage and administration methods were selected based on earlier research [6]. Thirty-five Wistar rats were randomly separated into the following five groups (n=7): The group received normal saline orally for 15 days and was designated as the negative control group. The group received normal saline orally for 15 days and was administered 1 ml of 80% ethanol [6] on day 15; this group was designated as the positive control group. The group received vonoprazan once daily orally for 15 days and was administered 1 ml of 80% ethanol on day 15; this group was designated as the standard group [26]. The group received saroglitazar orally (2 mg/kg once daily) for 15 days and administered 1 ml of 80% ethanol on day 15; this group was designated as the saroglitazar low-dose group [27]. The group received saroglitazar (4 mg/kg once daily) orally for 15 days and was administered 1 ml of 80% ethanol on day 15; this group was designated as the saroglitazar high-dose group [27]. The doses of saroglitazar (2 and 4 mg/kg) were determined based on prior preclinical investigations that proved its pharmaceutical efficacy and safety in rats [27]. On day 14, all the animals underwent a 24-hour fast, which permitted just the ability to drink water. On day 15, two hours after the final pretreatment dose of saroglitazar, vonoprazan, or normal saline, depending on the experimental group,

gastric ulcers were induced by oral administration of 1 ml of ethanol (80%) [6] to all groups except the negative control. Animals will be sacrificed following one hour from ethanol administration.

Saroglitazar preparation

Saroglitazar was synthesized from commercially obtainable Lipaglyn® tablets (4 mg; Zydus Lifesciences Ltd., Ahmedabad, India). The tablets were gently crushed up into a uniform powder and suspended in 0.5% (w/v) carboxymethyl cellulose (CMC) shortly prior to administration to achieve the necessary concentrations for oral dosage [27].

Gastric pH measurement

Gastric contents were extracted into a graded container. Afterward, the gastric juice was subjected to centrifugation at 4000 rpm for 10 minutes. Subsequently, 1 mL of supernatant was utilized to determine the pH with a digital pH meter [6].

Blood sampling

Blood samples were obtained via a standard heart puncture at the conclusion of the trial on day 15. The blood was divided into two tubes, one for measurement of CBC and related biomarkers, including measurement of eosinophil/neutrophil ratio (ENR), neutrophil/lymphocyte ratio (NLR), and systemic immune-inflammation index (SII); the other tube was centrifuged and serum was isolated and utilized for the evaluation of blood tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) levels employing an ELISA kit in accordance with the company's guidelines.

Macroscopic evaluation of gastric injury

Following sacrifice, the stomach was incised along the larger curvature, irrigated with normal saline solution (0.9% NaCl), and evaluated for gross lesions.

Histopathological evaluation

Tissue specimens were obtained from the stomach post-scarification and thereafter maintained in a ten percent neutral buffered formaldehyde solution for approximately 24 to 48 hours. Subsequently, pieces were arranged and secured in plastic tissue cassettes, later dehydrated by sequential immersion in increasing concentrations of ethanol (70%, 90%, and 100%), followed by two to three xylene-clearing procedures. Subsequently, the treated stomach tissues were infiltrated and placed in molten paraffin blocks utilizing an automated wax embedder at temperatures ranging from 60 to 70°C. Tissues embedded in paraffin were sectioned to a thickness of 4 µm utilizing a semi-automated rotary microtome. Subsequently, tissue sections were affixed to glass slides and desiccated. The tissue sections were subsequently deparaffinized and cleaned in a heated oven at 88 °C for 20 minutes. Tissue sections were ultimately stained with Harris's hematoxylin and eosin solution, subsequently washed with xylene, and covered with a slip.

Semi-quantitative histomorphometric analysis

A semi-quantitative histomorphometric analysis was conducted to evaluate the histopathological changes associated with gastric ulcer healing among the different experimental groups. Hematoxylin and eosin (H&E) were used for staining tissue specimens to facilitate microscopic examination. Histopathological assessment was performed on five animals from each experimental group. Several histopathological parameters were assessed to determine the extent of ulcer healing. Initially, under 4× magnification, the thickness of collagen deposition was evaluated and measured in micrometers (µm) as an indicator of tissue repair and extracellular matrix formation. Subsequently, under 40× magnification, additional parameters, including chronic inflammatory cell infiltration, vascular change, and fibroblast presentation, were numbered and assessed.

Ethical considerations

The study protocol was approved by the Local Research Ethics Committee of the Hawler Medical University, College of Medicine (Certificate No.: 4-35-9/4/2026).

Statistical analysis

Statistical analyses were conducted utilizing GraphPad Prism version 9 (GraphPad Software, La Jolla, CA, USA). The Shapiro–Wilk test was employed to evaluate the normality of the data. Data that followed a normal distribution were expressed as mean ± standard deviation (SD) and were subjected to one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. Where applicable, pairwise comparisons were articulated as mean differences accompanied by 95% confidence intervals (CIs). Data that do not follow a normal distribution are reported as the median with interquartile range and were analyzed using the Kruskal–Wallis test. A two-tailed p-value of less than 0.05 was considered statistically significant.

RESULTS

Figure 1A shows that the administration of ethanol to the positive control group elevates blood TNF-α levels in comparison to the negative control group. Pretreatment with saroglitazar (4.0 mg/kg; high dose) reduced serum TNF-α levels when compared with the positive control group; these alterations are considered statistically significant ($p< 0.05$). Furthermore, following ethanol induction, Figure 1B presented the IL-6 serum level of the positive group (7.37 ng/ml), exhibiting a small elevation relative to the negative control group (7.35 ng/ml), but they did not reach a significant level (mean difference= -0.85, 95% CI= CI-3.068 to 1.368, $p> 0.05$) however, a level

reduction was observed when comparing IL-6 concentration in the Saroglitazar (4 mg/kg; high dose) group (6.9 ng/ml) with the positive control, but they did not reach a significant level (mean difference= -0.5714, 95% CI: -2.708 to 1.566, $p > 0.05$).

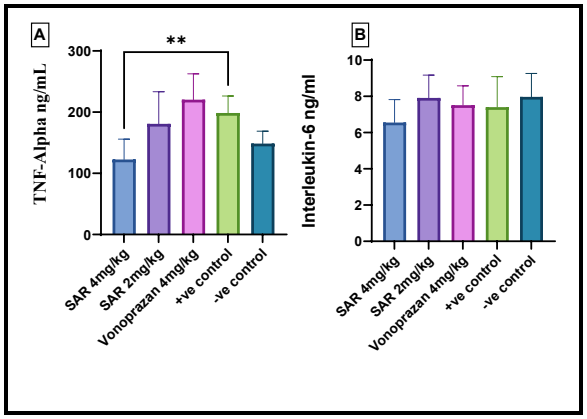

Figure 1: Effect of saroglitazar on (A) TNF-α, and (B) IL-6; Significantly different compared to the positive control group using one-way Anova. ** ($p < 0.01$).

Table 1 illustrated the impact of ethanol and saroglitazar on hematological markers, CBC-derived inflammatory parameters including NLR, ENR, and SII. The observed alterations across the various study groups aligned with the study hypothesis; however, these changes were statistically not significant ($p > 0.05$). Figure 2, when comparing the gastric juice pH of rats in the positive control group (5.7) with that of the normal group, a statistically significant increase was seen (3.3). Also, pre-treatment groups showed an additional increase in gastric pH with the highest values of 8.5 and 8.4 for vonoprazan and 4.0 mg/kg of saroglitazar, respectively, while the pH for the 2.0 mg/kg dose was recorded at 7.8. Statistical analysis demonstrated significant differences in gastric pH values when comparing other groups with the positive control group ($p < 0.05$). Histopathological results show deposition thickness, inflammation, vascular structure, and fibroblast presentation. The negative control group showed normal gastric histological architecture.

Table 1: Evaluation of hematological inflammatory indices (ENR, NLR, and SII) among the different experimental groups

Variables	SAR 4.0 mg/kg	SAR 2.0 mg/kg	Vonoprazan	+ve control	-ve control
SII					
Min - Max	7.18-33.54	3.82-89.73	22.09-249.2	4.99-464.6	14.04-209.5
Q1 -Q3	10.37-33.08	3.842-20.62	30.3-41.09	7.867-317.8	17.1-165.5
Median	15.15	5.82	34.88	32.17	23.12
IQR	22.71	16.78	10.79	309.93	148.4
NLR					
Min - Max	0.014-0.052	0.007-0.165	0.035-0.836	0.008-0.608	0.022-0.277
Q1 -Q3	0.022-0.048	0.007-0.034	0.048-0.066	0.015-0.438	0.027-0.260
Median	0.0308	0.009804	0.05882	0.05556	0.04128
IQR	0.02544	0.027203	0.0184	0.42276	0.23281
ENR					
Min - Max	0-0.231	0-0.125	0.009-0.057	0-0.042	0.004-0.103
Q1 -Q3	0-0.1	0-0.08	0.016-0.043	0-0.028	0.01-0.103
Median	0.02469	0.01399	0.0339	0.001901	0.02778
IQR	0.1034	0.08333	0.02647	0.02762	0.09298

Ratio of Eosinophil-to-Neutrophil Ratio (ENR), Ratio of Neutrophil to Lymphocyte Ratio (NLR), and Systemic Immune-Inflammation Index (SII), The comparison between the positive control group and the other groups while using Kruskal-Wallis's test did not yield statistical significance ($p > 0.05$).

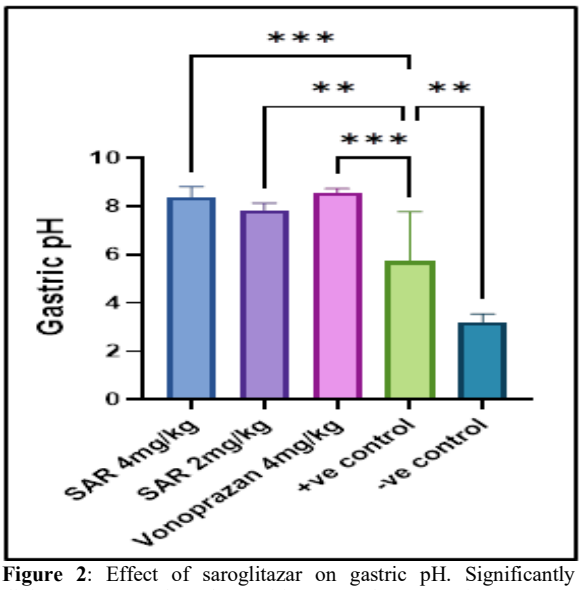

Figure 2: Effect of saroglitazar on gastric pH. Significantly different compared to the positive control group using one-way ANOVA. *($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$).

No inflammatory cell infiltration, vascular change, fibroblast proliferation, or collagen deposition was observed. Therefore, all parameters were graded as "no," corresponding to a score of 0**.** In contrast, the positive control group showed severe pathological alterations in the ulcerated areas. The ulcer bed was filled with highly vascularized tissue accompanied by marked inflammatory cell infiltration (35.00) and diffuse, widespread dense vascular congestion and destruction (17.80)**.** Both parameters were graded as marked score 3**.** Fibroblast presentation and collagen deposition were absent, both corresponding to grade "No" (score 0). In the standard treatment group and low-dose treatment group, both groups demonstrated a mild degree of inflammation with mean values of 13.0 and 12.6, respectively, corresponding to score 1. This finding was accompanied by a mild degree of vascular congestion, with mean values of 3.0 and 3.64, respectively, also corresponding to score 1.0. Both groups showed a moderate level of fibroblast presentation, with mean values of 24.4 and 24.8, respectively, which corresponded to score 2.0. No statistically significant differences were seen between the two groups when compared. Regarding collagen deposition, the standard group showed a low grade of collagen thickness (16.87 µm) corresponding to score

1.0, whereas the low-dose group showed moderate collagen deposition (17.71 µm) corresponding to score 2.0, although the difference remained statistically non-significant. In the high-dose treatment group, which represented the most effective therapeutic outcome, inflammatory cell infiltration and vascular congestion were absent throughout the tissue sections, both corresponding to grade No (score 0). In contrast, there was fibroblast presentation (26.0) and strong collagen restoration thickness (22.98 µm), corresponding to scores of 3.0, indicating advanced tissue structure preservation and accelerated preparation for the healing process. All histopathological findings and statistical comparisons among the experimental groups are presented in Table 2 and illustrated in Figures 3 and 4. Additionally, Figure 5 demonstrates the macroscopical appearance of the stomach mucosa at different treatment modalities.

Table 2: Semi-quantitative histopathological evaluation of collagen deposition thickness, inflammation, vascular congestion, and fibroblast restoration among the different experimental groups in gastric ulcer tissue.

Experimental group	Collagen deposition (µm)	Score	Grade
-ve Control	0±0.0^{a}	0	No
+ve Control	0±0.0^{a}	0	No
Vonoprazan	16.87±0.55^{b}	1	Low
Saroglitazar (2 mg/kg)	17.71±1.08^{b}	2	Moderate
Saroglitazar (4 mg/kg)	22.98±1.73^{c}	3	Strong
Experimental group	Inflammation	Score	Grade
-ve Control	0.0±0.0^{a}	0	No
+ve Control	35.00±1.58^{b}	3	Marked
Vonoprazan	13.00±0.7^{c}	1	Mild
Saroglitazar (2 mg/kg)	12.60±1.14^{c}	1	Mild
Saroglitazar (4 mg/kg)	0.0±0.0^{a}	0	No
Experimental group	Vascular change	Score	Grade
-ve Control	0.0±0.0^{a}	0	No
+ve Control	17.80±5.7^{b}	3	Marked
Vonoprazan	3.0±0.7^{c}	1	Mild
Saroglitazar (2 mg/kg)	3.64±0.54^{c}	1	Mild
Saroglitazar (4 mg/kg)	0.00±0.0^{a}	0	No
Experimental group	Fibroblast presentation	Score	Grade
-ve Control	0.00±0.0^{a}	0	No
+ve Control	0.00±0.0^{a}	0	No
Vonoprazan	24.4 ±0.89^{b}	2	Moderate
Saroglitazar (2 mg/kg)	24.8±1.92^{b}	2	Moderate
Saroglitazar (4 mg/kg)	26.0 ±1.0^{c}	3	Marked

Results are expressed as Mean ± Standard Deviation (SD), with n = 5 animals in each group. Note: Values with distinct superscript letters are significantly different at $p< 0.05$, as determined by the Tukey post hoc test after the one-way ANOVA.

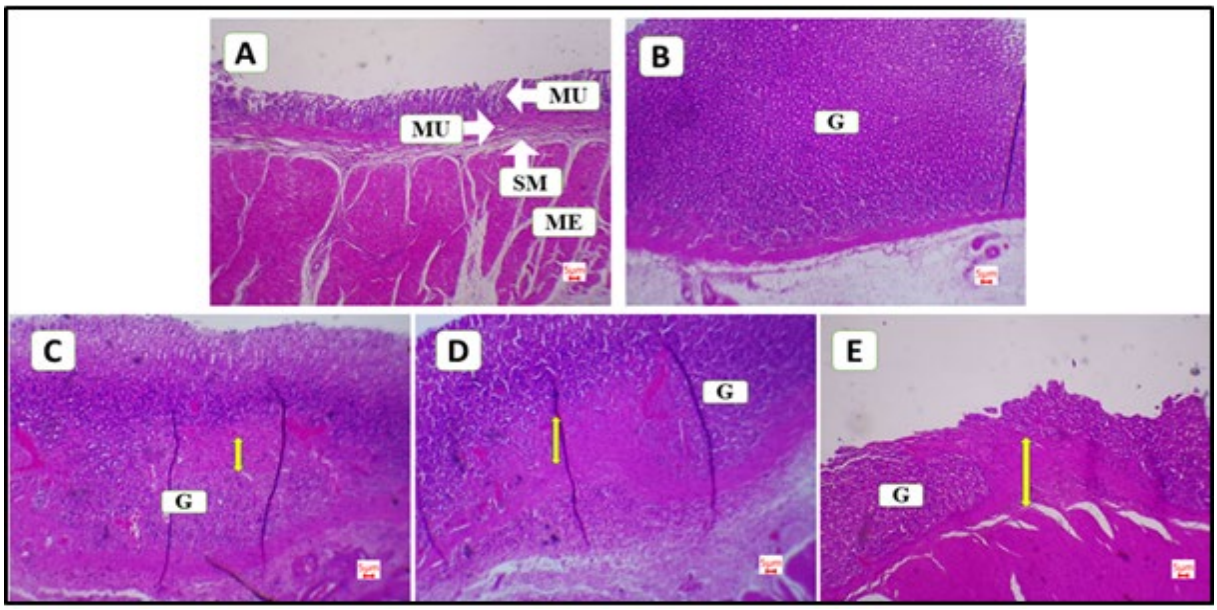

Figure 3: Histopathological evaluation of gastric tissue architecture and collagen restoration of different experimental groups. Panel (A) shows the normal group, demonstrating the preserved histological gastric wall architecture, including intact mucosa (M), muscularis mucosae (MM), submucosa (SM), and muscularis externa (ME), with no disruption or ulceration of the mucosal layer. Panel (B) represents the positive control (ulcer model) group, showing a gastric ulcer crater filled with granulation tissue (G), indicative of active ulceration and tissue repair. No collagen deposition was observed, corresponding to a collagen score of 0. Panel (C) illustrates the standard treatment group, where granulation tissue exhibits low-grade collagen deposition, with thin collagen fibers indicated by a bidirectional arrow, corresponding to score 1. Panel (D) shows the low-dose treated group, demonstrating a moderate degree of collagen deposition with increased collagen fiber thickness, corresponding to score 2. Panel (E) represents the high-dose treated group, where dense and thick collagen restoration is evident, corresponding to score 3. Hematoxylin and eosin (H&E) staining was used for staining of the specimen and examined at 4× magnification. Scale bar = 5 µm.

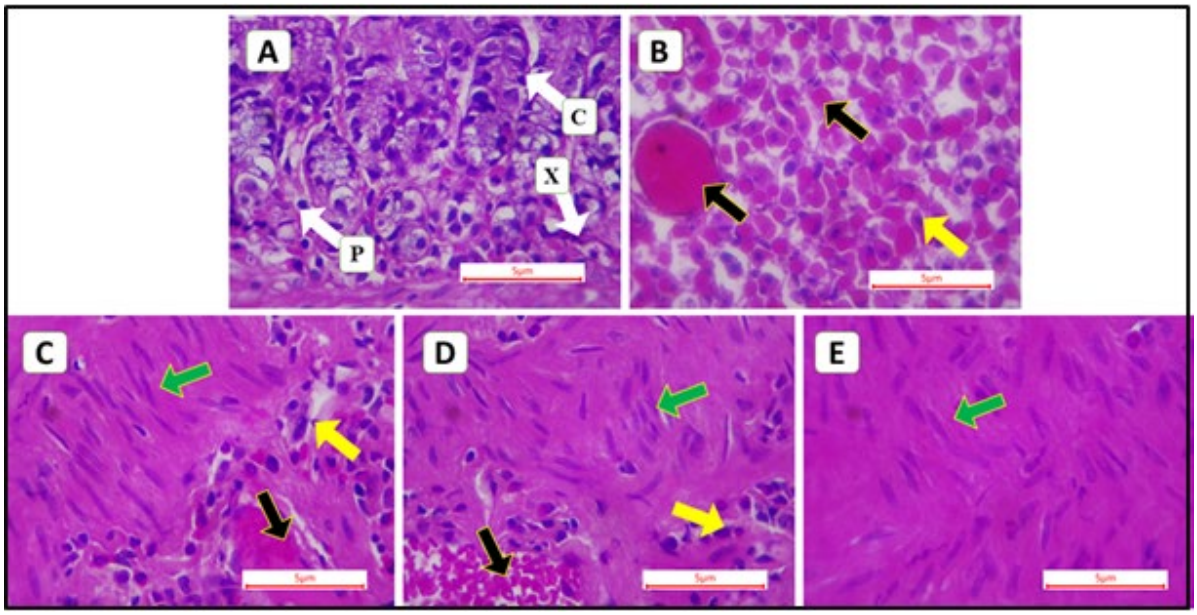

Figure 4: Representative Photomicrographs of Gastric Tissue Sections Showing Inflammatory and Vascular Changes. Panel (A) shows the normal control group with preserved gastric mucosal architecture, including intact foveolar columnar mucus-secreting cells (C), pale eosinophilic acid-secreting parietal cells (P), and dark-staining zymogen-secreting chief cells (X), indicating normal histological organization. Panel (B) represents the disease model group, where the ulcer bed is filled with highly vascularized granulation tissue characterized by marked angiogenesis (black arrow) and dense inflammatory cell infiltration (yellow arrow), corresponding to score 3, with no evidence of fibroblast proliferation. Panels (C) and (D) represent the standard-treatment and low-dose-treatment groups, respectively; both show partial histological improvement with mild residual inflammatory infiltration (yellow arrow) and mild vascular change and congestion (black arrow), corresponding to score 1, along with moderate fibroblast presentation (green arrow), corresponding to score 2. Panel (E) represents the high-dose treatment group, demonstrating marked regression of vascular change and congestion and absence of inflammatory cell infiltration (score 0), with prominent active fibroblast presentation (green arrow), corresponding to score 3, with H&E staining at 40× magnification (scale bar = 5 µm).

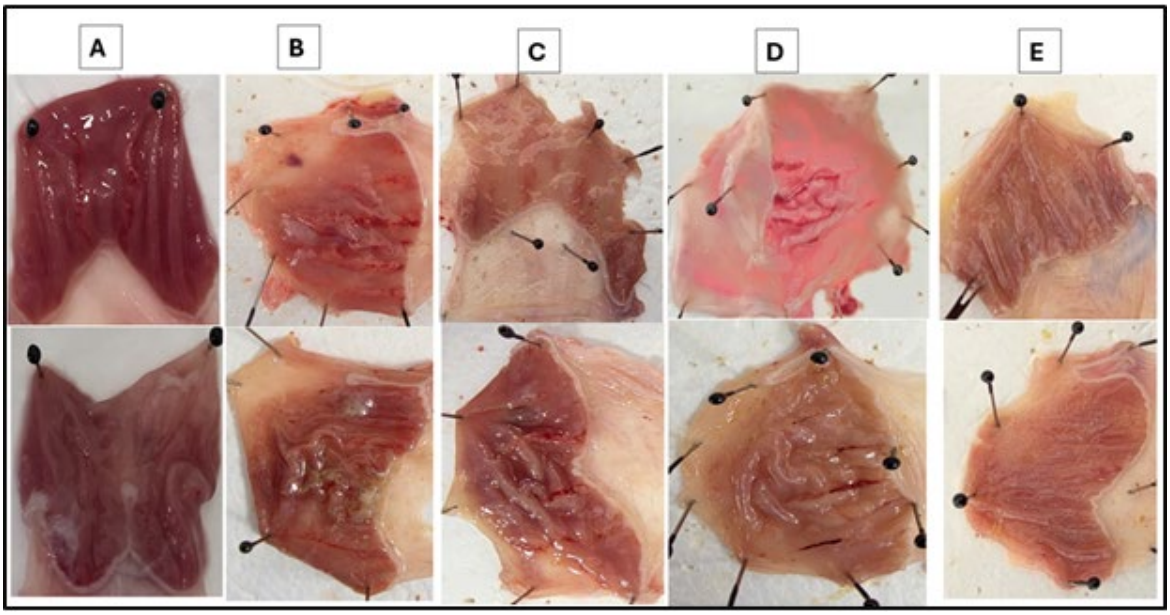

Figure 5: Representative images of stomachs from experimental groups. (**A**) Saroglitazar 4 mg/kg group. (**B**) Saroglitazar 2 mg/kg group. (**C**) Vonoprazan-treated group, (**D**) Positive control group (**E**) Negative control group.

DISCUSSION

A gastric ulcer is a worldwide health issue resulting from erosions of variable severity in the gastrointestinal mucosa. Various therapies exist for gastric ulcers; however, they frequently include restrictions stemming from side effects and potential consequences on other body organs [27]. Several studies have demonstrated the deleterious effects of ethanol toward the GIT and stomach. Gastric ulcer production with ethanol in rats is used as a model for investigating the gastroprotection action of plant agents and drugs [7,28]. The onset of gastric mucosa injury is a critical element, resulting from specific inflammatory reactions characterized by the buildup of pro-inflammatory cytokines in the gastric mucosa due to ethanol intake [22]. Alcohol use activates innate immunity, resulting in pro-inflammatory cytokine release, including TNF-α and IL-6 [28]. The production of inflammatory chemicals significantly contributes to the processes of lesions by creating an inflammatory environment that promotes the formation of acute stomach mucosa ulcers. [29]. TNF-α is a pivotal component in the pathogenesis of ethanol-induced stomach mucosal inflammation and damage [28]. It promotes neutrophil migration in

inflamed gastrointestinal regions, inhibits stomach microcirculation close to ulcerated mucosa, and prolongs the healing of stomach ulcers [30]. Studies indicate that gastric mucosa infection with H. pylori or damage with ethanol stimulates production of IL-6 [22]. Peripheral blood cell count as a measure of systemic inflammation has recently attracted more research interest [31]. The biomarkers are generated from two- or three-parameter combinations involving neutrophils, lymphocytes, platelets, and monocytes [32]. Different researchers have found a relationship between CBC-derived inflammatory biomarkers and C-derived inflammatory biomarkers with the development of metabolic dysfunction and heart failure [33]. A cross-sectional study showed relationships between CBC-derived biomarkers and the human prevalence of gastric ulcers [31]. The PPAR system has roles in regulating the function and homeostasis of multiple organs in our body, including the immune system and stomach [19]. Additionally, it serves as one of the regulators involved in the inflammation process. Several studies show the gastroprotective effect of different agents that activate this system [12-24]. Based on evidence about the PPAR system and agents that work on it, we hypothesized that saroglitazar is also a suitable candidate for gastric ulcers. In our study we explored the anti-inflammatory and healing effect of saroglitazar on ethanol-induced gastric lesions in mice. The result of the current study reveals that serum TNF-α is significantly decreased in the saroglitazar (4 mg/kg; high dose) group and when compared to the positive control group. These results align well with other studies' directions about the effects of saroglitazar on TNF-α [17,18]. Although TNF-α showed significant changes, IL-6 levels did not present a statistically significant difference among the experimental groups. Compared to most of the previous studies showing alterations in IL-6, the present data are in agreement with a previous report in which IL-6 levels did not change statistically [2,23]. The histopathology results showed that there was controlled inflammation in the saroglitazar (4.0 mg/kg; high dose) group and mild inflammation in the saroglitazar (2.0 mg/kg; low dose) group when compared with the positive control group, which was characterized by inflammatory cell infiltration. About the CBC inflammatory-related biomarker in our study, although the treatment group showed lower NLR and SII and higher ENR than the positive control group, the difference was not statistically significant. The results of the present study demonstrate the anti-inflammatory activity of saroglitazar from the significant reduction in TNF-α and histopathology results. The current finding suggests that saroglitazar may possess gastroprotective properties, potentially via mitigating the inflammatory responses associated with stomach ulcer formation, which is the primary treatment strategy for gastric ulcers [22,33]. The histopathological results showed that the decreased stomach collagen content in the positive control group following ethanol exposure could be attributed to the direct damage of ethanol to collagen fibers. Pretreatment with saroglitazar significantly restored the collagen levels, while vonoprazan had little restorative impact. These results are in agreement with previous observations that pretreatment with omeprazole or tert-butylhydroquinone prevents ethanol-induced collagen depletion and enhances collagen recovery in gastric tissue [7]. Our results revealed that ethanol administration in positive control groups makes vascular changes, including vascular congestion and injury. This change was mild with the saroglitazar (2.0 mg/kg, low dose) and vonoprazan groups while being strongly reversed with the saroglitazar (4.0 mg/kg, low dose). Li *et al*. observed that ethanol treatment could cause blood circulation disturbance and gastric microvascular integrity disruption, eventually leading to gastric tissue necrosis [7,29]. In the present study, significant presentation of fibroblast cells was observed with pretreatment groups in different amounts, consistent with prior studies showing early activation of spindle-shaped cells after induction of gastric ulcer in the positive control group; these cells act as activators of collagen production [36]. In our study, pre-treatment with Saroglitazar and Vonoprazan elevates gastric pH significantly when compared with the positive control group. This pH elevation has an important role in the gastroprotective and healing effect of saroglitazar against gastric ulcers. Excessive gastric acid production is a primary pathogenic component in the development of stomach ulcer disorders [37]. Histopathology results showed the important effect of saroglitazar on gastric structural protection, inflammation control, and enhancing healing processes through stimulating collagen deposition, restoration, and vascular structure protection. Several studies have mentioned the anti-inflammatory effect of protective agents as a practical strategy in the prevention or treatment of gastric ulcers in a rat model. Liu *et al*. evaluated butyrate gastroprotective effects through anti-inflammatory and antioxidant effects [38]. Another study evaluates gallic acid's gastroprotective effect against gastric ulcers through antioxidant and anti-apoptosis mechanisms [39].

Study Limitations and Future Prospects

This investigation was confined to an acute ethanol-induced gastric ulcer model, which may not comprehensively reflect other clinically pertinent etiologies of gastric ulceration. The brief testing period hindered the assessment of long-term efficacy and safety. Furthermore, other pathways contributing to stomach mucosal protection were not examined. Ultimately, given that this was an animal study, the results necessitate confirmation through clinical trials prior to use in humans. Future research should examine the drug in several stomach ulcer models, encompassing NSAID-, stress-, and *H. pylori*-induced ulcers, while also evaluating its long-term efficacy and safety. Additional mechanistic investigations are necessary to clarify the molecular processes that underlie its gastroprotective properties. Clinical trials will ultimately be required to validate its therapeutic efficacy in people.

Conclusion

The findings suggest that saroglitazar may exert gastroprotective effects on rats' stomach ulcers induced by ethanol by decreasing TNF-α levels, increasing stomach pH, yielding better histological results with less inflammation, restoring collagen content, increasing fibroblast presence, and protecting against vascular injury; however, additional research, particularly well-designed clinical trials in humans, is essential to validate its efficacy and safety and to determine its potential therapeutic role in managing gastric ulcer disorder.

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Conflict of interests

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Data sharing statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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