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Original Research Article

Psoralidin Shows Gastroprotective Activity Against Ethanol-induced Acute Gastric Mucosal Injury in Rats via Inhibiting Oxidative Stress and Inflammation

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Abstract

Background: Gastric ulcers, a predominant type of peptic ulcer disease, are defined by lesions in the stomach lining that extend into the muscularis mucosa. Optimal management of gastric ulcers requires a multidisciplinary approach, with nurses playing a vital role in monitoring gastrointestinal symptoms and educating patients to mitigate disease progression and promote healing. The limitations of existing therapeutics for stomach ulcers highlight the necessity for safe and alternative treatments.
Objectives: This study aims to examine the gastroprotective role of psoralidin in ethanol-induced acute gastric ulcer in rats.
Materials and Methods: In this study, the rats were orally pre-treated with 25 and 50 mg/kg of psoralidin for 14 days, and ethanol (5 mL/kg) was ingested on the last day of treatment to induce an acute gastric ulcer in rats. Omeprazole was employed as the standard drug. The ulcer area, ulcer inhibition rate, and mucus weight in the rats were evaluated. The concentrations of oxidative stress markers, inflammatory markers, and prostaglandin E2 (PGE2) in the experimental rats were evaluated using kits. The gastric tissues were obtained and utilized for histological analysis.
Results: The current findings demonstrate that psoralidin pre-treatment at dosages of 25 and 50 mg/kg effectively diminished ulcer area, increased the ulcer inhibition rate, and mucus production in the ethanol-administered rats. The psoralidin effectively decreased the inflammatory biomarkers and oxidative stress markers, and subsequently elevated the antioxidant levels in the ethanol-induced rats. Moreover, it also augmented the PGE2 in the stomach tissues of ethanol-induced rats. The results of the histological investigation also support the gastroprotective properties of the psoralidin.
Conclusion: This research indicates that psoralidin pre-treatment may prevent ethanol-induced acute stomach injury in rats. Future research is strongly advised to comprehensively elucidate the molecular mechanisms by which psoralidin exerts its therapeutic effects on stomach ulcers.

Keywords

Gastric ulcer, ethanol, prostaglandin E2, psoralidin, nitric oxide

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Introduction

Gastric ulcers, representing a significant subset of peptic ulcers, are defined by lesions in the stomach lining that penetrate the muscularis mucosa. These ulcers arise from an imbalance between aggressive factors, such as acid and pepsin, and protective mechanisms, including mucus secretion, bicarbonate production, and mucosal blood flow. The disruption of this equilibrium leads to the erosion of the gastric mucosa, culminating in ulcer formation. Gastric ulcers affect millions worldwide, with prevalence rates varying across geographical regions and populations, influenced by factors like *Helicobacter pylori* infection rates, non-steroidal anti-inflammatory drug (NSAID) usage, and lifestyle choices (Melcarne et al., 2016). The pathogenesis of gastric ulcers is multifactorial, with *H. pylori* infection and NSAIDs overuse being the predominant causative agents. These elements, along with acid-pepsin imbalance, genetics, and smoking, contribute to the development of peptic ulcers. Other factors implicated in gastric ulcer development include ischemia, chemotherapy, radiotherapy, gastric bypass surgery, and metabolic disturbances. The economic burden of peptic ulcer

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disease is substantial, encompassing direct medical costs, lost productivity, and diminished quality of life (Tarnawski et al., 2014).

The pathophysiology of gastric ulcers encompasses a complex interplay of inflammatory, immunological, and biochemical processes. *H. pylori* infection triggers an inflammatory cascade, leading to the release of cytokines and chemokines that recruit immune cells to the gastric mucosa (Fonseca da Silva et al., 2020). Chronic inflammation damages the gastric epithelium, impairing its ability to withstand the scarring effects of acid and pepsin. NSAIDs, on the other hand, inhibit cyclooxygenase enzymes, reducing prostaglandin synthesis and compromising mucosal defense mechanisms. Prostaglandins normally stimulate bicarbonate and mucus generation, augment mucosal blood flow, and enhance epithelial cell turnover, all of which are crucial for maintaining mucosal integrity (Galura et al., 2019). The resulting disruption of the mucosal barrier exposes the underlying tissue to acid and pepsin, initiating and perpetuating ulceration. Reactive oxygen species (ROS), generated during metabolic activities, further contribute to the damage by overwhelming antioxidant defenses, leading to lipid peroxidation and cellular injury (Kavitt et al., 2019).

Current treatment strategies for gastric ulcers primarily focus on acid suppression and eradication of *H. pylori* infection. Proton pump inhibitors (PPIs), like omeprazole, represent the keystone of acid-suppressive treatment, potently inhibiting gastric acid production by permanently blocking the H+/K+-ATPase enzyme in parietal cells. H2-receptor antagonists (RAs) competitively block histamine H2 receptors on parietal cells, reducing acid secretion, but are generally less effective than PPIs (Leng et al., 2023). Sucralfate, a mucosal protectant, forms a viscous gel that adheres to the ulcer base, shielding it from acid and pepsin. Bismuth subsalicylate has some anti-microbial properties and coats the ulcer. In *H. pylori*-positive ulcers, eradication therapy typically involves a combination of PPIs and antibiotics, like amoxicillin and clarithromycin. The goal of eradication therapy is to eliminate the bacteria from the stomach, thereby promoting ulcer healing and preventing recurrence. Furthermore, tranexamic acid, a synthetic agent, can be used as a medical treatment because of its anti-fibrinolytic effects (Manu et al., 2021).

Optimal management of gastric ulcers requires a multidisciplinary approach, with nurses playing a vital role in monitoring gastrointestinal symptoms, administering medications, and educating patients on self-care strategies to mitigate disease progression and promote healing. Nurses should also prioritize assessment of patients' nutritional status, as malnutrition can exacerbate gastric ulcer symptoms. By adopting a holistic approach to care, nurses can make a significant difference in patients' recovery outcomes and overall well-being (Yuan et al., 2024). Despite the effectiveness of current treatments, several challenges remain. *H. pylori* resistance to antibiotics is a growing concern, reducing the efficacy of eradication regimens. Antibiotic resistance is an increasing problem in *H. pylori* eradication, necessitating the development of alternative treatment strategies. Adherence to treatment regimens can also be a challenge, particularly with complex antibiotic combinations (Kamada et al., 2021). Some patients may experience side effects from medications, leading to non-compliance and treatment failure. Moreover, current therapies do not address the underlying causes of ulcer development in all cases, particularly in patients with NSAID-induced ulcers or those with idiopathic ulcers. Many patients who take PPIs experience unresolved physiological problems and further complications (Satoh et al., 2016). The limitations of current therapies underscore the need for safe and alternative treatments for gastric ulcers. Interestingly, the natural products, such as plant bioactive compounds, have demonstrated several pharmacological effects. These alternative therapies could potentially complement conventional treatments, improving ulcer healing rates and reducing the risk of relapse (Shipa et al., 2022). Psoralidin is a naturally occurring bioactive phenolic coumarin compound found in the *Psoralea corylifolia* seeds, has numerous biological effects, including anti-microbial, antioxidant, anti-allergic, anti-inflammatory, and anti-depressant properties (Sharifi-Rad et al., 2020). The numerous previous studies have reported that psoralidin has several biological activities, such as cardioprotective (Liang et al., 2022), neuroprotective (Lei et al., 2022), anti-cancer (Jin et al., 2016), and anti-osteoporotic (Xin et al., 2019) effects. However, the protective activity of psoralidin against gastric ulcers has not been thoroughly assessed, and the molecular mechanisms underlying its therapeutic effects remain unidentified. Hence, this work intends to examine the gastroprotective role of psoralidin in ethanol-induced gastric ulcer in rats.

Materials and Methods

Chemicals

The primary chemicals and pharmaceuticals, including psoralidin and ethanol, were sourced from Sigma–Aldrich (USA). The diagnostic kits for quantifying biochemical marker concentrations were procured from Abcam and MyBioSource, USA, respectively.

Experimental Animals

The current investigation employed healthy male Wistar rats aged 6–8 weeks, with 160 ± 40 g of body weight. The protocols for the animal tests were validated and sanctioned by the institutional animal ethics committee. The rats were acclimatized in a regulated laboratory setting for 7 days. The rats were housed in sterile polypropylene enclosures. Rigorous hygiene standards were maintained for the duration of the tests, and cages and bedding were consistently replaced.

Standard temperature and relative humidity were consistently upheld, along with a 12-h light/dark cycle. All rats were given full access to a standard pellet meal (Bio-Serv, USA) and drinking water.

Treatment Groups

The rats were randomly allocated into four groups, each comprising six rats ($n = 6$). Group I consists of normal control rats that are solely provided with a standard pellet diet and given distilled water (5 mL/kg) for 14 days. Rats in Group II, subjected to gastric ulcer induction using ethanol (5 mL/kg) on the 14th day. Groups III and IV rats underwent pre-treatment with 25 and 50 mg/kg of psoralidin, respectively (Yang et al., 2023) via oral gavage for a duration of 14 days and were induced with ethanol on the last day. Group V rats were pre-treated with 20 mg/kg of the standard drug omeprazole for 14 days and were subjected to ethanol induction on the last day.

Gastric Ulcer Induction

A 5 mL/kg of ethanol was administered orally to the rats to induce gastric ulcers. At the same time, the animals were food-restricted and were permitted unrestricted access to water until 2 h before the initiation of the study to ensure adherence to the stomach emptying protocol (Sibilia et al., 2003).

Analysis of Ulcer Area, Ulcer Inhibition Rate, and Mucus Weight

Rat's stomach was surgically incised, gastric tissue was obtained, and thoroughly rinsed with saline. The gastric tissues were mounted on a white background and photographed. The ulcer area was evaluated using the technique defined earlier (Kleine et al., 1993). The gastrointestinal mucosa was gently scraped using a clean glass slide, and the weight of the mucus was measured with a precise electronic scale (Precisa Gravimetrics AG, Switzerland) (Hobani et al., 2022).

To determine the inhibition percentage of stomach injury, the equation employed was:

$$\left[\left(\mathrm{UI}_{\mathrm{control}} - \mathrm{UI}_{\mathrm{treated}}\right) / \mathrm{UI}_{\mathrm{control}}\right] \times 100$$

where UI denotes the ulcer index.

Analysis of Oxidative Stress Markers

The concentrations of oxidative stress and antioxidants, like malondialdehyde (MDA), glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in the gastric tissue homogenates were evaluated using the commercially procured kits. The tests were performed in triplicates using the specifications specified by the manufacturer (Abcam, USA).

Analysis of Inflammatory Marker Levels

The serum concentrations of inflammation-related biomarkers, including nitric oxide (NO), interleukin (IL)-6, tumor necrosis factor (TNF)-α, and prostaglandin E2 (PGE2) in both control and experimental rats were assessed using commercially available assay kits. All assays were conducted in triplicate according to the manufacturer's guidelines (MyBioSource, USA).

Histopathological Analysis

The gastric tissues were excised from the experimental rats and subsequently preserved in formalin (10%) solution. The tissues were subsequently dehydrated and processed with a gradient mixture of ethyl alcohol, water, and xylene. The processed tissues were paraffinized and sectioned at 5 μm thickness. The excised tissues were then stained with eosin and hematoxylin and examined histopathologically in a blinded fashion using a light microscope. The pathological score of each gastric tissue was evaluated using the method specified previously (Liu et al., 2016). This score encompasses the assessment of gastric mucosal injury and inflammatory cell (neutrophilic) infiltrations.

Statistical Analysis

The findings were evaluated using GraphPad Prism (version 10.5.0), and the data were given as mean ± SD of triplicates. The one-way analysis of variance (ANOVA) was utilized for intergroup comparison, followed by Tukey's *post hoc* test for multiple group comparisons, with $p < .05$ deemed as significant.

Results

Effect of Psoralidin on the Ulcer Area, Inhibition Rate, and Mucus Weight in the Experimental Rats

The present findings suggested that ethanol administration led to a significant increase in ulcer area and reduced mucus secretion in the rats compared to the control rats. Whereas, the pre-treatment of 25 and 50 mg/kg of psoralidin significantly decreased the ulcer area and augmented the ulcer inhibition rate in the ethanol-administered rats. Furthermore, the psoralidin treatment also increased the mucus production in the ethanol-induced rats. The outcomes of the psoralidin treatment were further corroborated by the standard drug omeprazole, which similarly significantly diminished the ulcer area and increased the inhibition rate and mucus production in the ethanol-induced rats (Figure 1).

Effect of Psoralidin on the Oxidative Stress Markers in Experimental Rats

The present findings revealed a considerable elevation in the MDA along with the reduction in CAT, SOD, GSH, and GPx concentrations in the gastric tissues of

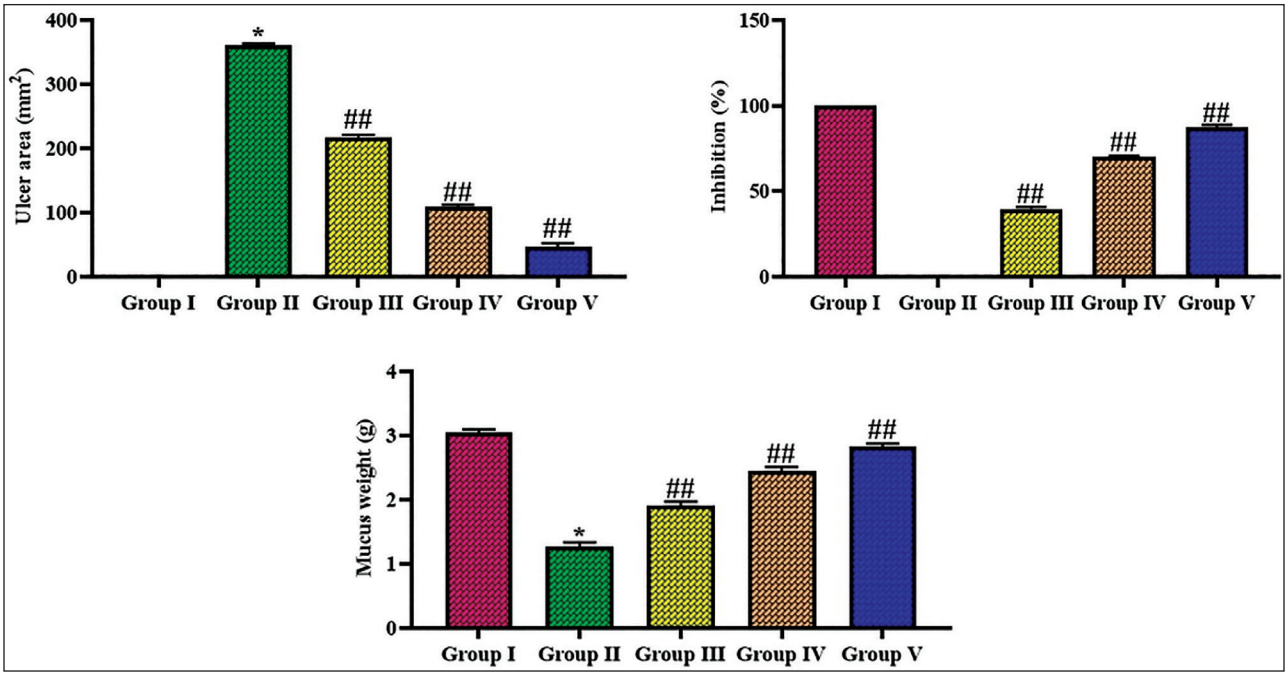


Figure 1. Effect of Psoralidin on the Ulcer Area, Inhibition Rate, and Mucus Weight in the Experimental Rats. The Results Were Analyzed Using GraphPad Prism, and the Data Were Expressed as Mean ± SD of Triplicates. The Statistical Significance Levels for Treatment Groups Were Established as "*" $p < .01$ for Comparisons Between the Control and Ethanol-induced Groups; "##" $p < .05$ for Comparisons Between the Ethanol-induced and the Psoralidin and/or Omeprazole-treated Groups.

ethanol-administered rats. Captivatingly, the oral pre-treatment of psoralidin at dosages of 25 and 50 mg/kg led to a marked reduction in the MDA and an elevation in the CAT, SOD, GSH, and GPx concentrations in the gastric tissues of the ethanol-administered rats (Figure 2). Omeprazole treatment concurrently showed a considerable reduction in MDA and an elevation in the antioxidant levels in the gastric tissues of the ethanol-induced rats, hence supporting the antioxidant effects of psoralidin.

Effect of Psoralidin on the Inflammatory Markers in the Experimental Rats

To assess the impact of psoralidin on the inflammatory condition, the concentrations of inflammatory markers were assessed in the serum of experimental rats. The ethanol-ingested rats exhibited a substantial increase in NO, TNF-α, and IL-6 concentrations along with a reduction in PGE2 levels compared with the control (Figure 3). Nonetheless, the psoralidin at 25 and 50 mg/kg concentrations significantly reduced the levels of inflammatory markers and subsequently elevated the PGE2 concentrations in the ethanol-ingested rats. Notably, these results are similar to the findings associated with the omeprazole treatment. These experimental results indicate that psoralidin has anti-inflammatory effects.

Effect of Psoralidin on Gastric Tissue Histopathology of Experimental Rats

The histological examination of gastric tissue from control rats exhibited typical structures with intact epithelium and glands. Figure 4 illustrates that hematoxylin and eosin (H&E) staining images revealed significantly increased histological scores due to the mucosal damage and leukocyte infiltration in the gastric tissues of the ethanol-ingested rats. Nevertheless, the damage to the stomach mucosa was considerably reduced in rats pre-treated with 25 and 50 mg/kg of psoralidin. Similarly, the omeprazole treatment also considerably reduced the gastric injury in the ethanol-ingested rats, which further supports the gastroprotective effects of the psoralidin.

Discussion

Gastric ulcers, representing a substantial challenge in gastroenterology, are characterized by discontinuities in the gastric mucosa extending beyond the muscularis mucosae, frequently resulting from an inequality between the factors like pepsin and acid and the defensive mechanisms safeguarding the gastric lining (Narayanan et al., 2018). The pathogenesis of gastric ulcers is multifaceted, with *H. pylori* infection and the utilization of NSAIDs being the predominant etiological factors. These disrupt the intricate balance of mucosal defense

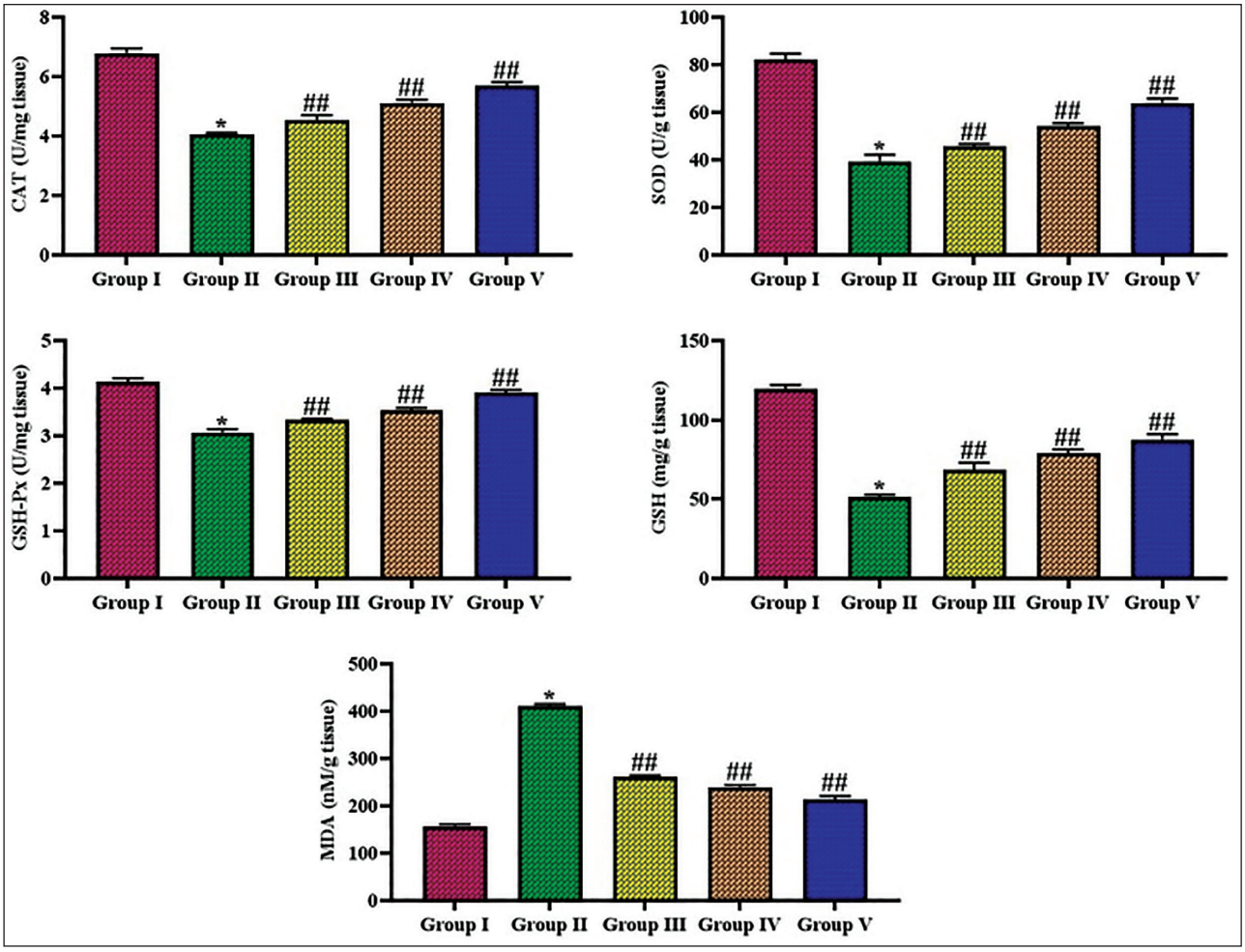


Figure 2. Effect of Psoralidin on the Oxidative Stress Markers in the Experimental Rats. The Results Were Analyzed Using GraphPad Prism, and the Data Were Expressed as Mean ± SD of Triplicates. The Statistical Significance Levels for Treatment Groups Were Established as "*" $p < .01$ for Comparisons Between the Control and Ethanol-induced Groups; "##" $p < .05$ for Comparisons Between the Ethanol-induced and the Psoralidin and/or Omeprazole-treated Groups.

and repair mechanisms. The implications of gastric ulcers extend beyond mere discomfort, encompassing a spectrum of complications like bleeding and gastric outlet obstruction, which can significantly impair the quality of life and necessitate extensive medical intervention (Lanas et al., 2015). Traditional therapies, including PPIs and histamine RAs, have shown efficacy in acid suppression and ulcer healing; however, these approaches are not without limitations, including potential side effects and the increasing prevalence of antibiotic resistance in *H. pylori* strains. The imperative to develop safe and effective alternative therapies is underscored by the chronicity and recurrence of gastric ulcers, coupled with the adverse effects associated with long-term conventional treatment (Chey et al., 2017). The exploration of alternative therapies for gastric ulcers has gained momentum, propelled by the limitations of conventional treatments and the escalating demand for patient-centered approaches.

The evaluation of mucus weight, ulcer area, and ulcer inhibition percentage represents a cornerstone in assessing the efficacy of plant bioactive compounds against gastric ulcers induced by ethanol in rat models (Cho & Ogle, 1992). The onset of gastric ulcers is intricately linked to causes like excessive acid production, diminished mucosal defense mechanisms, and the influence of noxious substances like ethanol. Ethanol, a widely recognized ulcerogenic agent, induces gastric damage by several mechanisms, including the generation of ROS, disruption of the gastric mucosal barrier, and impairment of local blood flow (Bujanda, 2000). Consequently, the use of plant bioactive compounds, renowned for their antioxidant, anti-inflammatory, and cytoprotective properties, has garnered considerable attention as a therapeutic strategy for mitigating gastric ulcers (Roy et al., 2023). The assessment of mucus weight plays a pivotal role in evaluating the protective effect of plant bioactive compounds

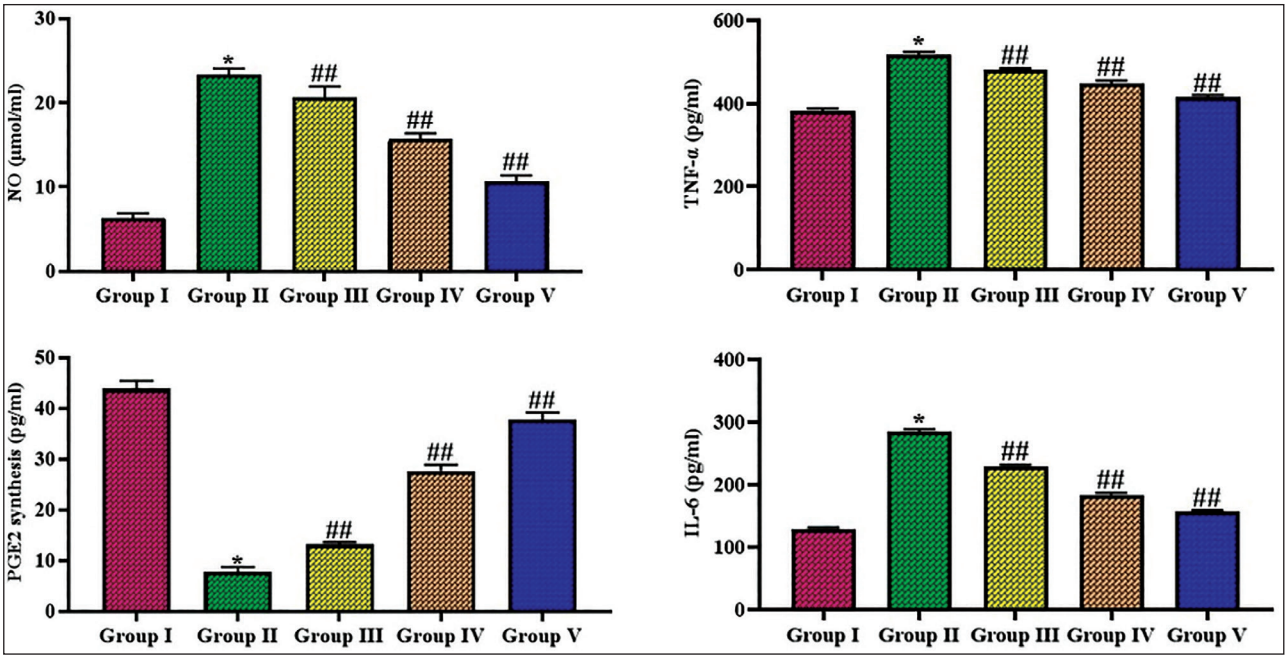


Figure 3. Effect of Psoralidin on the Inflammatory Markers in the Experimental Rats. The Results Were Analyzed Using GraphPad Prism, and the Data Were Expressed as Mean ± SD of Triplicates. The Statistical Significance Levels for Treatment Groups Were Established as "*" $p < .01$ for Comparisons Between the Control and Ethanol-induced Groups; "##" $p < .05$ for Comparisons Between the Ethanol-induced and the Psoralidin and/or Omeprazole-treated Groups.

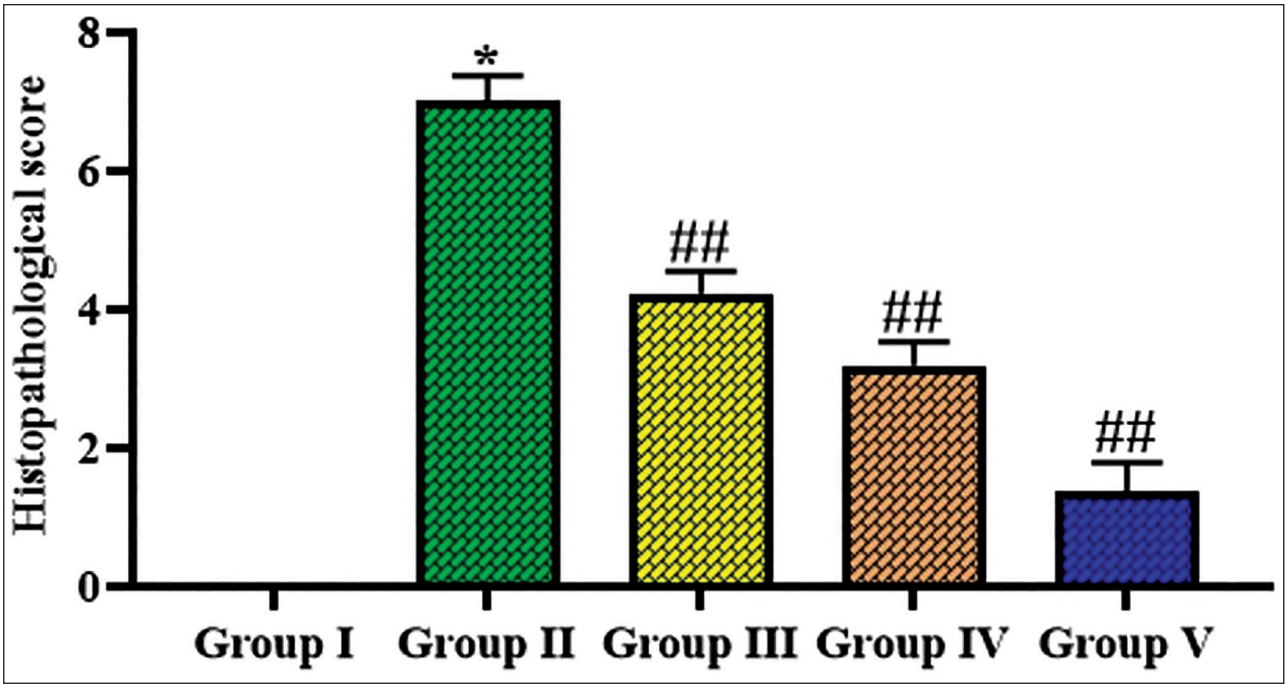


Figure 4. Effect of Psoralidin on the Gastric Tissue Histopathology of the Experimental Rats. The Results Were Analyzed Using GraphPad Prism, and the Data Were Expressed as Mean ± SD of Triplicates. The Statistical Significance Levels for Treatment Groups Were Established as "*" $p < .01$ for Comparisons Between the Control and Ethanol-induced Groups; "##" $p < .05$ for Comparisons Between the Ethanol-induced and the Psoralidin and/or Omeprazole-treated Groups.

on the gastric mucosa. Mucus, a viscous secretion produced by specialized cells in the stomach lining, forms a physical barrier that shields the epithelium from the harsh acidic environment and pepsin, thus preventing ulcer formation. An increase in mucus weight following treatment with sample compounds suggests an enhancement of the mucosal defense mechanisms, thereby contributing to ulcer healing and prevention (Johansson et al., 2013). The quantification of ulcer area provides a direct measure of the extent of gastric damage caused by ethanol exposure. A reduction in ulcer area in sample compound-treated rats indicates the therapeutic potential of these compounds in promoting ulcer healing and tissue regeneration (Yoo et al., 2022).

The ulcer inhibition percentage, calculated based on the reduction in ulcer area compared to control groups, serves as a quantitative index of the anti-ulcer efficacy of the tested compounds. A higher ulcer inhibition percentage signifies a greater protective activity against ethanol-ingested gastric damage. The analysis of these parameters provides valuable insights into the mechanisms of action of sample compounds in the context of gastric ulcer healing (Alirezaei et al., 2012). The integrity of the gastric mucosa is maintained by natural defense mechanisms that can neutralize gastric acid and pepsin. These mechanisms involve bicarbonate and mucus production, prostaglandins, and mucosal blood flow. The evaluation of these parameters is critical in the development of novel therapeutics for managing gastric ulcers and improving patient outcomes (Gong et al., 2021). In this work, we observed the increased ulcer area and reduced mucus secretion in the ethanol-induced rats. Captivatingly, the oral pretreatment of psoralidin remarkably diminished the ulcer area and augmented the ulcer inhibition rate in the ethanol-induced rats, which is similar to the results of omeprazole treatment.

Oxidative stress, fundamentally an imbalance between pro-oxidants and antioxidants, has garnered substantial attention over the past years, driven by advancements in understanding ROS, identification of oxidative damage biomarkers, and recognition of its link to chronic and acute health issues. The body's defense against oxidative stress relies on antioxidant systems, including SOD, GSH, and CAT. These antioxidant enzymes neutralize ROS generated during normal metabolic activities (Ermis et al., 2023). The excessive production of ROS can overcome the antioxidant mechanisms of cells, resulting in oxidative injury to tissue due to oxidative stress. When this equilibrium is disrupted, progressive oxidation of biological molecules ensues, directly affecting health by lipid peroxidation (Kolgazi et al., 2015). The pathogenesis of gastric ulcers involves a multifaceted cascade of events, wherein oxidative stress plays a pivotal role. Various aggressive factors disrupt the balance within the gastric environment, leading to ulcer formation and involving mechanisms such as the generation of oxygen radicals during normal cellular respiration. Oxidative stress affects a wide array of biological processes, encompassing not only cellular metabolism but also the intricate dynamics of the immune system and genetic regulation. MDA, a product of lipid peroxidation, serves as a biomarker of oxidative stress, reflecting the extent of damage to cell membranes (Vona et al., 2021). Antioxidants such as SOD, CAT, and GSH are crucial in maintaining redox balance and mitigating oxidative damage, thereby safeguarding the integrity of the gastric mucosa. Quantification of these products and the levels of antioxidant compounds can serve as indicators of the extent of oxidative stress in the body (Fagundes et al., 2021). The present findings indicated the drastic elevation in the MDA levels along with the decreased CAT, SOD, GSH, and GPx concentrations in the gastric tissues of ethanol-ingested rats. Interestingly, the psoralidin pretreatment considerably reduced the MDA levels and increased the antioxidant concentrations in the gastric tissues of the ethanol-induced rats. These results support the antioxidant effects of psoralidin.

The delicate balance between the gastrointestinal epithelium and the mucosal immune system is crucial for maintaining intestinal homeostasis, but disruptions can lead to chronic inflammatory diseases. Inflammation, orchestrated by an array of immune cells and signaling molecules, emerges as a central player in this pathological process, with inflammatory biomarkers serving as indicators and mediators of the associated tissue injury. The gastric mucosa is the major part of the body's immune system. This is due to its role in guarding against infection from harmful microorganisms and dangerous substances. When the gastric mucosa becomes chronically inflamed, as is the case with long-term *H. pylori* infection, the chance of acquiring stomach cancer rises significantly (Ciciliato et al., 2022). The role of inflammatory biomarkers like TNF-α, IL-6, and NO in the pathophysiology of gastric ulcers is crucial, as evidenced by their increased presence and activity in the gastric mucosa during ulcer development. These biomarkers, produced by immune cells and gastric epithelial cells, contribute to the inflammatory milieu, exacerbating tissue damage and hindering the healing process (Liang et al., 2018). Understanding the intricate roles of these inflammatory mediators is crucial for developing targeted therapeutic interventions to mitigate inflammation and promote ulcer healing.

TNF-α, a pleiotropic cytokine, occupies a prominent position in the inflammatory cascade connected with gastric ulcers. It is a key pro-inflammatory mediator involved in the pathogenesis of various inflammatory diseases. It exerts its effects by binding to TNF receptors on target cells, triggering intracellular signaling pathways that activate transcription factors, like NF-κB, resulting in the expression of numerous pro-inflammatory genes (de Souza et al., 2019). TNF-α stimulates the production of other pro-inflammatory cytokines like IL-1β and IL-6, which further enhance the inflammation and promote the neutrophil influx at the site of inflammation, contributing to the damage of the intestinal mucosal barrier. In the context of gastric ulcers, TNF-α contributes to mucosal damage by increasing gastric acid secretion, reducing mucus production, and disrupting the epithelial barrier function.

Furthermore, TNF-α can induce apoptosis of gastric epithelial cells, exacerbating ulcer formation and delaying the healing process (Tureyen & Ince, 2021).

IL-6, another key inflammatory cytokine, plays a significant role in the onset of gastric ulcers. As a multifunctional cytokine, IL-6 is involved in regulating immune responses, inflammation, and hematopoiesis. In the context of gastric ulcers, IL-6 contributes to the inflammation by promoting the immune cell influx to the gastric mucosa, stimulating the production of acute-phase proteins, and modulating the activity of other inflammatory mediators (Ganguly & Swarnakar, 2012). This shows that the IL-6 signaling pathway is essential for the development of both local and systemic consequences of inflammation. NO, a highly reactive free radical, exerts a complex and often paradoxical role in the pathophysiology of gastric ulcers. While low levels of NO can promote gastric mucosal protection by increasing blood flow and mucus production, excessive production of NO, particularly by iNOS, can participate in inflammation and tissue injury. In the setting of gastric ulcers, overproduction of NO can lead to vasodilation, increased vascular permeability, and leukocyte recruitment, contributing to the inflammatory cascade (Júnior et al., 2014). The current findings indicated the elevated levels of TNF-α, IL-6, and NO in the serum of ethanol-ingested rats. However, the psoralidin pre-treatment considerably decreased these inflammatory biomarkers in the ethanol-ingested rats, which is similar to the results of omeprazole treatment. These findings proved the anti-inflammatory effects of the psoralidin.

PGE2, a ubiquitous lipid mediator, plays a multifaceted role in various physiological and pathological processes, with its involvement in gastric ulcers being particularly noteworthy. PGE2, a key member of the prostaglandin family, exerts its influence through interactions with G protein-coupled receptors, which elicit unique downstream signaling cascades and contribute to the complexity of PGE2's effects on gastric physiology (Hatazawa et al., 2007). The synthesis of PGE2 is intricately linked to the activity of cyclooxygenases (COX), particularly COX-1 and COX-2, which convert arachidonic acid to prostaglandin precursors. The constitutive expression of COX-1 in the gastric mucosa is considered crucial for maintaining basal levels of PGE2, which are essential for cytoprotection, while COX-2 expression is typically activated due to inflammation, potentially contributing to both pro-inflammatory and pro-resolving actions depending on the context (Takeuchi et al., 2010).

The protective effects of PGE2 on the gastric mucosa are well-documented, encompassing a range of mechanisms that contribute to maintaining the integrity of the gastric lining. PGE2 stimulates the bicarbonate and mucus production, forming a protective layer that shields the epithelium from the damaging effects of acid and pepsin (Takeuchi et al., 2018). Furthermore, PGE2 enhances mucosal blood flow, ensuring adequate delivery of oxygen and nutrients to the gastric cells, thereby promoting their survival and repair. Additionally, PGE2 promotes cell proliferation and inhibits apoptosis, contributing to the maintenance of the gastric epithelial cell population. Conversely, the dysregulation of PGE2 synthesis or signaling can compromise these protective mechanisms and increase susceptibility to ulcer formation (Araki et al., 2000). NSAIDs show their activity by inhibiting COX activity, thereby reducing prostaglandin production, including PGE2. This reduction in PGE2 levels can disrupt the delicate balance between aggressive and protective factors in the stomach, leading to an increased risk of ulcer development, particularly with chronic NSAID use (Boelsterli et al., 2013). The present finding illustrates the decreased levels of PGE2 in the gastric tissues of ethanol-ingested rats. Fascinatingly, the psoralidin pre-treatment effectively increased the PGE2 levels in the gastric tissues of the ethanol-induced rats. These findings suggest that the psoralidin promotes the healing process of gastric injury via enhancing PGE2 production.

Conclusion

In conclusion, the present research demonstrates that psoralidin pre-treatment may prevent ethanol-induced acute gastric ulcers in rats. The psoralidin pre-treatment considerably decreased the ulcer area, augmented the ulcer inhibition rate, and mucus production in the ethanol-induced rats. Furthermore, psoralidin effectively reduced the inflammatory markers, increased the PGE2, and reduced the oxidative stress in the ethanol-ingested rats. The histological findings also indicated the gastroprotective effects of psoralidin. Consequently, psoralidin may exert a beneficial therapeutic impact against ethanol-triggered acute gastric ulcers in rats. Further studies are highly recommended in the future to fully comprehend the molecular mechanism underlying the therapeutic activities of psoralidin against gastric ulcers.

Abbreviations

CAT: Catalase; GSH: Glutathione; MDA: Malondialdehyde; NO: Nitric oxide; NSAID: Non-steroidal anti-inflammatory drug, PGE2: Prostaglandin E2; PPIs: Proton pump inhibitors.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval and Informed Consent

The experiment was approved by the committee of the Second Hospital of Tianjin Medical University (REC-48/05/1200).

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