

# Gastroprotective Activity of Dipsacoside B in Experimental Rats Against Ethanol-Induced Toxicity: Involvement of Antioxidant and Anti-Inflammatory Mechanisms

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## ABSTRACT

**Background:** Gastric ulcers, defined by lesions in the stomach lining, pose a considerable worldwide health issue with extensive ramifications in the gastrointestinal system. Effective nursing care is crucial in managing patients with gastropathy and gastric ulcers, particularly those undergoing endoscopy. Nurses should provide holistic care, including assessment, education, and emotional support, to promote optimal healing and prevent recurrence. **Objectives:** This study pursued to determine whether dipsacoside B acts as an anti-gastric ulcer agent and to examine its mechanism of action in an ethanol-induced gastric ulcer in experimental rats. **Materials and Methods:** The rats were pre-treated with 25 mg/kg of dipsacoside B for 21 days and then gastric injury was triggered by administering ethanol (5 mL/kg) via intragastric route. Following the conclusion of treatments, the changes in body weight of the experimental rats were determined. The concentrations of inflammatory cytokines, oxidative and antioxidative markers, and other biochemical markers such as PGE2, EGF, and MPO were evaluated using kits. The histopathological examination was conducted on the gastric tissues obtained from the experimental rats. **Results:** The treatment of dipsacoside B slightly decreased the body weight of ethanol-induced rats. Furthermore, the treatment with dipsacoside B considerably decreased MPO level, increased the PGE2 and EGF concentrations in the gastric tissues of ethanol-administered rats. The dipsacoside B treatment remarkably decreased the concentrations of inflammatory cytokines and oxidative marker via elevating antioxidant concentrations in the gastric tissues of ethanol-administered rats. The histological analysis also confirmed the gastroprotective effects of dipsacoside B. **Conclusion:** The findings of this work indicate that dipsacoside B protected the ethanol-induced gastric injury in rats. Consequently, it possesses the potential to serve as a potential therapeutic candidate for addressing gastric ulcer problems.

**Keywords:** Gastric lesions, Dipsacoside B, Prostaglandin E2, Ulcer index, Ethanol.

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## INTRODUCTION

Gastric ulcers, defined by lesions in the gastric mucosa extending through the muscularis mucosae, exhibit a considerable global public health issue with far-reaching consequences for people's well-being and healthcare systems. These lesions, typically located in the stomach, disrupt the normal physiological functions of the gastric environment, impacting digestion, nutrient absorption, and the protective mechanisms safeguarding the gastric lining.<sup>1</sup> The development of gastric ulcers is a multifaceted process influenced by an intricate interplay of endogenous and exogenous factors, challenging the integrity of the gastric mucosa. Gastric

ulcers arise when the aggressive forces, such as acid and pepsin, overwhelm the defensive mechanisms that normally protect the stomach lining.<sup>2</sup> The pathogenesis of gastric ulcers is complex and multifactorial, with *Helicobacter pylori* infection and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) emerging as the predominant causative agents. *H. pylori* usually colonizes the gastric mucosa, affects many individuals with estimates suggesting that nearly half of adults worldwide are infected.<sup>3</sup> The bacterium's capacity to grow in the extreme acidic conditions of the stomach is enhanced by its synthesis of urease, an enzyme that catalyzes the hydrolysis of urea into ammonia and carbon dioxide, thus neutralizing the surrounding gastric acid. Chronic *H. pylori* infection triggers a cascade of inflammatory reactions within the gastric mucosa, resulting in the progression of chronic gastritis, a precursor to gastric ulcers and, in some cases, gastric cancer. NSAIDs, extensively used for their analgesic, anti-inflammatory, and antipyretic activities, exhibit a considerable risk for gastric ulcer development.<sup>4</sup> These drugs inhibit cyclooxygenase enzymes, reducing the synthesis of prostaglandins, which are essential for



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preserving the integrity of the gastric mucosa by boosting mucus and bicarbonate secretion, enhancing mucosal blood flow, and suppressing acid secretion. Inhibition of prostaglandin secretion reduces the gastric mucosa more vulnerable to the deteriorating effects of acid and pepsin, increasing the likelihood of ulcer formation. Other factors such as genetics and smoking may also participate in the development and progression of peptic ulcers.<sup>5</sup>

The pathogenesis of gastric ulcers implicates a complex interplay of various factors that regulate the integrity of the gastric mucosa. The disruption of this delicate balance leads to mucosal injury, inflammation, and ultimately, ulcer formation. Gastric acid and pepsin, essential for digestion, can also damage the gastric mucosa if not adequately controlled. Prostaglandins play a vital role in sustaining mucosal integrity by triggering mucus and bicarbonate production, enhancing mucosal blood flow, and reducing acid secretion; their synthesis is inhibited by NSAIDs, increasing ulcer risk.<sup>6</sup> Gastric ulcers can arise from impaired mucosal defense, excessive acid and pepsin production, or a combination of both. *H. pylori* infection further exacerbates mucosal damage through direct bacterial effects and induction of inflammation. The resulting chronic inflammation contributes to mucosal atrophy, intestinal metaplasia, and an elevated risk of gastric cancer. Early detection and suitable therapy are essential to prevent complications and improve outcomes for individuals with gastric ulcers.<sup>7</sup>

Effective nursing care plays a crucial role in the management of patients with gastropathy and gastric ulcers, particularly those undergoing endoscopy. Nurses should prioritize assessment and monitoring of patients' gastrointestinal symptoms, vital signs, and laboratory results to promptly identify any complications. Additionally, nurses should provide emotional support and education to patients and their families on lifestyle modifications, medication adherence, and follow-up care to promote optimal healing and prevent recurrence. Furthermore, nurses should be knowledgeable about endoscopic procedures and provide pre- and post-procedure care to ensure patients' comfort, safety, and informed participation in their care.<sup>8</sup> Current treatment strategies primarily revolve around acid-suppressing drugs, which aim to decrease gastric acid production and promote ulcer healing. Antibiotics are also crucial in eradicating *H. pylori*, a bacterium recognized as a primary etiological factor in peptic ulcer. However, these conventional approaches face several limitations, including the rising prevalence of antibiotic-resistant *H. pylori*, the potential for adverse side effects with prolonged use of acid-suppressing drugs, and the incomplete efficacy in certain patient populations.<sup>9</sup> Moreover, NSAIDs contribute significantly to ulcer development by disrupting the protective mechanisms of the gastric mucosa. Therefore, alternative and complementary therapies are gaining attention, with a focus on natural products, particularly plant-derived bioactive compounds, as potential therapeutic agents.<sup>10</sup> Plant bioactive

compounds offer a hopeful avenue for gastric ulcer treatment due to their diverse pharmacological properties. Dipsacoside B is a major bioactive triterpenoid saponin compound, which is found extensively in the *Lonicerae japonicae* and *Lonicera macranthoides* plants. Several previous has already reported the immense pharmacological properties of the dipsacoside B such as anti-atherosclerosis,<sup>11</sup> neuroprotective,<sup>12</sup> and hepatoprotective<sup>13</sup> effects. Furthermore, dipsacoside B effectively inhibited the blunts neointimal development<sup>14</sup> and ameliorated the sepsis-associated encephalopathy<sup>15</sup> in an experimental model. However, the effectiveness of dipsacoside B in gastric ulcers has not been studied. Consequently, this work sought to determine whether dipsacoside B acts as an anti-gastric ulcer agent and to examine its mechanism of action in an ethanol-induced gastric injury in experimental rat model.

## MATERIALS AND METHODS

### Chemicals

The principal chemicals utilized in this work, such as ethanol and dipsacoside B, were acquired from Sigma Aldrich, USA. The diagnostic kits for the assessment of biochemical markers were obtained from Elabscience, MyBioSource, Abcam, USA, respectively.

### Animals

Healthy adult male Sprague-Dawley rats, weighing 200-250 g, were purchased from institutional animal facility and cleared approval from the institutional ethical committee. The rats were kept at a temperature of 20-25°C with 12-hr light/dark series, provided with conventional pellet meals and tap water. The rats were separately housed with wide-mesh wire bottoms to inhibit coprophagia during the studies. All rats were acclimated to the laboratory settings for one week prior to the initiation of the studies.

### Experimental groups

The rats were arbitrarily distributed into the following groups: Group I (normal saline control), Group II (ethanol-induced gastric ulcer), Group III (ethanol + dipsacoside B-treated rats), and Group IV (ethanol + omeprazole-treated rats). The group III and IV were given with 25 mg/kg of dipsacoside B and 20 mg/kg of standard drug omeprazole, respectively for 21 days. The control rats (group I) were given 5 mL/kg of saline for 21 days via oral route along with standard diet. Each group consisted of six animals for the studies ( $n=6$ ).

### Induction of ethanol-induced acute gastric ulcer in the experimental rats

Gastric ulcer was generated by administering a 96% ethanol at a dosage of 5 mL/kg via intragastric route. Animals were subjected to food restriction for 24 hr prior to ethanol induction, while

retaining access to water. After 1 hr of ethanol administration, the rats were sedated via injecting 50 mg/kg of ketamine and 10 mg/kg of xylazine. The stomach of the rats were dissected and incised along the greater curvature to assess the quantity and length of gastric lesions.<sup>16</sup> A portion of the stomach was excised and subsequently homogenized in a cold saline. The homogenate underwent centrifugation at 6000 rpm for 15 min. The supernatant was preserved at -80°C until the quantification of biochemical markers.<sup>17</sup>

### Evaluation of Ulcer Index (UI) and inhibition rate

Rat gastric tissues were surgically opened and meticulously washed with iced saline. The gastric tissues were affixed to a white background and captured in a photograph. The stomach UI were assessed using the previous technique.<sup>18</sup> The inhibition rate was calculated using the formula:

$$[(UI_{\text{control}} - UI_{\text{treated}}) / UI_{\text{control}}] \times 100$$

where UI denotes the ulcer index.

### Analysis of oxidative stress marker levels

The supernatant of gastric tissue homogenate was utilized to assess oxidative and antioxidative parameters using commercial assay kits. The quantities of Catalase (CAT), Superoxide Dismutase (SOD), and Malondialdehyde (MDA) were studied using the kits. The tests were conducted in triplicate according to the manufacturer's specified protocols (Elabsience, USA).

### Evaluation of inflammatory biomarker levels

The concentrations of inflammatory cytokines in the gastric tissue homogenates were studied using test kits. The concentrations of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 were assessed using commercial kits. The tests were conducted in triplicate using the manufacturer's specified protocols (Abcam, USA).

### Analysis of biochemical markers

The concentrations of the biochemical markers such as Prostaglandin E2 (PGE2), Myeloperoxidase (MPO), Epidermal Growth Factor (EGF) in the gastric tissue homogenates of the experimental rats was evaluated using commercial diagnostic kits. The tests were conducted using three replicates as per the manufacturer's specifications (MyBioSource, USA).

### Histopathological study

The gastric tissues from experimental rats underwent standard histopathological investigations. The tissues preserved in formaldehyde (10%) were dried using increasing concentrations of alcohol and subsequently paraffinized. Sections of a thickness of 3  $\mu$ m were dewaxed in xylene and rehydrated using decreasing concentrations of alcohol. Subsequently, slides were stained with eosin and hematoxylin before being assessed using a light microscope. Slides were scored using a scoring system that

encompasses graded analysis of mucosal damage, neutrophil influx, and hemorrhage.<sup>19</sup>

### Statistical analysis

The findings were analyzed using GraphPad Prism, presented as a mean $\pm$ SD of three replicates. The results are evaluated using one-way ANOVA and Tukey's *post hoc* assay, with significance established at  $p < 0.005$ .

## RESULTS

### Effect of dipsacoside B on the body weight changes in the experimental rats

The impact of dipsacoside B on the changes in body weight of experimental rats were assessed, as depicted in Figure 1. There were no significant alterations in the initial body weight of rats in all the groups. However, the ethanol administered rats showed slight increase in their body weight. Notably, the treatment of 25 mg/kg of dipsacoside B was slightly decreased the body weight of the ethanol-induced rats. These activity of the dipsacoside B treatment was similar to the results of standard drug omeprazole.

### Effect of dipsacoside B on the UI and ulcer inhibition rate in experimental rats

Figure 2 illustrates the UI and ulcer inhibition rate levels in the experimental rats. The rats with ethanol-induced gastric ulcer demonstrated a significant elevation in UI when compared with control. Nonetheless, the 25 mg/kg of dipsacoside B treatment exhibited a considerable diminution in UI and consequent elevation in ulcer inhibition rate in the ethanol-induced rats. Moreover, the treatment of omeprazole also substantially reduced UI level and increased ulcer inhibition rate in the ethanol-induced rats, which supports the results of dipsacoside B.

### Effect of dipsacoside B on the oxidative stress markers in the experimental rats

The impact of dipsacoside B on the antioxidative markers were evaluated, and the findings are illustrated in Figure 3. The results indicated a significant elevation in MDA and a decrease in CAT and SOD concentrations in the gastric tissues of the ethanol-induced rats in comparison with control. Fascinatingly, the treatment of 25 mg/kg of dipsacoside B significantly decreased MDA concentrations and increased the CAT and SOD concentrations in ethanol-induced rats. The similar findings are also found in the omeprazole-treated rats, which supports the activity of dipsacoside B.

### Effect of dipsacoside B on the inflammatory cytokines in the experimental rats

The concentrations of inflammatory cytokines were assessed in the gastric tissues of the experimental rats, with results presented in Figure 4. The ethanol-induced rats ulcer displayed elevated

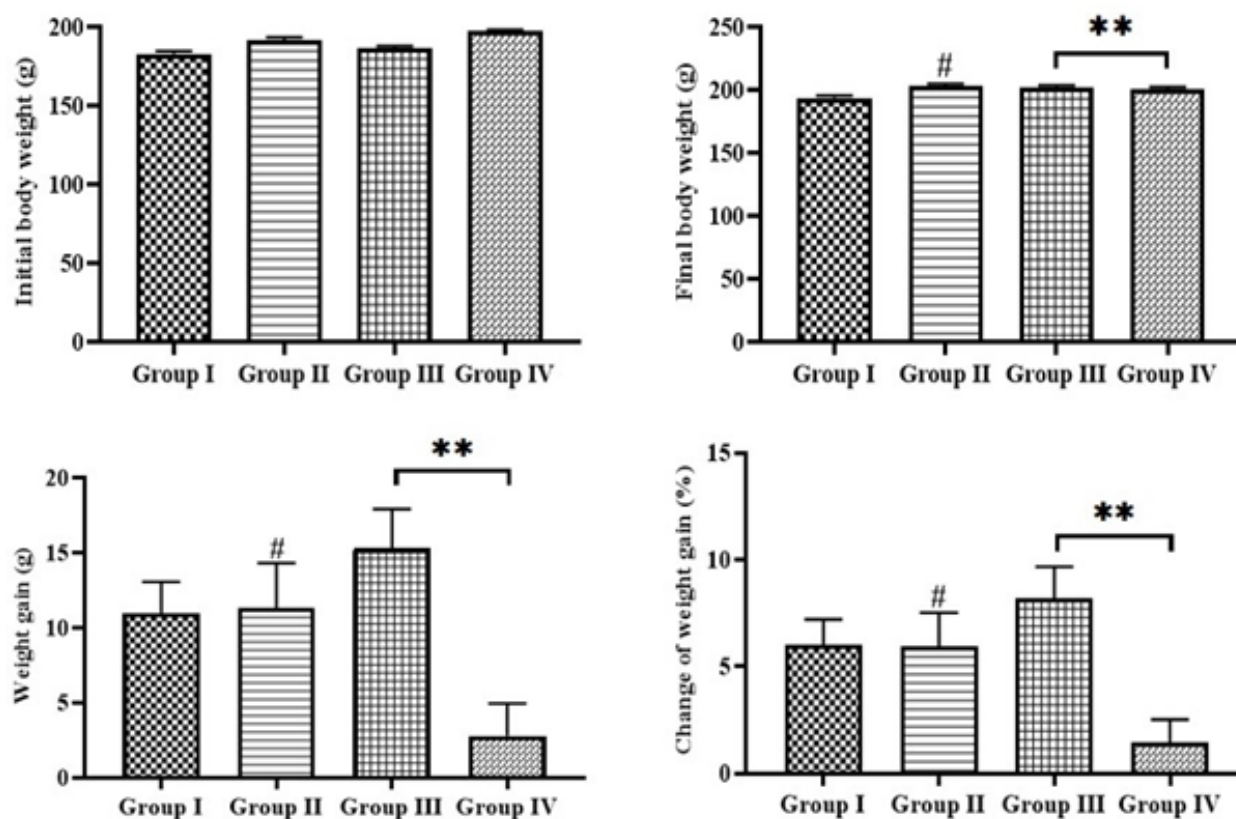


**Figure 1:** Effect of dipsacoside B on the body weight changes in the experimental rats. The results are denoted as the mean $\pm$ SD of triplicates, with statistical analysis conducted using GraphPad software. Data are assessed utilizing one-way ANOVA and Tukey's *post hoc* analysis. An asterisk '#' denoted statistical significance at  $p < 0.01$  relative to the control group (Group I); '\*\*' signified statistical significance at  $p < 0.05$  in comparison to the ethanol-induced group (Group II).

concentrations of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in their gastric tissues in comparison to the control. Nonetheless, the administration of dipsacoside B at 25 mg/kg concentration led to a considerable reduction in these cytokine levels of ethanol-induced rats. The results of omeprazole treatment also decreased the concentrations of these inflammatory cytokines, therefore supporting the anti-inflammatory effect of the dipsacoside B.

### Effect of dipsacoside B on the biochemical marker levels in the experimental rats

The concentrations of biochemical markers in the gastric tissues of the experimental rats were assessed, and the results are depicted in Figure 5. The decreased concentrations of PGE-2 and EGF along with increased MPO concentrations were observed in the gastric tissues of ethanol-induced rats in comparison to control. However, the treatment of 25 mg/kg of dipsacoside B notably elevated both PGE-2 and EGF levels while decreased the MPO in the gastric tissues of the ethanol-induced rats. Furthermore, similar results are also noted in the omeprazole-treated rats, which further supports the activity of dipsacoside B in regulating these biochemical markers in the ethanol-induced rats.

### Effect of dipsacoside B on the histopathological scores analysis of gastric tissues of experimental rats

The control group displayed typical structures. The histological study of gastric tissues indicated increased histological scores because of increased ulcer size and incidences in the ethanol-induced group than those of the other groups, with significant necrosis noted in the epithelial and glandular cells (Figure 6). The cells displayed dark nuclei with eosinophilic cytoplasm and were disconnected from the basal layer. Hemorrhages were also observed in this area. Whereas, some ulcers were noted in the 25 mg/kg of dipsacoside B-treated group with decreased incidences. Furthermore, the mucosal cells and the glands were found to be normal in the dipsacoside B-treated rats. The similar results were also noted in the omeprazole-treated group, which further supports the dipsacoside B's gastroprotective effects.

## DISCUSSION

Gastric ulcers, characterized by lesions in the stomach lining, exhibit a remarkable global public health challenge with far-reaching consequences beyond the gastrointestinal system. The pathophysiology of gastric ulcers is multifaceted, implicating an intricate interplay of various causes such as gastric acid, pepsin, and *H. pylori* infection, alongside weakened mucosal

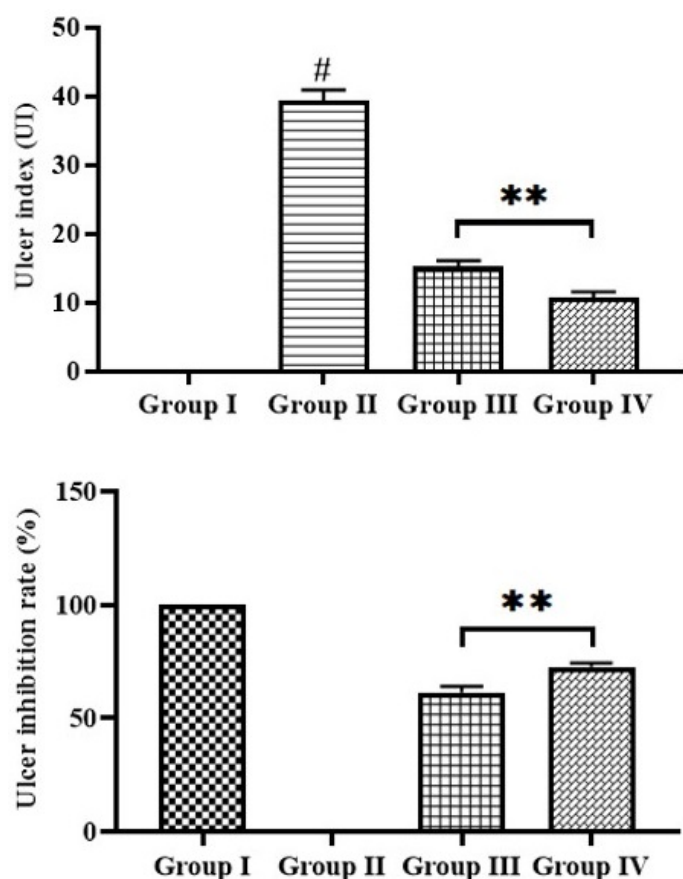


**Figure 2:** Effect of dipsacoside B on the UI and ulcer inhibition rate in the experimental rats. The results are denoted as the mean $\pm$ SD of triplicates, with statistical analysis conducted using GraphPad software. Data are assessed utilizing one-way ANOVA and Tukey's *post hoc* analysis. An asterisk '#' denoted statistical significance at  $p < 0.01$  relative to the control group (Group I); '\*\*' signified statistical significance at  $p < 0.05$  in comparison to the ethanol-induced group (Group II).

defense mechanisms. This delicate balance is further disrupted by lifestyle factors like diet, alcohol consumption, and smoking, as well as the use of NSAIDs.<sup>20</sup> The resulting ulceration can lead to a cascade of complications, including pain, bleeding, perforation, and gastric outlet obstruction, severely impacting the quality of life and placing a substantial burden on healthcare systems. Current therapies initially focus on acid reduction using proton pump inhibitors and H<sub>2</sub>-receptor antagonists, as well as antibiotic eradication of *H. pylori*. While these approaches have proven effective in many cases, they are not without limitations, including the emergence of antibiotic-resistant *H. pylori* strains and potential side effects associated with long-term acid suppression.<sup>21</sup> The human body possesses inherent defense mechanisms to sustain the integrity of the gastric mucosa, including superficial mucosal cells and prostaglandins that stimulate bicarbonate and protective mucus production, but these mechanisms can be overwhelmed by aggressive factors like oxygen radicals. The need for alternative therapies stems from several factors that limit the effectiveness and safety of conventional treatments. The search for alternative therapies for gastric ulcers has led to a growing

interest in plant-derived bioactive compounds, which offer a promising avenue for safe and effective treatment.<sup>22</sup> This study provided evidence that dipsacoside B demonstrates anti-gastric ulcer activity against ethanol-induced gastric ulcer model in rats.

The evaluation of the UI and ulcer inhibition rate stands as a cornerstone in assessing the efficacy of novel therapeutic interventions targeting gastric ulcers, particularly within the context of experimental models such as ethanol-induced gastric ulceration in rats. Gastric ulcers, characterized by lesions in the stomach or duodenum, pose a significant health challenge due to their painful nature and potential for complications. The induction of gastric ulcers in rats using ethanol serves as a widely accepted model that mimics the pathogenesis of human gastric ulcers, offering a valuable platform for studying the protective effects of various compounds. The UI, a quantitative measure reflecting the severity of ulceration, is determined by macroscopic examination of the gastric mucosa, where the number, size, and intensity of ulcers are meticulously assessed and scored.<sup>23</sup> This scoring system provides a comprehensive representation of the extent of gastric damage, enabling researchers to quantitatively compare the effects of treatments on ulcer severity. Simultaneously, the ulcer inhibition rate, calculated as the percentage decrease in UI compared with control, provides a normalized measure of the protective efficacy of the tested compound, allowing for a standardized comparison of anti-ulcer potential across different studies and experimental conditions. The applications of the UI and ulcer inhibition rate extend beyond mere quantification of ulcer severity and treatment efficacy; these parameters serve as critical endpoints in preclinical drug development, guiding the optimization of therapeutic strategies for gastric ulcer management.<sup>24</sup> The present results indicated that the ethanol-induced rats revealed a considerable elevation in UI levels. Whereas, the dipsacoside B treatment effectively decreased the UI level and consequently increased ulcer inhibition rate in the ethanol-induced rats.

MPO, a heme-containing peroxidase enzyme predominantly expressed and stored within the azurophilic granules of neutrophils and monocytes, plays an essential role in the innate immunity against invading pathogens. Upon activation of neutrophils, MPO is released into the extracellular space where it catalyzes the reaction of hydrogen peroxide with chloride ions to produce hypochlorous acid, a potent oxidant with antimicrobial properties.<sup>25</sup> However, uncontrolled or excessive MPO activity can contribute to tissue damage and inflammation. Neutrophils are essential sources of arachidonic acid, with the arachidonic acid pathway triggered by inflammatory stimuli resulting in the production of thromboxanes, leukotrienes and prostaglandins. In the context of gastric ulcers, MPO-derived oxidants can exacerbate mucosal injury by promoting lipid peroxidation, protein modification, and DNA damage, thereby disrupting the delicate balance between pro-inflammatory and protective

mechanisms in the gastric mucosa.<sup>26</sup> PGE2 is a multifaceted lipid mediator critically involved in wound healing processes and exhibits diverse physiological functions mediated through four G-protein coupled receptors, namely EP1-4, which trigger

distinct signaling pathways upon activation. PGE2 exerts its cellular effects through binding to these E-prostanoid receptors that belong to the family of G protein-coupled receptors.<sup>27</sup> Upon tissue injury, the synthesis of PGE2 is significantly

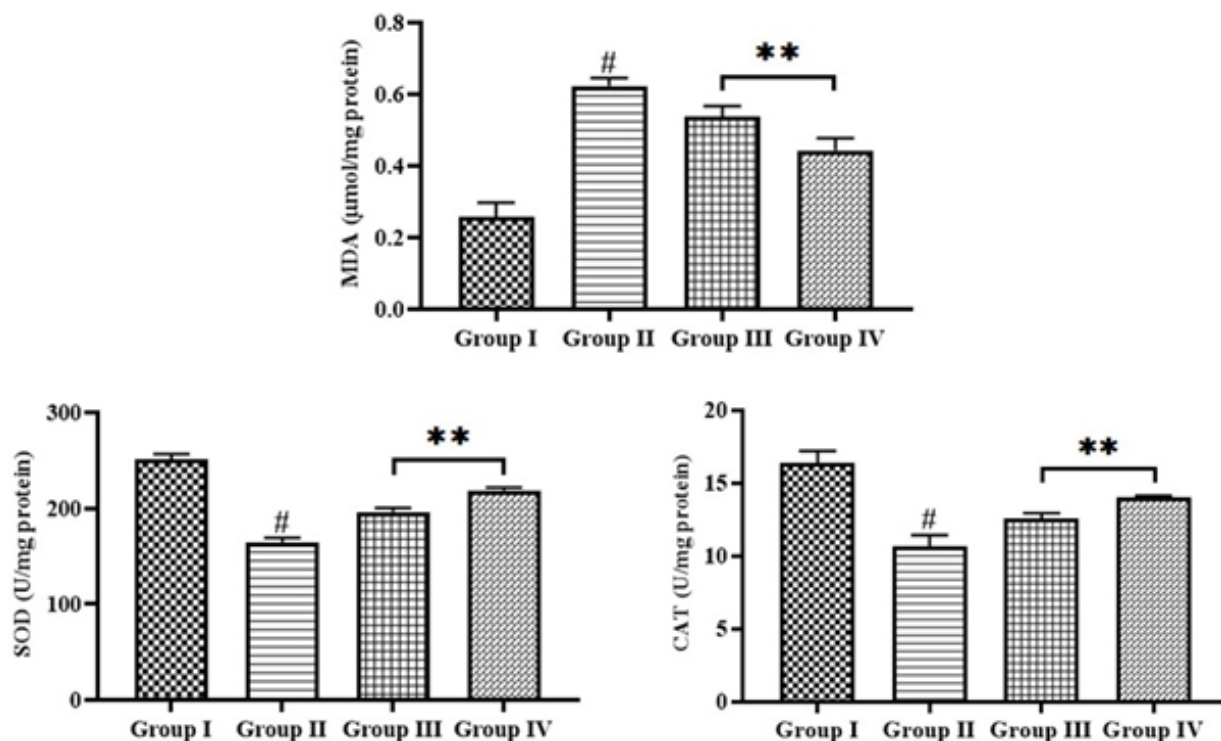


**Figure 3:** Effect of dipsacoside B on the oxidative stress markers in the experimental rats. The results are denoted as the mean±SD of triplicates, with statistical analysis conducted using GraphPad software. Data are assessed utilizing one-way ANOVA and Tukey's *post hoc* analysis. An asterisk '#' denoted statistical significance at  $p<0.01$  relative to the control group (Group I); '\*' signified statistical significance at  $p<0.05$  in comparison to the ethanol-induced group (Group II).

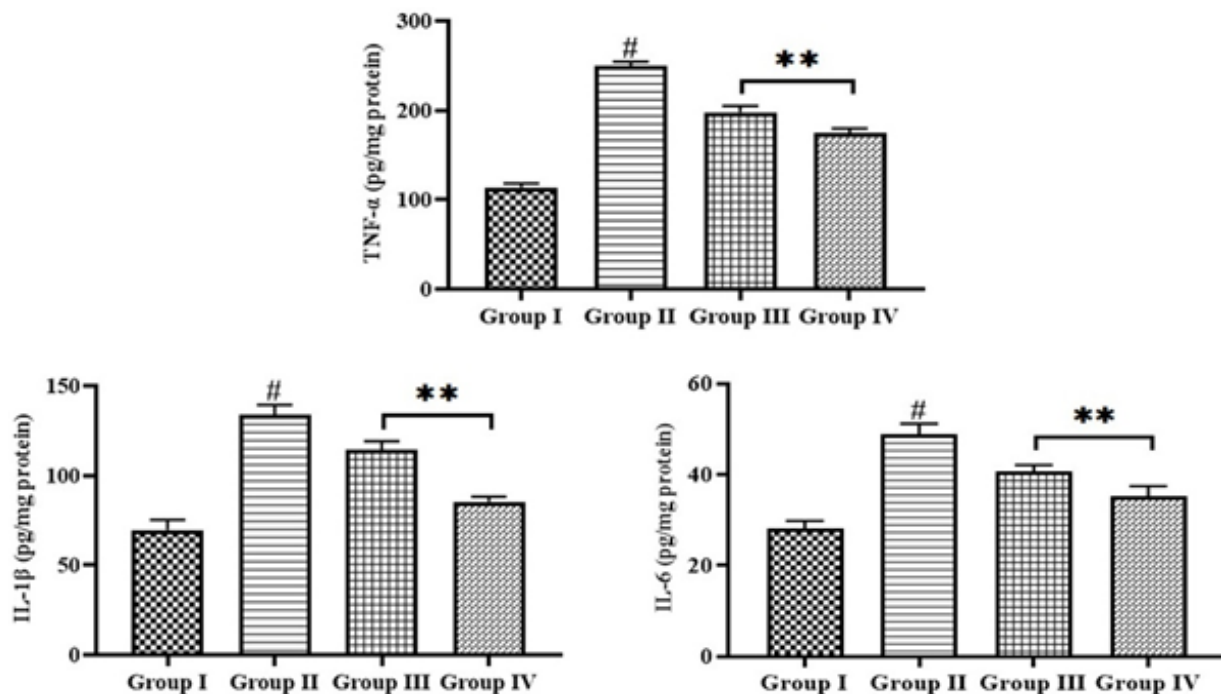


**Figure 4:** Effect of dipsacoside B on the inflammatory cytokines in the experimental rats. The results are denoted as the mean±SD of triplicates, with statistical analysis conducted using GraphPad software. Data are assessed utilizing one-way ANOVA and Tukey's *post hoc* analysis. An asterisk '#' denoted statistical significance at  $p<0.01$  relative to the control group (Group I); '\*' signified statistical significance at  $p<0.05$  in comparison to the ethanol-induced group (Group II).

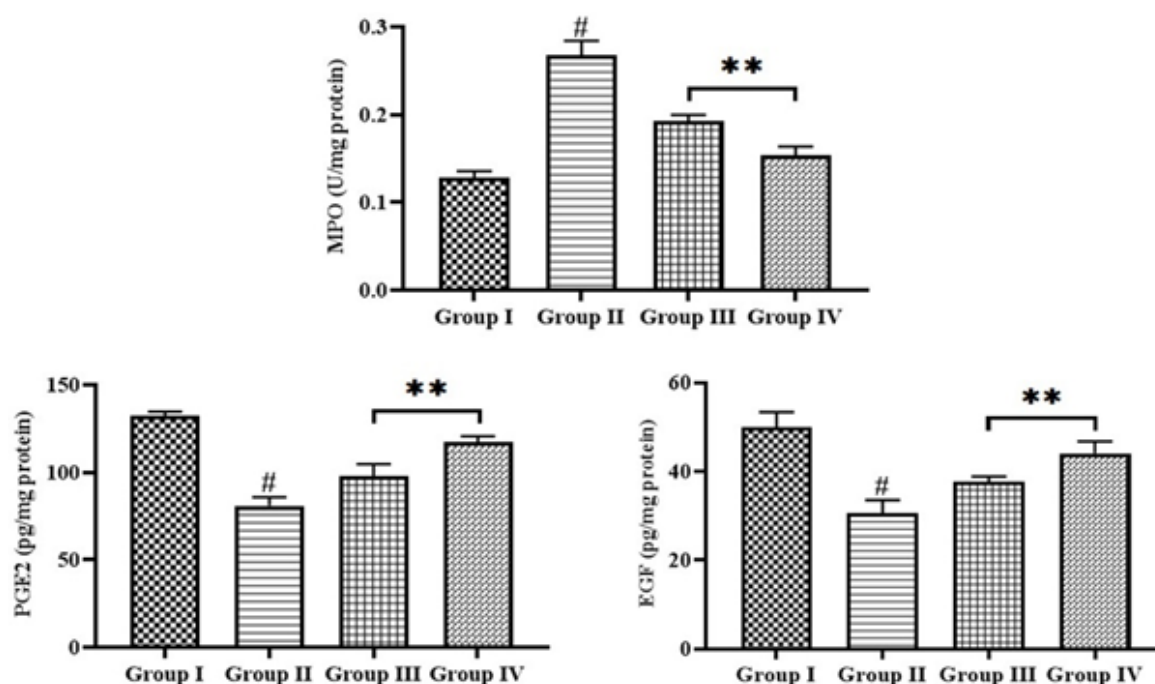


**Figure 5:** Effect of dipsacoside B on the biochemical marker levels in the experimental rats. The results are denoted as the mean±SD of triplicates, with statistical analysis conducted using GraphPad software. Data are assessed utilizing one-way ANOVA and Tukey's *post hoc* analysis. An asterisk '#' denoted statistical significance at  $p < 0.01$  relative to the control group (Group I); '\*\*' signified statistical significance at  $p < 0.05$  in comparison to the ethanol-induced group (Group II).

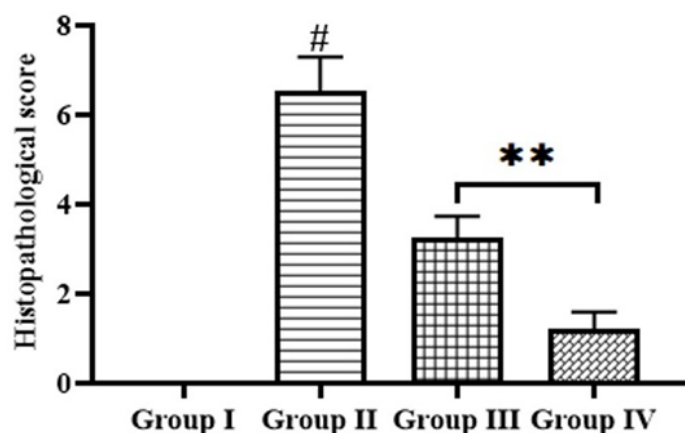


**Figure 6:** Effect of dipsacoside B on the histopathological analysis of gastric tissues of experimental rats. The results are denoted as the mean±SD of triplicates, with statistical analysis conducted using GraphPad software. Data are assessed utilizing one-way ANOVA and Tukey's *post hoc* analysis. An asterisk '#' denoted statistical significance at  $p < 0.01$  relative to the control group (Group I); '\*\*' signified statistical significance at  $p < 0.05$  in comparison to the ethanol-induced group (Group II).

upregulated, arising from arachidonic acid, a fatty acid liberated from membrane phospholipids via phospholipase A2 activity. Subsequently, cyclooxygenases metabolize arachidonic acid into PGH<sub>2</sub>, which is then converted to PGE<sub>2</sub> by PGE synthases. The intricate interplay between PGE<sub>2</sub> and its receptors underscores its significant role in inflammation and homeostasis, with its effects varying based on the specific receptor subtype activated and the cellular context.<sup>28</sup>

EGF, a potent growth factor that stimulates cell proliferation, differentiation, and survival, plays an essential role in sustaining

tissue homeostasis and enhancing wound healing in various organs, including the stomach. EGF exerts its effects by binding to the EGF receptor, a receptor tyrosine kinase that activates downstream pathways like MAPK/ERK and PI3K/Akt pathways.<sup>29</sup> Activation of these signaling results in elevated cell growth, migration, and extracellular matrix production, which are essential for repairing damaged tissues. In the context of gastric ulcers, EGF promotes the growth and migration of gastric epithelial cells, thereby accelerating the closure of ulcers and restoring the integrity of the gastric mucosa. EGF protects the digestive mucosa by stimulating mucus production and inhibiting gastric secretion.<sup>30</sup> Dysregulation of EGF signaling can disrupt these processes and contribute to the development or progression of gastric ulcers. Growth factors have developed as a potential tool for the management of intestinal inflammation and repair, playing a significant role in cell growth, differentiation, and angiogenesis.<sup>31</sup> The intricate interplay between PGE<sub>2</sub>, MPO, and EGF dictates the pathophysiology of gastric ulcers. Understanding the precise mechanisms by which PGE<sub>2</sub>, MPO, and EGF contribute to gastric ulcer pathophysiology is crucial for developing effective therapeutic strategies. Targeting these molecules or their signaling pathways may offer novel approaches for preventing and treating gastric ulcers, particularly in patients at high risk or those who are refractory to conventional therapies. In this study, the findings unveiled the decreased concentrations of PGE-2 and EGF along with elevated MPO levels in the gastric tissues of the ethanol-administered rats. Interestingly, the treatment of dipsacoside B considerably elevated the PGE-2 and EGF levels and reduced the MPO levels in the gastric

tissues of the ethanol-induced rats. These findings proved that the dipsacoside B treatment effectively reduced inflammatory circumstances and promoted wound healing in the gastric tissues of ethanol-administered rats.

Oxidative stress, characterized by the disproportion between the ROS generation and the ability of the antioxidants to neutralize them, has emerged as a major cause of the pathogenesis of gastric ulcers. This intricate process involves a complex interplay of molecular mechanisms, ultimately leading to cellular damage and tissue injury in the gastric mucosa. The disruption of equilibrium between pro-oxidants and antioxidants leads to an overabundance of ROS, while simultaneously diminishing antioxidant defenses, resulting in oxidative stress.<sup>32</sup> The presence of food ingredients, interactions between immune cells, and microbes contributes significantly to pro-oxidant generation in the gastrointestinal tract, highlighting its vulnerability to oxidative stress. The pathophysiology of gastric ulcers is intricately linked to the generation of ROS, which can overwhelm the inherent antioxidant defense of the gastric mucosa, leading to oxidative damage. Several risk factors exacerbate the imbalance, including *H. pylori* infection, abuse of anti-inflammatory agents, and lifestyle factors like alcohol consumption.<sup>33</sup> Gastric ulcers arise from multifaceted interactions between these etiological agents and the host's physiological responses, where oxidative stress acts as a central mediator. While the gut is predominantly anaerobic because of oxygen utilization by bacteria, gut cells are able to generate ROS. These reactive species initiate lipid peroxidation, protein oxidation, and DNA damage, culminating in cellular dysfunction and necrosis.<sup>34</sup>

Elevated quantities of ROS can surpass cellular antioxidant defenses, resulting in oxidative tissue damage due to oxidative stress. Antioxidant enzymes such as SOD and CAT are essential for neutralizing ROS. SOD catalyzes the dismutation of superoxide radicals into hydrogen peroxide, whereas CAT accelerates the decomposition of hydrogen peroxide into water and oxygen. MDA, a byproduct of lipid peroxidation, functions as a marker of oxidative damage to cellular membranes.<sup>35</sup> Oxidative stress can initiate a series of events that ultimately compromise the integrity of the gastric mucosa, making it more susceptible to ulceration. In gastric ulcer pathophysiology, monitoring the levels of antioxidants and MDA provides valuable insights into the extent of oxidative stress and its impact on tissue injury. In this work, we found that the rats with gastric ulcer demonstrated significant elevation in MDA and a diminution in CAT and SOD concentrations in their gastric tissues. Captivatingly, the treatment of dipsacoside B considerably diminished the MDA and increased the CAT and SOD in rats with ethanol-induced gastric ulcer. This observation highlights the antioxidant effects of dipsacoside B.

Inflammation, a multifaceted biological response to detrimental stimuli such as pathogens, injured cells, or irritants, is crucial in

the development of stomach ulcers. This intricate process involves a cascade of cellular changes, cytokine release, and immune cell infiltration, all orchestrated to defend and heal the affected tissue. However, in the context of gastric ulcers, this normally protective response can become dysregulated, contributing to tissue damage and hindering the healing process. The gastric mucosa is a crucial component of the immune system and gut-associated lymphoid tissue, functioning as the initiation location for antigen-specific and cell-mediated immunity.<sup>36</sup> The disruption of immune tolerance can lead to an imbalance, causing abnormal secretion of inflammatory cells and mediators that damage the intestinal mucosal barrier. TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are key inflammatory cytokines associated in the pathophysiology of gastric ulcers. TNF- $\alpha$ , a potent proinflammatory mediator, is integral to the inflammatory process and has been found to be genetically associated with ulcerative colitis, with elevated levels observed in patients.<sup>37</sup> TNF- $\alpha$  stimulates the production of IL-1 $\beta$  and IL-6, further amplifying the inflammatory cascade and promoting neutrophil influx at inflammatory sites, which can damage the intestinal mucosal barrier. These cytokines, acting as messengers between immune cells, orchestrate a complex network of interactions that can either promote healing or exacerbate tissue damage. Excessive production of inflammatory cytokines like TNF- $\alpha$  and IL-6 can disrupt the delicate balance within the gastric mucosa, impairing cellular function and leading to epithelial damage.<sup>38</sup> The present results showed an elevated concentrations of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in the gastric tissues of ethanol-administered rats. Fascinatingly, the dipsacoside B treatment notably reduced the concentrations of these cytokines in the gastric tissues of ethanol-induced rats. These findings witnessed the anti-inflammatory properties of the dipsacoside B.

## CONCLUSION

The findings of this work indicate that dipsacoside B treatment protected the ethanol-induced gastric ulcer in rats. The dipsacoside B treatment considerably reduced the UI level, increased ulcer inhibition rate, reduced the MPO level, and elevated the PGE2 and EGF concentrations in the ethanol-induced rats. Furthermore, the dipsacoside B treatment significantly reduced inflammatory cytokines and oxidative stress by increasing antioxidants in the ethanol-induced rats. The histopathological findings of gastric tissues also evidenced the gastroprotective properties of the dipsacoside B. Consequently, it possesses the potential to serve as a hopeful therapeutic candidate for addressing gastric ulcer problems. Furthermore, it is imperative to conduct further research to attain a more accurate comprehension of the beneficial effects of dipsacoside B on gastric ulcers.

## ABBREVIATIONS

**NSAIDs:** Nonsteroidal anti-inflammatory drugs; **CAT:** Catalase; **SOD:** Superoxide dismutase; **MDA:** Malondialdehyde; **IL-1 $\beta$ :** Interleukin-1 $\beta$ ; **IL-6:** Interleukin-6; **TNF- $\alpha$ :** Tumor necrosis

factor- $\alpha$ ; **PGE2**: Prostaglandin E2; **MPO**: Myeloperoxidase; **EGF**: Epidermal growth factor; **UI**: Ulcer index; **H&E**: Hematoxylin and eosin.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of Interest.

## ETHICAL APPROVAL

The project approved by the committee of the Second Hospital of Tianjin Medical University.

## SUMMARY

This work sought to determine whether dipsacoside B acts as an anti-gastric ulcer agent in an ethanol-induced in experimental rat model. Following the conclusion of treatments, the changes in body weight of the experimental rats were determined. The concentrations of inflammatory cytokines, antioxidative markers and biochemical markers were evaluated using kits. The histopathological examination was conducted on the gastric tissues obtained from the experimental rats. The dipsacoside B treatment considerably reduced the UI, MPO level, inflammatory cytokines and oxidative stress. Furthermore, increasing antioxidants and biochemical marker levels in the ethanol-induced rats. The histopathological findings of gastric tissues also evidenced the gastroprotective properties of the dipsacoside B.

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