This study was conducted to investigate the influence of various extracts of *S. striata* in ethanol-induced gastric ulcer model in rats. 100 male rats were divided into 10 groups and received the following medications: Normal control group without treatment; comparative standard control group received 20 mg/kg omeprazole; Groups 4-9 were given aqueous, hydroalcoholic and etheric extracts at 100 and 400 mg/kg, respectively; vehicle control group given DMSO as solvent solution. After one hour all the rats (except normal control group) and also ulcer control group were given 4 mL/kg 75% EtOH solution to induce ulceration. The rats were sacrificed after one hour; the gastric mucosal injuries were estimated through assessment of the gross appearance of ulcer areas, histopathology and parameters including MDA, TAC, PGE2 and HSP70 in the gastric tissue homogenate. The ulcer control group showed severe mucosal injury compared with aqueous and etheric extracts which grossly showed significant reduction of ulcer areas and histopathologically showed marked reduction of mucosal necrosis, edema and leukocytes infiltration. A significant increase in the levels of HSP70, PGE2 and TAC with a reduction in the level of MDA was observed in the rats treated with etheric and especially aqueous extracts. The results of the present study revealed significant protection of *S. striata* towards ethanol-induced gastric mucosal injury.

**Key words:** Ethanol, Gastric ulcer, Gastroprotective, *Scrophularia striata*, Antioxidant, Histopathology

**ABSTRACT**

This study was conducted to investigate the influence of various extracts of *S. striata* in ethanol-induced gastric ulcer model in rats. 100 male rats were divided into 10 groups and received the following medications: Normal control group without treatment; comparative standard control group received 20 mg/kg omeprazole; Groups 4-9 were given aqueous, hydroalcoholic and etheric extracts at 100 and 400 mg/kg, respectively; vehicle control group given DMSO as solvent solution. After one hour all the rats (except normal control group) and also ulcer control group were given 4 mL/kg 75% EtOH solution to induce ulceration. The rats were sacrificed after one hour; the gastric mucosal injuries were estimated through assessment of the gross appearance of ulcer areas, histopathology and parameters including MDA, TAC, PGE2 and HSP70 in the gastric tissue homogenate. The ulcer control group showed severe mucosal injury compared with aqueous and etheric extracts which grossly showed significant reduction of ulcer areas and histopathologically showed marked reduction of mucosal necrosis, edema and leukocytes infiltration. A significant increase in the levels of HSP70, PGE2 and TAC with a reduction in the level of MDA was observed in the rats treated with etheric and especially aqueous extracts. The results of the present study revealed significant protection of *S. striata* towards ethanol-induced gastric mucosal injury.

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**INTRODUCTION**

Peptic ulcer disease is one of the most common disruptions of the mucosal integrity of the stomach (a gastric ulcer) and small intestine (a duodenal ulcer) (1). It has generally been accepted that gastric ulcers are multifactorial and appear to be due to an imbalance among the aggressive factors (such as acid/pepsin, bile, alcohol, tobacco and caffeine, *H. pylori* infection, NSAIDs, stresses) and mucosal defensive mechanisms (including mucus secretion, bicarbonate production, mucosal blood flow, cellular repair mechanisms, prostaglandin E2, growth factors) (2).

Peptic ulcer treatment using synthetic drugs (such as H2 blockers, proton pump inhibitors and NSAIDs) results in adverse effects, relapses and drug interactions (3). Therefore, herbal medicines containing active chemical components are considered as the main source of new drugs and appropriate alternatives for treatment of the various diseases including peptic ulcer.
Scrophularia striata, commonly known as figwort, belongs to a family of flowering plants called Scrophulariaceae. It is native to Iran and grows wild in meadows, hillsides and impassable areas of Ilam Province (4). The Scrophulariaceae family consists of about 3000 species and 220 genera. Species of Scrophularia share square stems, opposite leaves and open two-lipped flowers forming clusters at the end of their stems (5).

Several chemical components including cinnamic acid, three flavonoids (quercetine, isorhamnetin-3-O-rutinoside and nepritin) and one phenylpropanoid glycoside (acteoside 1) have been identified in the aerial parts of S. striata (6). It appears that some compounds isolated from this species have the inhibitory effects on a variety of malignant and inflammatory disorders (7). Hence, the present study was carried out to determine the gastroprotective effects of Scrophularia striata on ethanol-induced gastric ulcer.

EXPERIMENTAL

Omeprazole

In the present study, omeprazole was used as a comparative standard control drug for antiulcer study. The drug was dissolved in distilled water and administered orally to the rats at 20 mg/kg (5 mL/kg) according to previous study (8).

Plant specimen and preparation of extraction

The aerial parts of S. striata were collected from the Zagros mountain range, Kermanshah Province, in May 2014. The plant sample was authenticated and voucher specimen was deposited at the Herbarium of Faculty of Sciences, Kharazmi University, Tehran, Iran (No: 5379). The plant aerial parts were air dried at room temperature and made into powder using a blender. The aqueous, hydroalcoholic and etheric extracts were obtained by maceration of the 200 g plant powder with 1L distilled water, ethanol/water (70/30) and petroleum ether for 2 days at room temperature, respectively. Extracts were filtered through a Whatman#1 paper and the solvents were evaporated under reduced pressure at temperature below 45 °C with a rotary evaporator. Then the filtrates were lyophilized in a lyophilizer and stored under light protection and low temperature (-4 °C) prior to use.

The aqueous and hydroalcoholic extracts were then dissolved in distilled water and etheric extract was dissolved in dimethyl sulfoxide (DMSO). The extracts were administered orally (4 mL/kg) to rats at dosages of 100 and 400 mg/kg.

Experimental animals for gastric ulcer

100 adult healthy male rats of Sprague Dawley strain weighing 200–250 g were housed in stainless steel cages and allowed to adapt to the conditions of the animal house for 14 days before the experiments. Animals were divided randomly into 10 equal groups of 10. 24 hours before the experiment, the rats were fasted and allowed access to water. Their access to water was inhibited for 2 hours before the start of experiment.

Gastric ulcer induction by ethanol

The experimental protocol is detailed below: Normal control group (NC) was left without treatment. Standard control group (SC) received omeprazole (20 mg/kg) orally. Experimental groups were orally administered with aqueous extract at 100 mg/kg (AE100) and 400 mg/kg (AE400), hydroalcoholic extract at 100 mg/kg (HA100) and 400 mg/kg (HA400) and etheric extract at 100 mg/kg (EE100) and 400 mg/kg (EE400). Vehicle control group (VC) received DMSO (4 mL/kg) orally. After one hour all the rats (except normal control group) and also ulcer control group (UC) were orally administered with 75% ethanol (4 mL/kg).

After one hour, rats were sacrificed by an overdose of ether and stomachs were isolated and cut open along the greater curvature. Stomachs were gently rinsed with 0.9% normal saline solution to remove gastric contents and blood.

Gross evaluation of gastric lesions

The ulcer area (mm²) of each individual hemorrhagic lesion was measured and analyzed using computer software (Axiovision, Carl Zeiss Microimaging GmbH, Germany). According to the method of Andrade et al. (9), a score for the ulcer was noted and the ulcers were classified as: Level I ulcer area<1 mm²; Level II ulcer area=1-3 mm²; Level III ulcer area >3 mm².

The following parameters were determined:

Ulcerative lesion index (ULI)=(number of ulcers level I)+(2×number of ulcers level II)+(3×number of ulcers level III).

Percentage protective ratio=100-[ULI pretreated]/ [ULI control]×100.

Histopathological evaluation

A portion of gastric tissue was collected from animals and fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 µm and stained with haematoxylin and eosin (H&E) for light microscopic examination.

Preparation of homogenate

Tissue homogenates were prepared for the PGE2, MDA, TAC and HSP70 assays in gastric tissue of experimental groups. All the processes were handled at 4°C throughout according to previous study (10). The gastric mucosa was weighed, minced with scissors, and homogenized using 0.1 M phosphate buffer (pH 7.4) (5 cc for each g of tissue) in homogenizer. After centrifugation at 2000-3000 rpm for 20 min, the supernatant was extracted and frizzed in -80 °C for later use.

Measurement of PGE2

The supernatants were subjected to a PGE2 assay using a rat PGE2 Eliza kit (Shanghai Crystal Day Biotech Co., LTD).

Measurement of membrane lipids peroxidation (MDA)

Tissue malondialdehyde (MDA) (mmol/L) was determined according to the method of Lykkesfeldt. A reaction mixture containing 8.1% sodium dodecyl sulfate, 20% acetate buffer (pH 3.5) and 0.8% thiobarbituric acid (TBA) was mixed well and heated at 90°C for 30 min. After centrifugation at 4000 rpm for 10 min, the absorbance of the supernatant was measured at 532 nm.
with 0.2 mL of stomach tissue homogenate for 3 min and then incubated at 95°C for 60 min. After cooling with running water, the TBA-reactive substance (MDA) was extracted with 1 mL of H₂O and 2.5 mL of n-butanol: Pyridine mixture (15:1, v/v). The upper organic layer containing the MDA, which was produced by lipid peroxidation, was measured at 532 nm (11,12).

**Measurement of total antioxidant capacity (TAC)**

Determination of total antioxidant capacity (TAC) in tissue homogenate by commercial kit (Labor Diagnostika Nord (LDN) Com, Nordhorn, Germany) was based on the reaction of peroxides with peroxidase followed by a color reaction of the chromogenic substrate tetramethylbenzidine. The change in color was measured colorimetrically at 450 nm and expressed as millimoles per liter.

**Measurement of heat shock protein 70 (HSP70)**

The supernatants were subjected to a HSP70 assay using a rat HSP Eliza kit (Shanghai Crystal Day Biotech Co., LTD).

**Statistical analysis**

The results were expressed as mean ± standard deviation (SD). The data were analyzed statistically by one-way ANOVA with Tukey's post-hoc test, using SPSS software, version 20. P<0.05 was considered as significant.

**Animal ethics**

This experiment was accomplished under the approval of the state committee on animal ethics, Shiraz University, Shiraz, Iran. Also, the recommendations of European Council Directive (86/609/EC) of November 24, 1986, regarding the standards in the protection of animals were used for experimental purposes.

**RESULTS**

**Gross evaluation of gastric lesions**

Gastroprotective effects of *S. striata* extracts on ethanol-induced gastric ulcer are shown in Figure 1 and Table 1. The ulcer control rats showed severe mucosal injury with ulcer area 20.75±11.09 mm². In the rats treated with aqueous and...
etheric extracts, the ulcer area was significantly reduced in a dose-dependent manner (p<0.05). The ulcer area was significantly decreased from 20.75±11.09 mm² in ulcer control group to 1.00±0.86 mm² in the rats treated with 400 mg/kg of aqueous extract. Also, in the rats treated with omeprazole, a decrease was observed in ulcer area (5.70±4.47 mm²). Although the ulcer area in all groups had statistically significant difference with the rats treated with hydroalcoholic extract and ulcer control group, the significant inhibition of gastric ulcer in rats treated with aqueous and etheric extracts of *S. striata* was comparable to omeprazole (a standard drug used for gastric ulcer).

**Histopathological evaluation of gastric lesions**

No lesions were observed in the tissue sections from the rats of normal control group (Figure 2a), while the rats of ulcer control group showed extensive damage to the gastric tissue, including mucosal hemorrhage and necrosis, severe edema and leukocyte infiltration in the submucosal layer (Figure 2b).

In the rats treated with omeprazole, mild mucosal damage with moderate edema and infiltration of leukocytes in the submucosal layer was observed (Figure 2c).

The tissue sections of the group treated with aqueous extract at 400 mg/kg was near-normal architecture and no edema and leukocyte infiltration were seen. The rats treated with 100 mg/kg aqueous extract showed the normal glandular pattern with mild edema and little leukocyte infiltration in the submucosal layer (Figure 2d and 2e).

The tissue sections of groups treated with 100 and 400 mg/kg etheric extract revealed mild mucosal damage with mild edema and infiltration of leukocytes Figure 2f.

In the rats treated with 100 and 400 mg/kg hydroalcoholic extract, moderate edema and infiltration of leukocytes in the gastric submucosal layer with mucosal necrosis was observed in which mucosal damage was more severe at 400 mg/kg (Figure 2g).

In the tissue sections of vehicle group, lesions were similar to the rats treated with omeprazole.

**Evaluation of parameters in the gastric tissue homogenate**

The mean ± SD of parameters values, including MDA, TAC, PGE₂ and HSP70 in the gastric tissue homogenate of rats are presented in Table 2.

MDA increased in all groups in comparison with ulcer control group and the highest amount of MDA was observed in the rats of ulcer control group which showed a significant difference with all groups (p<0.05). There was no significant difference between normal control group and rats treated with aqueous extract of *S. striata*. The MDA level in the groups treated with etheric extracts and omeprazole had statistically significant difference with the normal control group and the rats treated with aqueous extract (Figure 3).

The most significant reduction in TAC was observed in rats of ulcer control group. Although the TAC level of normal control group showed a significant difference with all groups (p<0.05), this parameter increased in the rats treated with various extracts and was statistically significant in groups treated with aqueous and etheric extracts in comparison with the ulcer control group. In addition, the TAC level in rats treated with aqueous extract was higher as compared with the rats treated with omeprazole and showed significant difference (Figure 4).

Although the PGE₂ level presented significant difference between normal control group and other groups, this parameter increased in the rats treated with aqueous and etheric extracts in comparison with ulcer control group and showed significant difference. There was no significant difference between the rats treated with hydroalcoholic extract and ulcer control group (Figure 5).

| Table 2. The mean ± SD of parameters value in the gastric tissue homogenate of rats |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Group                          | PGE₂ (ng/mL)    | HSP70 (ng/mL)   | MDA (nmol/ml)   | TAC (mmol/L)    |
| NC                             | 0.26±0.01a      | 0.53±0.06a      | 2.96±0.11b      | 2.96±0.11a      |
| UC                             | 0.13±0.01b      | 0.39±0.05b      | 3.66±0.18a      | 1.73±0.25b      |
| SC                             | 0.22±0.01c      | 0.46±0.04b      | 3.27±0.05c      | 2.01±0.03ce     |
| AE100                          | 0.23±0.01c      | 0.50±0.04a      | 3.08±0.05a      | 2.28±0.05d      |
| AE400                          | 0.23±0.01c      | 0.51±0.04a      | 3.01±0.04a      | 2.28±0.03d      |
| HA100                          | 0.14±0.01b      | 0.40±0.06b      | 3.43±0.10a      | 1.82±0.11b      |
| HA400                          | 0.13±0.01b      | 0.40±0.10a      | 3.46±0.08a      | 1.84±0.09bc     |
| EE100                          | 0.22±0.01c      | 0.48±0.04ab     | 3.28±0.05c      | 2.01±0.03ce     |
| EE400                          | 0.21±0.00c      | 0.47±0.03ab     | 3.28±0.05b      | 2.03±0.04a      |
| VC                             | 0.21±0.01c      | 0.45±0.03ab     | 3.07±0.03b      | 2.24±0.03d      |

Different letters indicate statistically significant differences (p<0.05)
No statistically significant difference was observed in the HSP70 level between the rats treated with aqueous extract and the normal control group, but there was a significant difference between these groups with ulcer control group ($p<0.05$). Although this parameter increased in the rats treated with etheric extract and omeprazole, no significant difference was seen with other groups (Figure 6).

In general, the most curative effect of *S. striata* was related to aqueous extract. Although the hydroalcoholic extract resulted in improvement of some parameters, it did not have curative effects.

**DISCUSSION**

A key experimental model for evaluation of agents with potential anti-ulcer effect is ethanol-induced gastric injury as ethanol has been considered as a cause of gastric ulcer in humans (13). Oral administration of ethanol results in gastric mucosal damage and alterations in vascular (14). In fact, ethanol causes gastric mucosal injury via direct effects including dehydration, disruption of cellular membranes and cytotoxic effects and also indirect effects via the recruitment of leukocytes (15). In addition, ethanol leads to stasis of blood flow and disruption of gastric microvessels, which in turn inflict hemorrhage and necrosis (15,16). Ethanol-induced necrotic lesions decrease defensive factors such as the mucus production and secretion of bicarbonate (17).

The mentioned effects are probably because of biological actions like lipid peroxidation, intracellular oxidative stress, formation of free radicals, changes in permeability and depolarization of the mitochondrial membrane (18). The defensive mechanism against free radicals is weakened by ethanol (19). Ethanol consumption results in hemorrhagic damage, severe submucosal edema and epithelial cell injury. In the present study, similar lesions were also observed in gastric tissue sections of ulcer control group. The results of this study revealed aqueous extract of *S. striata*, especially at 400 mg/kg have therapeutic effects on ethanol-induced gastric ulcer as tissue structure was near-normal architecture and no edema and leukocyte infiltration were seen in tissue sections.

With both short and long-term use, omeprazole is effective in the treatment of gastroesophageal reflux and peptic ulcer disease (20). Omeprazole functions as an acid inhibitor and offers a protective role such as gastric mucosa (21). Also, this agent, as mucosal protection, is effective in the treatment of nonacid dependent models like ethanol-induced ulcer (22). In the rats treated with omeprazole, mild mucosal damage

![Figure 3](image3.png)  **Figure 3.** The effect of *S. striata* extracts on MDA levels in the gastric tissue homogenate of rats

![Figure 4](image4.png)  **Figure 4.** The effect of *S. striata* extracts on TAC levels in the gastric tissue homogenate of rats

![Figure 5](image5.png)  **Figure 5.** The effect of *S. striata* extracts on PGE2 levels in the gastric tissue homogenate of rats

![Figure 6](image6.png)  **Figure 6.** The effect of *S. striata* extracts on HSP70 levels in the gastric tissue homogenate of rats
with moderate edema and infiltration of leukocytes in the submucosal layer were seen which were similar to those observed in the rats treated ethereal extract.

Treatment of the rats with S. striata extract showed significant antioxidant activity by reduction of MDA and increase of the TAC level in response to ethanol-induced oxidative stress. Oxidative stress plays a key role in the pathogenesis of different diseases including gastric ulcer, and antioxidants perform a significant role in protection of gastric mucosa against necrotic injury (23). Several studies have reported the involvement of oxidative stress in the pathogenesis of ethanol-induced gastric injury (13,15). Ethanol causes damage to the gastric mucosal microcirculation, resulting in hypoxia, formation of free radicals and lipid peroxidation (24).

It seems free radicals formation plays an important role in the production of lipid peroxides together with interference in antioxidant activity (25). Free radicals can reduce enzyme activity such as antioxidant enzymes (26).

MDA is the final product of lipid peroxidation (27). An important pathophysiologic event in various diseases containing gastric ulcer is lipid peroxidation (28) which leads to impaired membrane integrity and ion transport, and finally, loss of cellular function. Oxygen free radicals produced in the gastric tissue might damage cell membranes and increase MDA level (29).

One mechanism involved in the healing of ulcer is removal of oxygen free radicals (Mei 30). Antioxidants like catalase and SOD are the first defensive barrier against free radicals by removing them and preventing their harmful effects (15). Various studies have reported the cytoprotective effect of some antioxidants in the healing of gastric lesions. For instance, melatonin prevented ethanol-induced gastric damage, probably because of its antioxidant effect (31).

Previous studies have shown prostaglandins affect various components of the mucosal defense, including maintaining blood flow, stimulating bicarbonate and mucus secretion, increasing the resistance of epithelial cells to injury and preventing leukocyte recruitment (32). In the present study, ethanol consumption led to decreasing PGE2 that was consistent with previous studies (13,22). PGE2 is the most abundant prostaglandin of alimentary system which performs the gastroprotective effect of irritants (33). The findings of the present study revealed that the prostaglandin effect of S. striata is related to PGE2 because its mucosal level was elevated by compound.

HSPs play an important role in both normal and pathologic situations (35). HSPT0 is a 70 kDa protein and a member of heat shock proteins family (36) which is expressed by mammalian cells. These proteins act as a molecular chaperone and protect the cellular homeostatic processes from various injurious agents through preservation of the structure of normal proteins and repair or removal of damaged proteins (37,38). HSP70 protects mitochondria and interferes with the stress-induced apoptosis, resulting in cytoprotection (38). Ethanol-induced oxygen reactive species inhibit the expression of HSP70 and increase the expression of BAX, while HSP70 protects cells from oxidative stress or heat shock (39).

Jin et al. (40) reported that when the PGE2 level is decreased by NSAID, HSP70 can play an important role in gastric mucosal adaptation. In the present study, the HSP70 levels increased in various groups, which was observed as a significant difference between the rats treated with aqueous extract and ulcer control group. Oyake et al. (41) showed the overexpression of Hsp70 protects gastric mucosal against monochloramine-induced damage. Also, HSP70 induction protected rats from ethanol-induced gastric mucosal injury (15).

In conclusion, the findings of the present study indicated the efficiency of S. striata extract in improving free radicals-induced injury and exerting the protective effects in ethanol-induced gastric ulcer model. These effects were related to increased PGE2 secretion, prevention of consumption of antioxidant sources and maintaining MDA at normal level.

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