



Original Research Article

Gastroprotective and antioxidant potential of *Glycyrrhiza glabra* on experimentally induced gastric ulcers in albino mice

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ABSTRACT

Glycyrrhiza glabra L. (Fabaceae) also known licorice has been widely used as multipurpose ancient herbal medicine. In present study gastro protective effect of *G. glabra* was studied in adult male albino mice against aspirin induced ulcer. This study investigated the gastroprotective effect of *G. glabra* on experimentally induced gastric ulcers in albino mice. Thirty-six mice were divided randomly into 6 equal groups (n = 6). Group 1 was control; group 2 received aspirin for 7 days; group 3 received omeprazole + aspirin for 7 days; groups 4, 5, and 6 received *G. glabra* 250, 500, and 750 mg/kg, respectively along with aspirin, for 7 days. Total oxidant status (TOS), Total antioxidant capacity (TAC), Catalase (CAT), and Malondialdehyde (MDA) were determined to check the gastric damage. Ulcer score, gastric volume, gastric pH, and total acid output were also estimated to determination gastroprotective potential of *G. glabra*. *G. glabra* exhibit gastroprotective potential with significant reduction in the ulcer score, acid output, and gastric volume while the pH of gastric mucosa increases significantly at the dose of 750 mg/kg when compared to aspirin treated group. Biochemical analysis showed significant increase in TAC and CAT activity while it significantly decreased in the levels of TOS and MDA which indicate reduction in gastric damage. *G. glabra* proved to be gastroprotective at 250, 500 and 750 mg/kg showed gastric protection of 46.8, 57.4, and 75.3%, respectively. It also has potent antioxidant properties.

Keywords

Gastroprotective,
Antioxidant,
Aspirin,
Omeprazole

Introduction

Ulcer is the lesion that pierces the muscularis mucosa which does not show the tendency to heal. Its etiology mainly includes imbalance between offensive and protective factors in mucosa of stomach such as mucosal barriers, cellular regeneration, acid-pepsin secretion, blood

flow and epidermal growth factors (Lima *et al.*, 2006). This imbalance usually happened as consequence of *H. pylori* infection and extensive usage of non-steroidal anti-inflammatory drugs (NSAIDs) and clopidogral drugs; which ultimately resulted in peptic ulcer (Padussis and Pappas, 2010).

Most widely used NSAIDs include aspirin as treatment of fever, rheumatic fever, pain, pericarditis and Kawasaki disease. Aspirin has been reported to reduce the chances of cardiovascular and cerebral accidents and mortality rate has also been reduced with the use of aspirin in patients with atherothrombotic disease (Wolff *et al.*, 2009). However, usage of aspirin is getting limited due to severe gastrointestinal effects including peptic ulceration particularly gastric ulcer (Neville, 2010).

Several plant and their extracts have been used to treat gastric ulcers (Eswaran *et al.*, 2010; Sunil *et al.*, 2011). These herbal remedies are of utmost importance in peptic ulcer as compare to synthetic drugs like cimetidine, omeprazole, sucralfate etc. As synthetic drugs have possibility of relapse of peptic ulcer, several side effects and drug interactions (Cheng *et al.*, 2003).

Glycyrrhiza glabra, commonly known as licorice (Mulathi in Pakistan) is one of the oldest and extensively used natural drugs throughout the world. It belongs to family *Fabaceae*. It is native to southeastern Europe and many parts of Asia. Licorice roots are straight pieces of wrinkled, fibrous wood, which are long and cylindrical and grow horizontally underground. The licorice extract can be used as a sugar substitute, where it has an antioxidant action in food and strengthens food aroma. The sweet taste of licorice is entirely due to glycyrrhizin, which is 50 times sweeter than sugar (Hanrahan, 2001).

Traditionally, licorice had been used to treat the disorders of gastrointestinal tract, respiratory tract, genitourinary system, cardiovascular system, skin and eye along with its reported anti-viral effects (Fiore *et al.*, 2005). The hepatoprotective and anti-oxidative effect of

G. glabra and glycyrrhizin (major constituent of *G. glabra*) have been reported in rats (Rajesh and Latha, 2004; Tripathi *et al.*, 2009; Visavadiya *et al.*, 2009). Studies have shown that *G. glabra* has antioxidant, pro-oxidant, free radical scavenging and immunostimulating activities, and can be used in treating the diseases in which oxidants or production of free radicals is involved (Cheel *et al.*, 2010). *G. glabra* compounds have also been reported to prevent oro-dental diseases (Messier *et al.*, 2012). It has also been proved to be a potent antifungal agent (Messier and Grenier, 2011). Glabridin is the major active isoflavan which is obtained from *Glycyrrhiza glabra* and has been reported to reverse the learning and memory deficits occurring in diabetic rats (Hasanein, 2011).

In spite of these actions performed by *G. glabra*, its antiulcer efficacy has not been yet studied in mice where gastrotoxicity is induced by aspirin. The present study was designed to evaluate the gastroprotective effect of *G. glabra* in ulcerated albino mice.

Materials and Methods

Experimental animals

Thirty six adult male albino mice weighing 175 ± 20.5 g were selected for the current study and divided into six equal groups. Animals were housed in experimental animal room, Department of Physiology and Pharmacology, University of Agriculture, Faisalabad (UAF), Pakistan at temperature $22 \pm 2^\circ\text{C}$, humidity 65-70% and a 12 h light/dark cycle for a week before start of experiment and during experiment. Animals were provided with standard feed and water *ad libitum*. Further, the institutional ethical committee of UAF, Pakistan approved all procedures adopted in this study.

Plant material

Roots of *G. glabra* were purchased from the herbal dealers of Faisalabad. The plant material was authenticated by Dr. Mansoor Hameed, Department of Botany, Faculty of Sciences, UAF, Pakistan. A voucher specimen of *G. glabra* rootshave been deposited in the Herbarium maintained of Department of Botany, UAF, Pakistan. The samples were preserved in the pharmacology laboratory of Department of Physiology and Pharmacology, UAF, Pakistan. The material was finely powdered with the help of a special electrical grinder. This process was done with precaution that the temperature did not raise up to 40°C. This powder was passed through mesh sieve no. 200 and then stored in airtight container for further experimental use. Five ml distilled water was used to dilute the *G. glabra* root powder before administration to the rabbits.

Treatment protocol

All the mice were divided into six equal groups (n = 6). Group 1 served as untreated control and received normal diet throughout the experiment(0-7 days), group 2 received aspirin (Disprin®; *Reckitt Benckiser(Pakistan) Ltd.* Karachi, 150 mg/kg orally) for 7 days(Brzoowski *et al.*, 2000). Group 3 received omeprazole (Omega®; Ferozsons Laboratoies Ltd. Karachi, 20 mg/kg) + aspirin (150 mg/kg) for 7 days (Herbert *et al.*, 2011). Groups 4, 5, and 6 received *G. glabra* root powder 250, 500, and 750 mg/kg, respectively along with aspirin 150 mg/kg for 7 days.

Surgical procedures

The animals were fasted for at least 24 h before the surgical procedure. On the 7th day of experiment these animals were

sacrificed. After this, the stomach of the animal was isolated with the help of sharp scissors. The stomach was cut along the greater curvature and the contents were collected into small tubes for biochemical parameters. These gastric contents were then centrifuged at 3000 rpm for 5 minutes. The supernatant was separated and its volume was expressed as ml/100 g body weight.

Blood sampling

Blood samples were collected at 0 and 7 days. The samples were allowed to clot for 20 minutes at refrigeration temperature and then centrifuged for 5 min at 4000 rpm to separate serum. Serum was stored at -4°C till the estimation of different antioxidant parameters.

Acid output

The acid output was calculated by titrating the supernatant fluid collected from the stomach with 0.05N NaOH. Acidity was expressed as mEq/L/100 g of body weight (Maity *et al.*, 2003).

$$\text{Acidity} = \frac{\text{volume of NaOH} \times \text{normality}}{0.1} \times 100$$

Ulcer index

The number of ulcers was noted and the severity was determined with the following scores: Normal coloration (0.0), Red coloration (0.5), Spot ulcer (1.0), Hemorrhagic stress (1.5), Deep ulcers (2.0), Perforation (3.0). Ulcer index (UI) was calculated using the formula (Vogel, 2002).

$$\text{UI} = \frac{\text{US} + \text{UN} + \text{UF}}{10}$$

Where, US = mean severity of ulcer score.
UN = average number of ulcers per animal.

UP = percentage of animals with ulcer incidence.

Curative ratio

The curative ratio from the ulcer was calculated for the treated groups by using the following equation.

$$\text{Percentage (\%)} = \frac{[\text{CUI-TUI}]}{\text{CUI}} \times 100$$

Where, CUI = ulcer index of control groups.
TUI = ulcer index of treated groups.

Biochemical examination

Malondialdehyde (MDA) was determined according to the method developed by Ohkawa *et al.* (1997). Enzymatic activity of enzyme catalase (CAT) was measured by method of Goth (1991). The total oxidant status (TOS) and the total antioxidant capacity (TAC) in serum were measured by methods developed by Erel (2004, 2005) using spectrophotometer.

Statistical analysis

The values were expressed as mean \pm SE. Statistical analysis was performed by one way analysis of variance (ANOVA) at 5 % level of significance (Steel *et al.*, 1997).

Result and Discussion

Antiulcer parameters

The roots powder of *G. glabra* 250-750 mg/kg, given orally once daily for seven days showed dose dependent protective effect against gastric ulcer induced by aspirin. *G. glabra* at the dose rate of 750 mg/kg significantly protected the animal and healed ulcer after seven days of treatment.

Mean ulcer score of group 2 was 2.25 that increased significantly ($p < 0.05$) after administration of aspirin, while it significantly decreased for group 3 as 0.67 which was treated with omeprazole + aspirin and also it was decreased for group 6 which was treated with the highest dose of test plant, having value of mean ulcer score 0.17 presented in table 1.

Ulcer index also showed the similar pattern of results as that of ulcer score. After 7 days of the treatment ulcer index for groups 1, 2, 3, 4, 5, and 6 was 1.43, 9.98, 3.66, 5.30, 4.25, and 2.46, respectively. Group 3 (Omeprazole + aspirin) and highest plant dose in group 6 showed the significant ($p < 0.05$) reduction in ulcer index. The percent curative ratio of *G. glabra* root powder at 250, 500, and 750 mg/kg was 46.8, 57.4, and 75.3%, respectively as presented in table 1.

Total acid output (mEq/L/100 g body weight) of rabbits in after 7 days are presented in Table 2. The mean values for acid output showed that the aspirin increased the acidity in group 2 having mean value 154.58 mEq/L/100 g as compared to the group 1 which has mean value for acidity 45.46 mEq/L/100 g, while the groups treated with *G. glabra* root powder showed significant results at dose 500 and 750 mg/kg as 49.88 and 36.25 mEq/L/100 g, respectively. It was also observed that pH was decreased significantly in aspirin (group 2) treated rabbits compared to group 1, from 2.22 to 1.07. Omeprazole (group 3) enhanced pH (2.17) of gastric mucosa. Our test plant also increased the pH of gastric mucosa which was 2.19 at the dose of 750 mg/kg. It was observed from the result that gastric volume also increased after the administration of aspirin (3.63) while administration of omeprazole and *G. glabra* (750 mg/kg) significantly decreased mean gastric volume 2.60 and 2.11, respectively presented in table 2.

Biochemical parameters

Results of the study showed that mean values of TAC for the group 1 was 0.98 mmol/L. TAC decreased (0.64 mmol/L) with ulcer (group 2) production in stomach by the use of aspirin while it significantly ($p < 0.05$) increases up-to normal values for groups 3 and 6 as 0.97 and 0.95 mmol/L, respectively presented in table 3.

The mean values of TOS of group 1 was 2.65 $\mu\text{mol/L}$. TOS increased (4.51 $\mu\text{mol/L}$) with ulcer production in stomach by the use of aspirin while it significantly ($p < 0.05$) decrease up to normal values for groups 3 and 6 as 2.69 and 2.72 $\mu\text{mol/L}$, respectively when compared with aspirin treated group presented in table 3.

Results of the current study also demonstrated that the mean values of MDA activity was increased (from 2.45 to 4.34 nmol/L) when aspirin was used alone for the production of ulcer in stomach. The mean values decrease significantly ($p < 0.05$) for groups 3, 4, 5, and 6 as 2.65, 3.94, 3.21, and 2.25, respectively presented in table 3.

The mean values of CAT activity decreased up to 5.95 KU/L when aspirin was used alone for the production of ulcer in stomach. This value is significantly ($p < 0.05$) decreased from normal value i.e. 9.51 KU/L and its value seems to increased significantly when treated with omeprazole (8.28 KU/L) when compared with aspirin treated group. It also has normal range of values for CAT activity when plant was used at highest dose as in group 6 (9.37 KU/L) which presented in table 3.

Gastric ulcer is a break in the normal gastric mucosa of the stomach that extends throughout the muscularis mucosa into the submucosa or deeper. In ulcer condition erosions are formed and superficial

epithelium of mucosa is lost. In the alimentary tract ulcer may occur everywhere. Prostaglandins play an important protective role in the stomach by stimulating the synthesis and secretion of mucus and bicarbonate, increasing mucosal blood flow and promoting epithelial proliferation. The major mechanism via NSAIDs cause ulcers is the inhibition of PGs by the inhibition of COX, which is key enzyme in the bio-synthesis of PGs (Hamidet *al.*, 2012). So to avoid all these adverse reactions of the drugs, herbal remedies should be given to the ulcer patient to cure the ulcer. Many natural products in plants have multifunctional molecules that protect them from infections of bacteria, viruses and other microorganisms. For this reason we evaluated the antiulcer activity of graded dose of *G. glabra* root powder in albino rabbits.

In present study, results demonstrated that ulcer scores were significantly increased in animals treated with aspirin. Administration of synthetic antiulcer drug, omeprazole at dose of 20 mg/kg along with aspirin significantly reduced the ulcer scores in comparison with aspirin treated rabbits. Concomitant administration of *G. glabra* root powder at dose rate of 250, 500, and 750 mg/kg along with aspirin significantly reduced the ulcer scores. The mean value of *G. glabra* at dose rate of 750 mg/kg was not significantly different from omeprazole. The results of our study coincide with other studies (Aslamet *al.*, 2013; Begum *et al.*, 2014).

pH of gastric secretions was measured in the current study. Administration of aspirin significantly reduced the pH of gastric mucosa as described in previous studies (Aslamet *al.*, 2013). The administration of omeprazole along with aspirin significantly enhanced the pH of gastric mucosa.

Concomitant administration of *G. glabra* root powder with aspirin significantly enhanced the pH of gastric secretions at three different doses 250, 500, and 750 mg/kg. *G. glabra* at dose rate of 750 mg/kg significantly enhanced the pH and it produced similar results as synthetic antiulcer drug omeprazole. Aspirin causes the gastric damage by making the stomach pH more acidic which increases the acidity in the gastric mucosa by enhancing the concentration of hydrogen ions. These results are similar as described in previous studies (Alsabriet *et al.*, 2013).

The gastric volume was significantly increased in groups 2. Aspirin increases the acid secretions in gastric mucosa due to its acidic nature which enhances the volume of gastric secretions. Administration of omeprazole along with aspirin significantly reduces the gastric volume. Concomitant administration of *G. glabra* along with aspirin significantly reduced the gastric volume at 250, 500, and 750 mg/kg. *G. glabra* at dose of 750 mg/kg significantly reduced gastric volume and its results were statistically similar with synthetic antiulcer drug omeprazole. The above mentioned results are in accordance with previous research studies on aspirin induced gastric ulcer (Goswami *et al.*, 2011). Pretreatment with an oral dose of *G. glabra* could partially decrease the ulcer index and permit the healing of gastric lesions induced by administration of aspirin.

The antioxidant (TAC, TOS, MDA, and CAT) activity of *G. glabra* was also determined. Phytochemical screening showed positive result for the steroids, terpenoids, alkaloids, di- and triterpenoids, phenols, flavonoids, tannins and volatile oils. These constituents have different activities which are helpful in healing ulcer. Flavonoid has free radical scavenging and

antioxidant activity. The important derivative of flavonoids is quercetin. Flavonoids increase the mucus production and also have antihistaminic properties which reduce the histamine production and reduction of mast cells which are produced by the aspirin. The main mechanisms of action for the gastroprotective effects of this flavonol are its proton pump inhibitor and antioxidant properties. Oral administration of NSAIDs, such as aspirin, indomethacin have several undesirable effects on the gastrointestinal tract and increase the chances of myocardial infarction. Flavonoids also have anti-inflammatory properties without any ulcerogenic action as a side effect and thus show a great advantage in the treatment of peptic ulcers (Kelly *et al.*, 2009).

Our study gives the suggestion that in case of gastric ulcer the oxidative stress is increased then the MDA activity and levels of TOS are also increased in ulcerated group, while the levels of TAC and CAT are decreased for the same group. Antioxidants have defensive properties against gastric ulcer and many other ailments (Saravanan, 2011). The oxidative alteration in the cellular membrane or intracellular molecules occurs by the imbalance between ROS and antioxidant defense mechanism. LPO causes loss of membrane fluidity, impaired ion transport and membrane integrity (Tandon *et al.*, 2004).

It has been concluded from the results that when aspirin was given at a dose rate of 20 mg/kg, TOS and MDA were enhanced significantly while TAC and CAT activity were reduced significantly. Aspirin encourages the reactive oxygen metabolites that may play a role in gastric damage. These reactive species cause damage to the biochemical markers e.g. lipid and increased the production of free radicals that increased

MDA production and decreased CAT and these free radicals production also because of impairment of cellular enzyme that involve in defensive mechanism of gastric ulcer such as total antioxidant capacity and CAT activity(Filho *et al.*, 2012).

The curative ratio for ulcer of treated groups was calculated. *G. glabra* decreased gastric lesions dose dependently. *G. glabra* significantly decreased the gastric MDA content while it increased the CAT activity compare to aspirin. This showed

that the antiulcer activity of the *G. glabra* might be recognized by these tests.

In conclusion to present study *G. glabra* root powder proved to be gastroprotective. It also significantly enhanced the TAC and CAT activity comparable to synthetic antiulcer drug while it caused a significant reduction in TOS and MDA levels which indicate it as antioxidant. Overall study revealed that extract of *G. glabra* at 250, 500, and 750 mg/kg showed gastric protection of 47.5, 58.1, and 73.5%, respectively.

Table.1 Mean values of ulcer score, ulcer index and curative ratio after 7 days of treatment with per-oral drugs and *G. glabra* root powder in albino mice

Groups	Ulcer Score	Ulcer index	Curative ratio %
1. Control (Routine diet)	0.08 ± 0.02 ^d	1.43 ± 0.10	-
2. Asp (150 mg/kg)	2.25 ± 0.61 ^a	9.98 ± 0.33	-
3. OMP (20 mg/kg) + Asp	0.67 ± 0.25 ^{cd}	3.66 ± 0.12	63.3
4. <i>G. glabra</i> (250 mg/kg) + Asp	1.33 ± 0.68 ^b	5.30 ± 0.27	46.8
5. <i>G. glabra</i> (500 mg/kg) + Asp	1.00 ± 0.45 ^{bc}	4.25 ± 0.35	57.4
6. <i>G. glabra</i> (750 mg/kg) + Asp	0.17 ± 0.06 ^d	2.46 ± 0.29	75.3

Similar letters on means in a column (n=6) are statistically non-significant ($P \geq 0.05$). Asp = Aspirin, OMP = Omeprazole.

Table.2 Mean values of acid output, pH and gastric volume after the 7 days of treatment with per-oral drugs and *G. glabra* root powder in albino mice

Groups	Acid output (mEq/L/100g)	Gastric pH	Gastric volume (ml/100g)
1. Control(Routine diet)	45.46±9.62 ^{bc}	2.22±0.22 ^a	2.35±0.45 ^a
2. Asp(150 mg/kg)	154.58±31.68 ^a	1.07±0.31 ^c	3.63±0.42 ^b
3. OMP (20 mg/kg) +Asp	53.75±10.36 ^{bc}	2.17±0.26 ^a	2.60±0.58 ^a
4. <i>G. glabra</i> (250 mg/kg) + Asp	64.42±16.97 ^b	1.68±0.40 ^b	3.36±0.52 ^b
5. <i>G. glabra</i> (500 mg/kg) + Asp	49.88±15.45 ^{bc}	1.94±0.27 ^{ab}	2.49±0.35 ^a
6. <i>G. glabra</i> (750 mg/kg) + Asp	36.25±11.59 ^c	2.19±0.15 ^a	2.11±0.28 ^c

Similar letters on means in a column (n=6) are statistically non-significant ($P \geq 0.05$). Asp = Aspirin, OMP = Omeprazole.

Table.3 Mean values of TOS, TAC, MDA and CAT after the 7 days of treatment with per-oral drugs and *G. glabra* root powder in albino mice

Groups	TOS ($\mu\text{mol/L}$)	TAC (mmol/L)	MDA (nmol/L)	CAT (KU/L)
1. Control(Routine diet)	2.65 \pm 0.19 ^a	0.98 \pm 0.07 ^a	2.45 \pm 0.3 ^a	9.51 \pm 0.5 ^a
2. Asp(150 mg/kg)	4.51 \pm 0.7 ^b	0.64 \pm 0.2 ^b	4.34 \pm 1.6 ^b	5.95 \pm 1.4 ^b
3. OMP (20 mg/kg) +Asp	2.69 \pm 0.16 ^a	0.97 \pm 0.1 ^a	2.65 \pm 0.4 ^a	8.28 \pm 1.2 ^a
4. <i>G. glabra</i> (250 mg/kg) + Asp	3.90 \pm 0.03 ^c	0.75 \pm 0.05 ^c	3.94 \pm 0.8 ^c	6.47 \pm 0.6 ^a
5. <i>G. glabra</i> (500 mg/kg) + Asp	3.34 \pm 0.15 ^{ac}	0.80 \pm 0.23 ^c	3.21 \pm 0.5 ^{ac}	7.93 \pm 0.9 ^{ac}
6. <i>G. glabra</i> (750 mg/kg) + Asp	2.72 \pm 0.26 ^a	0.95 \pm 0.11 ^a	2.25 \pm 0.2 ^a	9.37 \pm 0.4 ^a

Similar letters on means in a column (n=6) are statistically non-significant ($P \geq 0.05$). Asp = Aspirin, OMP = Omeprazole.

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