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Prophylactic Role of Echinacea, Green Tea and Boswellia Extracts in Pyloric Ligation-Induced Gastric Ulcer in Rats

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Abstract: Peptic ulcer is a common disorder of the stomach and duodenum. Herbs and medicinal plants are considered to be a potential source to combat various diseases including gastric ulcer. The present study was conducted to evaluate the gastro protective effects of Echinacea extract, Green tea extract and Boswellia extract on a pyloric ligation-induced gastric ulcer. Six groups of rats were intraperitoneally pre-treated with saline as normal group, saline as ulcer group, 20 mg/kg of ranitidine as positive group, Echinacea extract (25 mg/kg, I.P), Green tea extract (25 mg/kg, I.P) and Boswellia extract (200 mg/kg, I.P) for 15 consecutive days before pyloric ligation. Gastric acidity, ulcer index and histology were assessed. Gastric homogenates were determined for Malondialdehyde (MDA) content, Glutathione (GSH) content in addition to blood Superoxide Dismutase (SOD) activity. Pyloric ligation elevated gastric acidity, ulcer index and malondialdehyde content, while glutathione content and superoxide dismutase activity were significantly decreased. Prior administration of extracts mitigated the injurious effects of pyloric ligation. Echinacea, Green tea and Boswellia extracts separately ameliorated all the altered biochemical parameters. These results were confirmed histologically. These data suggested that Green tea, Echinacea or Boswellia extract could have a protective role in gastric ulcer probably via regulation of oxidant/anti-oxidant balance.

Keywords: Boswellia, echinacea, gastric ulcer, green tea, pyloric ligation

INTRODUCTION

Peptic ulcer embraces both gastric and duodenal ulcers and has been a major threat to the world's population over the past 2 centuries, with a high morbidity and substantial mortality (Pahwa *et al*., 2010). Ulceration of the gastrointestinal mucosa is caused by disruption of normal balance of the corrosive effect of gastric juice and the protective effect of mucus on gastric epithelial cells. Pyloric ligation induces gastric ulceration in rats through accumulation of acidic gastric juice in the stomach. It alters the cytoprotective prostaglandins, membrane lipid per oxidation and endogenous glutathione content (Singh *et al*., 2008).

Some plant extracts are recognized as sources of natural antioxidants that can protect against oxidative stress and thus can play an important role in the chemoprevention of diseases resulting from lipid per oxidation (Nakatani, 2000). Echinacea species are rich in bioactive metabolites such as alkamides, water-soluble phenolic compounds (mainly caffeic acid derivatives) and polysaccharides. It has been reported that Echinacea extract possesses multifunctional effects, such as immune stimulating, anti-inflammatory, antiviral, anticancer and radio protective effects in addition to anti-oxidative and free radical scavenging properties (Agnew *et al*., 2005; Aherne *et al*., 2007; Masteikova *et al*., 2007).

Tea is second only to water in popularity as a beverage. Green tea (Camellia sinensis) is rich in flavanols known as catechins such as epicatechins (Graham, 1992). Green tea polyphenols are potent free radical scavengers due to the hydroxyl groups in their chemical structure.

The plant Boswellia serrata (Family Burseraceae) is commonly known as Indian Olibanum in English and is reported to have antiulcer activity Zeeyauddin *et al.* (2011), Ammon (1996) and Hostanska *et al.* (2002) indicated that boswellic acids have a number of effects including anti-inflammatory, immunomodulatory, anti-tumor and antioxidant.

The aim of the present study is to investigate the possible protective effects of Echinacea extract, Green tea extract and Boswellia extract in pyloric ligation-induced gastric ulcer models. Ranitidine was chosen as the reference standard in gastric ulcer protection.

MATERIALS AND METHODS

Drugs and chemicals: All chemicals for laboratory experimentation were purchased from Sigma-Aldrich (St. Louis, MO, USA). Green tea extract was obtained

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by Mepaco Company, Egypt and defined as having a polyphenolic content of 55±5%. Echinacea extract was supplied by Mepaco Company, Egypt. Boswellia extract has been prepared according to the method described by Singh *et al.* (1996).

Animals: Adult albino rats, weighing 140-160 g each, were used. Rats were obtained from the Research Institute of Ophthalmology (Giza, Egypt) and were kept under appropriate laboratory conditions. They were kept under standard conditions of temperature (25±2°C) with 12 h light/12 h dark cycle throughout the period of investigation. They were fed a standard diet and allowed free access to water. All procedures in this study were carried out according to guidelines of Ethics Committee of Faculty of Pharmacy, Cairo University.

Experimental design:

Gastric ulcer: A total of 60 rats were allocated in six groups, 10 rats each group. First group served as normal group and second group served as control group and were given saline once daily for 15 consecutive days. Third group, fourth group, fifth group and sixth group were administered ranitidine (20 mg/kg, IP), Echinacea extract (25 mg/kg, IP), Green tea extract (25 mg/kg, IP) and Boswellia extract (200 mg/kg, IP) respectively for 15 consecutive days. All drugs and extracts were prepared in saline by aid of 1% Tween 80. Animals were individually housed in a metal cage with a wide-meshed bottom to prevent coprophagy. The animals were fasted for 48 h but allowed free access to water except for the last hour before pyloric ligation. Pyloric ligation method was performed according to the method of Shay (1945) and Kurasawa *et al.* (2005).

Biochemical examination: Titratable acidity was determined according to the method described by Grossman (1963). Ulcer index was calculated according to the method described by Shay *et al.* (1954) and the protection percentage was calculated by the method described by Hano *et al.* (1976).

Lipid peroxides were determined in gastric mucosal homogenate as Thiobarbituric Acid Reactive Substances (TBARS) as MDA following the method of Mihara and Uchiyama (1978). The stomach content of glutathione was determined in stomach homogenate according to the method of Beutler *et al.* (1963). Superoxide dismutase activity was determined in blood following the pyrogallol autoxidation method of Marklund and Marklund (1974).

For histopathological examination, stomachs were fixed in 10% formaldehyde solution, sectioned and embedded in paraffin then stained with hematoxylin and eosin and then examined under a light microscope. The specimens were assessed according to the criteria of Laine and Weinstein (1988).

Statistical analysis: Data analysis was achieved using a software program Prism (version, 5). Data were presented as means±S.E. Comparisons between different treatments were done using one way ANOVA followed by Student-Newman-Keuls as a post-ANOVA test. Criterion for significance was chosen to be at $p<0.05$.

RESULTS

Effect of administration of ranitidine, echinacea extract, green tea extract as well as boswellia extract individually for two weeks before pyloric ligation on gastric acidity and ulcer index: Pyloric ligation induced gastric ulcer with a significant increase in both titratable acidity and ulcer index. Treatment with ranitidine, Echinacea extract, Green tea extract as well as Boswellia extract significantly reduced titratable acidity to about 55.95, 66.08, 62.00 and 74.01%, respectively compared to the ulcer control value (Table 1).

Similarly, ranitidine, Echinacea extract, Green tea extract as well as Boswellia extract significantly inhibited ulcer index by 48.20, 33.18, 41.67 and 24.12%, respectively compared to the ulcer control value. The inhibition of ulcer index produced by Green tea extract was similar to that produced by ranitidine, while the inhibition of ulcer index produced by Echinacea extract or Boswellia extract was significantly lower than that produced by ranitidine (Table 2).

Table 1: Protective effect of two weeks daily treatment with ranitidine, echinacea extract, green tea extract or boswellia extract on ulcer index in pyloric ligation-induced gastric ulcer in rats

	Titratable acidity	
Drugs and doses	$\bar{X}$±SEM (mEq/L)	Ulcer control (%)
Ulcer control (pyloric ligation)	94.58±7.21	100.00
Ranitidine (20 mg/kg)	52.92[b]±6.32	55.95[b]
Echinacea extract (25 mg/kg)	62.50[b]±5.92	66.08[b]
Green tea extract (25 mg/kg)	58.64[b]±5.22	62.00[b]
Boswellia extract (200 mg/kg)	70.00[b]±5.71	74.01[b]

Each value represents the mean of 10 experiments ±SEM; Statistical analysis was carried out by one way Analysis of Variance (ANOVA) followed by Student-Newman-Keuls multiple comparisons test; [b]: Significantly different from ulcer control value at $p<0.05$

Table 2: Protective effect of two weeks daily treatment with ranitidine, echinacea extract, green tea extract as well as boswellia extract on ulcer index in pyloric ligation-induced gastric ulcer in rats

Drugs and doses	Ulcer index $\bar{X}$±SEM	Protection (%)
Normal control (1% tween 80)	0.85±0.02	96.51
Ulcer control (pyloric ligation)	24.38[a]±0.98	00.00[a]
Ranitidine (20 mg/kg)	12.63[b]±0.26	48.20[b]
Echinacea extract (25 mg/kg)	16.29[b,c] ±1.02	33.18[b,c]
Green tea extract (25 mg/kg)	14.22[b]±0.49	41.67[b]
Boswellia extract (200 mg/kg)	18.50[b,c]±1.12	24.12[b,c]

Each value represents the mean of 10 experiments ±SEM; Statistical analysis was carried out by one way Analysis of Variance (ANOVA) followed by Student-Newman-Keuls multiple comparisons test; [a]: Significantly different from normal control value at p<0.05; [b]: Significantly different from ulcer control value at p<0.05; [c]: Significantly different from ranitidine value at p<0.05

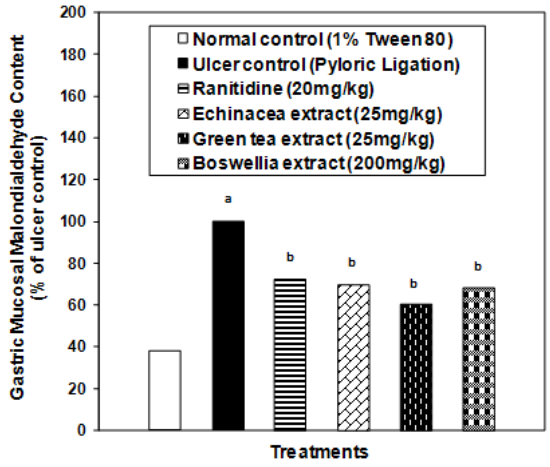

Fig. 1: Protective effect of two weeks daily treatment with ranitidine, echinacea extract, green tea extract as well as boswellia extract on gastric mucosal malondialdehyde content in pyloric ligation-induced gastric ulcer in rats
Each bar represents the mean of 8-12 experiments; statistical analysis was carried out by one way Analysis of Variance (ANOVA) followed by Student-Newman-Keuls multiple comparisons test; [a]: Significantly different from normal control value at p<0.05; [b]: Significantly different from ulcer control value at p<0.05

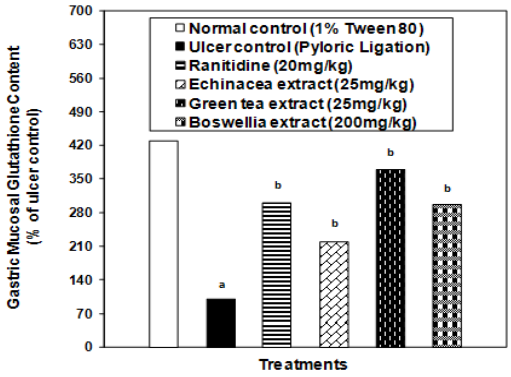

Fig. 2: Protective effect of two weeks daily treatment with ranitidine, echinacea extract, green tea extract as well as boswellia extract on gastric mucosal glutathione content in pyloric ligation-induced gastric ulcer in rats
Each bar represents the mean of 8-12 experiments; Statistical analysis was carried out by one way Analysis of Variance (ANOVA) followed by Student-Newman-Keuls multiple comparisons test; [a]: Significantly different from normal control value at p<0.05; [b]: Significantly different from ulcer control value at p<0.05

Effect of administration of ranitidine, echinacea extract, green tea extract as well as boswellia extract individually for two weeks before pyloric ligation on oxidative stress biomarkers: Pyloric ligation significantly increased gastric mucosal MDA content compared to normal control value. Pre-treatment with ranitidine, Echinacea extract, Green tea extract as well as Boswellia extract significantly reduced gastric mucosal MDA content to 72.14, 69.48, 59.93 and 68.13%, respectively compared to the ulcer control value (Fig. 1).

Pyloric ligation induced a significant decrease in GSH content in rat gastric mucosa compared to normal control value. Administration of ranitidine, Echinacea extract, Green tea extract as well as Boswellia extract significantly increased mucosal GSH content to 300.00,

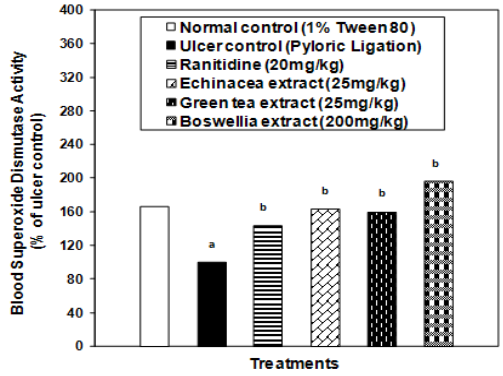

Fig. 3: Protective effect of two weeks daily treatment with ranitidine, Echinacea extract, Green tea extract as well as Boswellia extract on blood superoxide dismutase activity in pyloric ligation-induced gastric ulcer in rats
Each bar represents the mean of 8-12 experiments; Statistical analysis was carried out by one way Analysis of Variance (ANOVA) followed by Student-Newman-Keuls multiple comparisons test; [a]: Significantly different from normal control value at p<0.05; [b]: Significantly different from ulcer control value at p<0.05

218.52, 370.37 and 296.30, respectively compared to the ulcer control value (Fig. 2).

Pyloric ligation significantly decreased blood SOD activity. Ranitidine, Echinacea extract, Green tea extract and Boswellia extract significantly increased blood SOD activity by 142.83, 163.27, 159.76 and 195.99%, respectively as compared to the ulcer group (Fig. 3).

Histopathological examination: Figure 4a shows a normal histological structure of rat gastric mucosa. Pyloric ligation resulted in severe congestion of blood vessels, hemorrhage, tissue infiltrations, tissue necrosis, edema and several ulcers (Fig. 4b). Ranitidine showed better protection of gastric mucosa as seen by mild blood vessels congestion and mild tissue infiltrations (Fig. 4c). Echinacea extract and Green tea extract showed partial loss of mucosal surface, sub mucosal congestion, interruption of serosal layer and no necrosis (Fig. 4d and e). Boswellia extract showed mild blood vessels congestion, mild tissue infiltrations, no necrosis and no ulcers (Fig. 4f).

DISCUSSION

Pyloric ligation causes ulceration mainly via increased accumulation of gastric acid and pepsin leading to auto digestion of gastric mucosa (Jainu and Devi, 2006). In the present study, pyloric ligation significantly increased gastric acidity and ulcer index which is in consistence with the results of Sood and Muthuraman (2009).

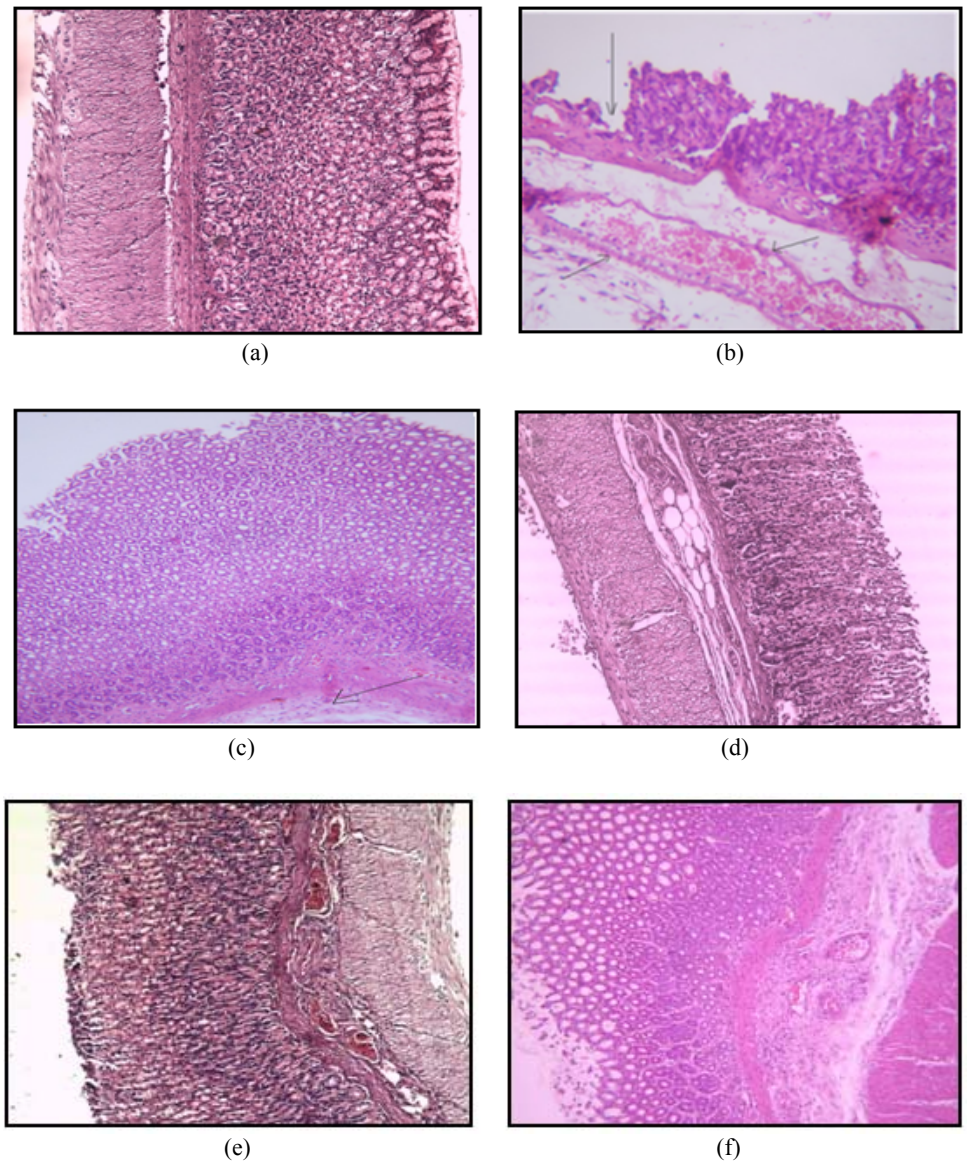

Fig. 4: Photomicrograph of stomach sections from normal rats, (a) pyloric ligated rats, (b) rats treated with 20 mg/kg ranitidine, (c) 25 mg/kg echinacea extract, (d) 25 mg/kg green tea extract, (e) 200 mg/kg boswellia extract (f) (H and E stain x200)

According to the results of the present investigation, ranitidine significantly decreased gastric acidity and ulcer index. These findings are in agreement with the results obtained by Kim *et al.* (2005). The effect of ranitidine is mediated through histamine receptors. H_2-receptor on the parietal cell mediates the stimulatory effect of histamine on acid secretion. Ranitidine, a histamine H_2-receptor antagonist, blocks the H_2-receptors results in a decrease in the secretory actions of gastrin and acetylcholine on parietal cells (Norlen *et al.*, 2005).

The results of the present study showed that the tested extracts have an effective antisecretory and antiulcer activity against pyloric ligation-induced gastric ulcer in rats. Green tea extract significantly decreased gastric acidity. Studies of Rao and Vijayakumar (2007) revealed that catechin, one of the main active constituents of Green tea extract, caused reduction in histamine concentration and attenuated the elevated mucosal H^+K^+ATPase (the enzyme responsible for H^+ secretion by the gastric parietal cells) in gastric mucosal injury induced by ischaemia-reperfusion.

Similarly, treatment with Boswellia extract significantly decreased gastric acidity which is in accordance with results of Singh *et al.* (2008). Boswellic acids increase in synthesis of cytoprotective prostaglandins (Singh *et al.*, 2008). Prostaglandins produce a wide variety of actions in the stomach including control of acid secretion, bicarbonate secretion, mucosal blood flow and mucus production (Takeeda *et al.*, 2004). PGE_2 inhibits gastric acid secretion through EP_3 receptors which inhibit H^+K^+ATPase (Hoogerwerf and Pasricha, 2006). Quercetin, an active constituent of Boswellia extract, was reported to decrease the number of mast cells and to reduce the area of gastric erosions (Kahraman *et al.*, 2003). These results suggest that the gastro protective effect of quercetin could be due to its antioxidant and antihistaminic effects.

Echinacea extract significantly decreased gastric acidity. However, no studies were reported about the effect of Echinacea extract on gastric acid secretions.

Study of oxidative stress parameters showed that pyloric ligation resulted in a significant increase in gastric mucosal MDA content along with a decrease in gastric mucosal GSH content and blood SOD activity. These results are in accordance with those obtained by Sood and Mutharaman (2009) and Kath and Gupta (2006) respectively. Several studies demonstrated that pyloric ligation alters the cytoprotective prostaglandins, membrane lipid per oxidation and endogenous glutathione content (Singh *et al*., 2008).

Depletion of gastric mucosal glutathione content in counteracting free radicals and reactive oxidant intermediates leads to gastric ulcer (Demir *et al.*, 2003). In the present study, pyloric ligation resulted in a significant decrease in gastric mucosal GSH content. This result is in harmony with those obtained by Sood and Mutharaman (2009). The reduction of gastric mucosal glutathione content may be attributed to increase in calcium level which stimulates free radical generation (Lutnicki *et al.*, 1992). This increase in free radicals is documented to induce peptic ulcer (Rainsford, 1999) and triggers a cascade of events leading finally to cell death (Orrenius *et al.*, 1991).

Similarly, results of the present study revealed that pyloric ligation decreased blood SOD activity. This result is in agreement with the work of Kath and Gupta (2006). The reduction of SOD activity could be attributed to the increase in free radical generation (Lutnicki *et al*., 1992) where SOD protects organisms from ROS-mediated damage to cell components (Halliwell and Gutteridge, 1990).

In the current study, ranitidine decreased gastric mucosal MDA content which is in agreement with Dursun *et al.* (2009). It has been reported that ranitidine has antioxidant and immunosuppressive actions, which may also be responsible for its anti-ulcerative activity (Van Zyl *et al.*, 1993; Ardestani *et al.*, 2004).

The present data revealed that ranitidine increased gastric GSH content and blood SOD activity which is in harmony with that of Panneerselvam and Arumugam (2011) and Kath and Gupta (2006) respectively. GSH detoxifies hydrogen peroxide (H_2O_2) and/or organic acids chemically; H_2O_2 accumulates in the absence of GSH (Dalle-Donne *et al.*, 2003) and in the presence of transition metals, H_2O_2 reacts with superoxide anion resulting in the formation of hydroxyl radical, the most reactive and cytotoxic form of ROS (Malo and Wilson, 2000). Ranitidine was also reported to stimulate glutathione reductase activity (Dengiz *et al.*, 2007).

Results of the present study showed that Echinacea extract decreased gastric mucosal MDA content. Similar results have been reported by Kour and Bani (2011) using chicoric acid which is the main active constituent of Echinacea extract. In addition, the reduction in MDA content induced by Echinacea extract could be related to its antioxidant activity including free radical scavenging (Agnew *et al.*, 2005) and transition metal chelating properties (Hu and Kitts, 2000).

The present data showed that Echinacea extract increased gastric mucosal GSH content. Several studies reported that caffeic acid phenethyl ester (one of the main active constituents of Echinacea) scavenges free oxygen and increases the antioxidant enzyme activity (Gurel *et al.*, 2004).

In the present study, Echinacea extract increased blood SOD activity. Mishima *et al.* (2004) assumed that SOD activity in peripheral blood was increased because of antioxidants such as echinacocide and caffeine acid in Echinacea extract.

In the current study treatment with Green tea extract significantly reduced gastric mucosal MDA content which is in harmony with the data obtained by Adhikary *et al.* (2011) using epigallocatechin gallate. It was reported that epicatechines can react with superoxide radical to form the corresponding

semiquinone (Wang *et al.*, 2003). In addition, epicatechins may chelate metal ions, which in turn, inhibit generation of hydroxyl radicals and degradation of lipid hydro peroxides which cause reactive aldehyde formation (Azam *et al.*, 2004).

According to the findings of the present investigation, Green tea extract increased gastric mucosal GSH content. This finding is in accordance with that obtained by Adhikary *et al.* (2011) who reported that epigallocatechin gallate was found to reduce protein oxidation and the depletion of thiol-dependent antioxidant defensive gastric tissues. Antioxidant activity of Green tea extract could be also mediated through activation of glutathione per oxidize and glutathione-s-transferase (El-Beshbishy, 2005).

In the present experiment, treatment with Green tea extract resulted in increased blood SOD activity. This result is in harmony with the study of other investigators (Rao and Vijayakumar, 2007). The antioxidant activity of Green tea extract could be attributed to induction or mutually protective interaction of SOD (Shull *et al.*, 1991; El-Beshbishy, 2005).

In the current study, Boswellia extract decreased gastric mucosal MDA in pyloric ligated rats. This finding is in agreement with the results of Coskun *et al.* (2004). In addition, Boswellia extract increased gastric GSH content and blood SOD activity. The protective effect of Boswellia extract could be mediated via the free radical-scavenging properties of quercetin which is an active constituent of Boswellia extract (Suzuki *et al.*, 1998). It was also reported that quercetin acts as an inducer of antioxidant enzymes like SOD and Catalase (CAT) (Coskun *et al.*, 2004).

In the present study, the pretreatment with ranitidine, Echinacea extract, Green tea extract and Boswelliae xtract apparently ameliorated the histological alterations induced by pyloric ligation. The histological observations of ranitidine and Green tea extract are in accordance with the study of Kim *et al.* (2005) and Lee *et al.* (2005), respectively.

CONCLUSION

Based on the results of the present study, it could be concluded that:

- Administration of Green tea, Echinacea and Boswellia extracts ahead of pyloric ligation alleviated all the morphological and biochemical features of gastric ulcer.
- The modulation of oxidant/anti-oxidant balance in gastric tissue could possibly account for the protective role of Green tea, Echinacea and Boswellia extracts in gastric ulcer model.
- The present study emphasizes the protective effect of medicinal plants against gastric ulcer.

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