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A Protective Effect for *Panax ginseng* in the Rat Stomach

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Abstract : The effect of ginseng on gastric ulcer and gastric acid secretion was investigated in pylorus-ligated rats. Methods: Sprague-Dawley strain rats were used after 24 hours fast. Pylous-ligation was performed under light ether anaesthesia, then gastric mucosal damage was evoked in conscious pylorus-ligated rats by the administration of subcutaneous (s.c.) indomethacin (20 mg/kg), s.c. histamine (150 mg/kg) or by pylorus-ligation (Shay ulcer). Ginseng was given by intragastric (i.g.) or intraperitoneal (i.p.) route simultaneously with the ulcerogens. Rats were killed after 3 h (indomethacin and histamine models) or after 18 h (Shay ulcer), when the gastric secretory responses, the number and severity of gastric mucosal lesions and mucosal mucus content determined. The effect of i.p. ginseng on basal gastric acid secretion and on gastric acid secretion in indomethacin (20 mg/kg, s.c.)-treated rats was also investigated in urethane anesthetized rats. Gastric acid secretion was measured by flushing of the gastric lumen with saline every 15 min through an oesophageal cannula. Results: In conscious pylorus-ligated rats, i.g. ginseng (12.5-50 mg/ml; 50-200 mg/kg) protected against gastric mucosal lesions evoked by s.c. indomethacin or s.c. histamine in the 3-h pylorus-ligated rat, without modifying gastric acid secretory responses. Ginseng given i.p. (150 or 200 mg/kg) did not reduce the gastric lesions produced by histamine or by ligating the pylorus (Shay ulcer). Ginseng given orally in 50 mg/ml (200 mg/kg) increased gastric mucus secretion in saline- and indomethacin-treated conscious pylorus-ligated rats. In anaesthetized rats ginseng (50 or 200 mg/kg) did not modifiy basal gastric acid secretion or gastric acid secretion in the indomethacin-treated rats. Conclusions: ginseng given orally exerts gastroprotective effects in the rat stomach. Such anti-ulcer effect does not involve changes in gastric acid secretory responses. In addition, ginseng possesses stimulatory effect on gastric mucus secretion, which could be one mechanism by which the compound exerts its antiulcer effect. Our data are in favor for a beneficial effect for topically applied ginseng on the gastric mucosa.

Key words : *Panax ginseng*, indomethacin, histamine, gastric acid, gastric mucosa

INTRODUCTION

For some 2000 years the roots of *Panax ginseng* (Araliaceae) have held an honoured place in Chinese medicine. In Asia the drug is held in esteem for the treatment of diverse group of diseases including anaemia, diabetes, gastritis, sexual impotence and the many conditions arising from the onset of old age. In the west, recently, it has become a popular remedy particularly for the improvement of concentration, resistance to stress and to disease; in this sense the action of the drug is described as 'adaptogenic'. Ginseng is thus used in general to enhance physical and psychological performance and is mainly viewed as a tonic and restorative agent.[1]

The drug is one of the major botanical drugs of US foreign trade. In 1995, ginseng (Asian *Panax* and American *Panax quinquefolius*) has been listed as one of the top ten selling herbs.[2] Very recently, however, many researchers have expressed increasing concerns regarding the safety of some herbal products.[3,4] In experimental ulcer research, few studies have investigated the effect of ginseng on the stomach.[5] Since ginseng is widely consumed by the healthy and many different patient populations, it therefore looks pertinent to evaluate the effects of this herb on the gastric mucosa. In the present study we evaluated the effect of ginseng on gastric mucosal damage and on gastric acid secretion in the indomethacin, histamine and pyloric-ligation-induced gastric ulcers in the rat. And these effects were compared with the routes of administration (topical or systemic).

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MATERIALS AND METHODS

1. Animals

Female,[6-8] Sprague-Dawley strain rats, 180-200 g of body weight were used throughout the experiments. Animals were housed under standardized conditions for light and temperature and kept in cages with wide meshed floors to help prevent coprophagy. Animals were fasted for 24 h prior to the experiments, but allowed free access to tap water. Animals were randomly assigned to different experimental groups (n = 6-9 per group). All experiments were done on pylorus-ligated rats. Pylorus-ligation was done accroding to Shay *et al.* [9] Rats were lightly anaesthetised with ether and a silk ligature was tied around the pylorus, care being taken not to interfere with the blood supply to the stomach and duodenum.[9]

2. Experiments in conscious pylorus-ligated rats

(1) Gastric ulcer and secretory studies

Ginseng alone : Rats were lightly anaesthetized with ether and laparatomy was performed. The pylorus of each rat was then ligated and the abdominal wall closed in layers. In order to assess the effect of ginseng on the normal stomach, the drug was i.g. given in 12.5, 25 or 50 mg/ml (50, 100 or 200 mg/kg) (in 1 ml volume of saline). Control rats received i.g. saline (1 ml) instead. Three hours later, rats were killed by cervical dislocation, after being lightly anaesthetized with ether. The oesophagus was then ligated and the stomach excised. Gastric juice was carefully collected in graduated tubes after removal of the oesophageal ligature and stomachs were opened along the greater curvature and inspected for the presence of gastric mucosal damage.

(2) The indomethacin-induced gastric mucosal damage

Rats were lightly anaesthetized with ether and laparatomy was performed. The pylorus was ligated, then indomethacin (dissolved in 5% sodium bicarbonate) was given s.c. in a single dose of 20 mg/kg and 0.2 ml volume.[10] Immediately thereafter, rats received 1 ml of physiological saline i.g. (control group), or ginseng in different concentrations (12.5, 25, 50 mg/ml; 50, 100, 200 mg/kg) dissolved in 1 ml of saline. Three hours later, rats were killed by cervical dislocation, after being lightly anaesthetized with ether. The oesophagus was then ligated and the stomach excised. Gastric juice was carefully collected in graduated tubes after removal of the oesophageal ligature and stomachs were opened along the greater curvature and inspected for the presence of gastric mucosal damage.

(3) The histamine-induced gastric mucosal damage

A modification of the method used by Okabe *et al*[11] was employed to evoke ulcers. Rats were lightly anaesthetised with ether and laparatomy was performed. The pylorus of each rat was ligated and histamine dihydrochloride was given i.p. in a single dose of 150 mg/kg. Immediately thereafter, rats received 1 ml of physiological saline i.g. (control group), or ginseng in different concentrations (12.5, 25 mg/ml; 50, 100 mg/kg) in 1 ml of saline.

In order to examine the effect of i.p. ginseng on the histamine-induced ulcers, another group of rats (n=7) received orally 1 ml of saline and ginseng was administered i.p. in a dose of 150 mg/kg. Three hours later, rats were killed by cervical dislocation, after being lightly anaesthetised with ether. The oesophagus was then ligated, stomach excised. Gastric juice was carefully collected in graduated tubes after removal of the oesophageal ligature and stomachs were opened along the greater curvature and inspected for the presence of gastric mucosal damage.

(4) Pylous-ligation (Shay)-ulcer

The effect of i.p. administration of ginseng on gastric mucosal damage induced by ligating the pylorus in rats (Shay ulcer) was studied. Pylorus ligation was performed under light ether anaesthesia, according to Shay et al [9]. Saline (1 ml)(control group) or ginseng (200 mg/kg, i.p.) was given and rats were loaded with 5 ml saline to correct for possible dehydration. Rats were killed 18 h later, gastric juice was collected and stomachs opened along the greater curvature and inspected for the presence of gastric mucosal lesions.

(5) Assessment of gastric mucosal damage

The number and severity of mucosal lesions were noted. Lesions were scaled as follows: petechial lesions=1, lesions less than 1 mm=2, lesion between 1 and 2 mm=3, lesions between 2 and 4 mm=4, and lesions more than 4 mm=5.[12]

(6) Gastric secretory studies

Before cutting upon the stomachs, gastric juice was carefully collected in graduated tubes after removal of the oesophageal ligature. The volume of gastric secretion was noted and gastric acid output determined by automatic titration to pH 7.0 with 0.01 N NaOH and expressed as μmol/rat/3 h (means ± SEM).

(7) Determination of mucosal mucus content

Mucus secretion was determined by the method of Corne *et al.*[13] Briefly, the glandular portion of the stomach was excised, weighed and immersed for 2 h in 10 ml of 0.1 % w/v Alcian blue 8 GX dissolved in 0.16 mol/l

sucrose solution buffered to pH 5.8 with 0.05 mol/l sodium acetate and adjusted to pH 5.8 with HCl. The excess dye was removed by two successive rinses of 15 min each in 0.25 mol/l sucrose. The mucus-bound dye was extracted by immersing the gastric tissue in 0.5 mol/l $MgCl_2$ solution, which was intermittently shaken for 1 min at intervals of 30-min intervals for 2-hrs. The blue extract thus obtained was shaken with equal volume of diethylether for 10 min and the resulting emulsion was centrifuged at 3600 rpm for 10 min and the optical density of the aqueous phase was measured at 600 nm in a spectrophotometer. The quantity of Alcian blue extracted per gram of wet glandular tissue was then calculated from standard curves.

3. Experiments in anaesthetized rats

(1) Gastric secretory studies

The effect of i.p. administration of ginseng (50 or 200 mg/kg) on basal gastric acid secretion and on gastric acid secretion in the indomethacin (20 mg/kg, s.c.)-treated rats was studied in anaesthetized rats.

(2) Surgical procedure

A technique similar to that of Blair *et al*[14] was used. Fasted rats were anaesthetized with urethane 1.25 g/kg, given i.p., then the pylorus was ligated and a polyethylene cannula 2 mm in diameter was passed through the oesophagus. Prior to collecting gastric acid secretion, the stomach was flushed with saline to clear any food particles present. A period of at least 30-min was then allowed for stabilization of gastric acid secretion. The stomach was then flushed with 2 ml of saline through the oesophageal cannula, followed by air bolus every 15 min, 2 ml of gastric secretion were withdrawn every 15 min, H^+ output determined by titration to pH 7.0 with 0.01N NaOH and expressed as μmol/15 min.

(3) Study design

Basal gastric acid secretion : To examine the effect of i.p. administration of ginseng on basal gastric acid secretion, basal gastric acid secretion was collected over a 60 min period, then ginseng (50 or 200 mg/kg) was given i.p. and gastric acid secretion measured over another period of 60 min. Rats received s.c. saline (1 ml/h) to correct for possible dehydration during the experiment. Rats were then killed by cervical dislocation, their stomachs opened and inspected for the presence of gastric mucosal lesions if any. Results of gastric acid output were expressed as μmol/15 min or total gastric acid output was calculated for the hour before and following injection of ginseng and expressed as μmol/60-min.

Gastric acid secretion in indomethacin-treated rats: Other experiments were designed to examine the effect of i.p. ginseng administration on gastric acid response in indomethacin (20 mg/kg, s.c.)-treated rats.

Basal gastric acid secretion was collected over a 60 min period, then indomethacin (20 mg/kg, s.c.) (control group, n=6) was given and gastric acid secretion measured over a period of 90 min. Another group of rats (n=6) followed the same experimental design and time schedule as above, but received in addition to indomethacin (20 mg/kg, s.c.) and at the same time, i.p. ginseng in a dose of 200 mg/kg (in 1 ml volume). Rats received s.c. saline (1 ml/h) to correct for possible dehydration during the experiment. Rats were then killed by cervical dislocation, their stomachs opened and inspected for the presence of gastric mucosal lesions if any. Results of gastric acid output were expressed as μmol/15 min or total gastric acid output was calculated for the 60 min before or the 60 or 90 min following injection of indomethacin with or without ginseng administration and expressed as μmol/60 min or μmol/90 min.

Chemicals : Indomethacin (Kahira Pharm & Chem. Ind. Co. Egypt), Histamine dihydrochloride (BDH Chemicals, England), Alcian blue 8 GX (Sigma, USA), and urethane (Sigma, USA) were used. Ginseng (Korean ginseng) was obtained from The Egyptian International Pharmaceutical Industries Company (E.I.P.I.Co, 10th of Ramadan City, Egypt). Powder of ginseng was soked with water (1:25, w/w) in a glass flask for 3 hours, then the container was put on boiling water for 40 minutes. After filtration, the solid residue was subjected to the same process once again, then the two filtrates were mixed and freez dried. The dried extract equaled about to 20% (w/w) of the raw drug. The dried extract was dissolved in physiological saline before experiments to obtain the necessary concentrations.

Analysis of data : Results were expressed as means ± SEM. Data are analyzed using analysis of variance and Student's t test, P values < 0.05 were considered as significant. The Mann Whitney's test was applied for mathematical analysis of non-parametric results (ulcer severity). The number of rats used in experiments is presented in the text in parenthesis.

RESULTS

1. Experiments in conscious pylorus-ligated rats

(1) Gastric ulcer and secretory studies

Ginseng alone : Gastric acid secretion in the saline-treated control group was 186.7 ± 20.3 μmol/rat/3h. Intra-

gastrically given ginseng had no significant effect on gastric acid secretion in the 3-h conscious pylorus-ligated rats, which averaged 176±15.7, 182.5±22 and 192.3±18.2 μmol/rat/3h for ginseng in 12.5, 25 and 50 mg/ml, respectively. Ginseng, on the other hand, in 25 or 50 mg/ml increased mucosal mucus content relative to the saline-treated control group by 17.1 and 33.6%, the latter being of statistical significance ($p<0.05$). Mucosal mucus content in saline-treated control rats was 481±41.3 μg/gm. This was increased by ginseng in 25 and 50 mg/ml to 532.2±38 and 641±30 μg/gm, respectively

(2) Effect of ginseng on the indomethacin-induced gastric mucosal damage

In the indomethacin control group, the number and severity of gastric mucosal lesions evoked by s.c. indomethacin, were 5.3±0.8 and 8.0±1.2, respectively (incidence 100%). This was significantly reduced by ginseng co-administration in the concentration of 12.5 mg/ml (50 mg/kg), with the number and severity of lesions being 1±0.8 and 1.5±1.0 ($p<0.005$ and $p<0.001$, respectively vs control values), and only one third of animals exhibiting visible gastric mucosal injury (33.3%). The severity of mucosal damage was reduced by 81.3%, relative to the control group. The number of mucosal lesions was similarly reduced by 81.1%. Increasing the concentration of the drug did not effect more protection, although the incidence of animals showing gastric lesions was less than the control group. The number and severity of lesions were 2.5±1.3 and 3.1±1.5 in those treated with ginseng in 25 mg/ml and 2.0±0.6 and 2.7±0.8 in those given ginseng in 50 mg/ml, respectively (Fig. 1A).

The gastric acid secretory responses during this 3-h period did not show any significant difference between the different treatment groups. Gastric acid output in the indomethacin control group was 207±48.0 μmol/rat/3h compared with 205±47.2, 299±40.1 and 265.7±33.6 μmol/rat/3h for those treated with ginseng in 12.5, 25 and 50 mg/ml, respectively.

The administration of ginseng into the rat stomach in a

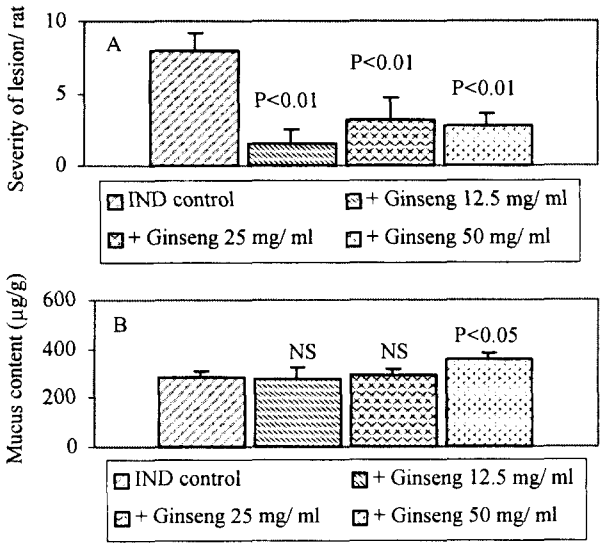

Fig. 1. The effect ginseng on the severity of gastric mucosal lesions (**A**) and on gastric mucosal mucus content (B) of the indomethacin-treated (20 mg/kg, s.c.) 3-h pylorus-ligated rat. Ginseng was i.g. given together indomethacin immediately after pylorus-ligation and animals killed 3-h later. Control rats received the vehicle. Results are means ± SEM. N = 6 per group.

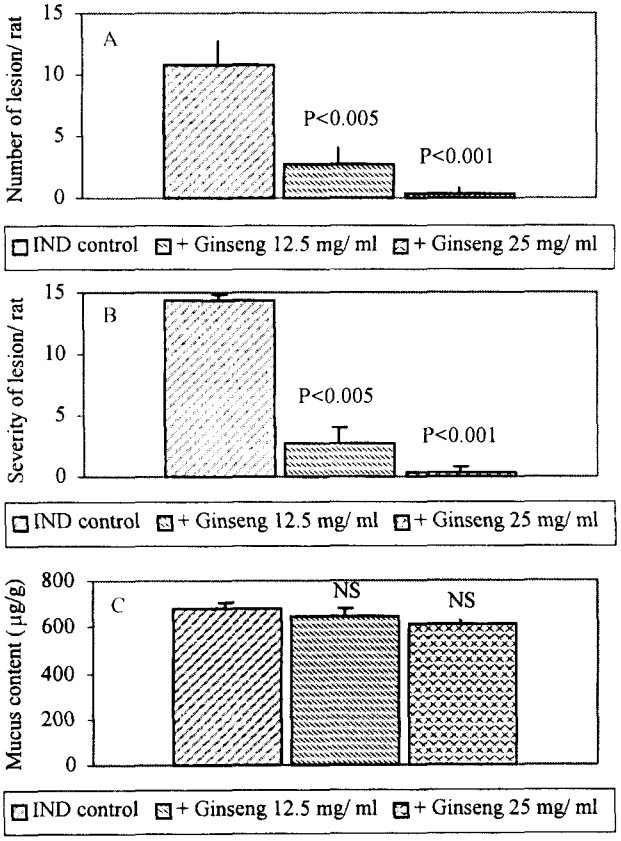

Fig. 2. The effect of ginseng on the number (**A**) and severity (**B**) of gastric mucosal lesions and (**C**) on mucosal mucus content in the histamine (150 mg/kg, i.p.)-treated 3-h pylorus-ligated rat. Ginseng given i.g. together histamine immediately after pylorus-ligation and animals killed 3-h later. Control rats received saline. Results are means ± SEM. N = 6-7 per group. NS = not significant relative to the histamine control group.

concentration of 50 mg/ml to the indomethacin-treated rats increased mucosal mucus content by 24.4% compared with the control group that received s.c. indomethacin and i.g. saline (354± 31 vs 285± 20 μg/gm, $p<0.05$) (Fig. 1B).

(3) Effect of ginseng on the histamine-induced gastric mucosal damage

In the histamine control group, the number and severity of gastric mucosal lesions evoked by the administration of histamine (150 mg/kg, i.p.) were 10.8± 1.9 and 14.4± 0.5, respectively (incidence 100%). This was significantly reduced by intragastric ginseng coadministration in the concentration of 12.5 mg/ml (50 mg/kg) or 25 mg/ml (100 mg/kg). The severity of mucosal damage was reduced by 74.1% ($p<0.005$) and 96.3% ($p<0.001$) by both doses respectively, relative to the control group that received i.g. saline. The number of mucosal lesions was similarly reduced (Fig. 2A & B, Fig. 3A & B). The gastric acid secretory response during 3-h period did not show any significant difference between them. Ginseng given i.p. in a dose of 150 mg/kg simultaneously with s.c. histamine failed to reduce the histamine-induced gastric injury, with the number and severity of lesions being 15.6± 4.6 and 18.4± 6.1, respectively. The i.g. administration of ginseng in a concentration of 12.5 or 25 mg/ml to the histamine-treated rats did not increase mucus secretion above that seen in rats that received s.c. histamine and i.g. saline (Fig. 2C).

(4) Effect of ginseng on the gastric mucosal damage induced by ligating the pylorus (Shay ulcer)

The number and severity of gastric mucosal lesions in the saline-treated control group were 11.0±5.1 and 13.2 ±4.8, respectively. These scores did not differ significantly in the ginseng-treated group with the number and severity of lesions being 5.7±1.5 and 10.2±2.8, respectively. There were no significant differences with regard to the volume (7.36±0.4 ml vs 5.5±0.6 ml) or to the H^+ output (318.4±39 μmol/rat vs 365.7±27.4 μmol/rat) in both the control and ginseng-treated groups, respectively.

2. Experiments in anesthetized rats

(1) Effect of ginseng on basal gastric acid secretion

Basal gastric acid secretion in anaesthetized rats was 25.7 ± 2.1 μmol/15 min and 102.7± 14.6 μmol/60 min (n=9). Ginseng given i.p. in 50 or 200 mg/kg had no significant effect for the next hour on gastric acid secretion, which averaged 26.6± 2.4 μmol/15 min for ginseng in 50 mg/kg and 23.2± 1.6 μmol/15 min for ginseng in 200 mg/kg, respectively. The total acid response obtained after ginseng in 50 or 200 mg/kg was 106± 14.5 μmol/60 min (n=9) and 92.6 ± 8.6 μmol/60 min (n=8), respectively (Fig. 4).

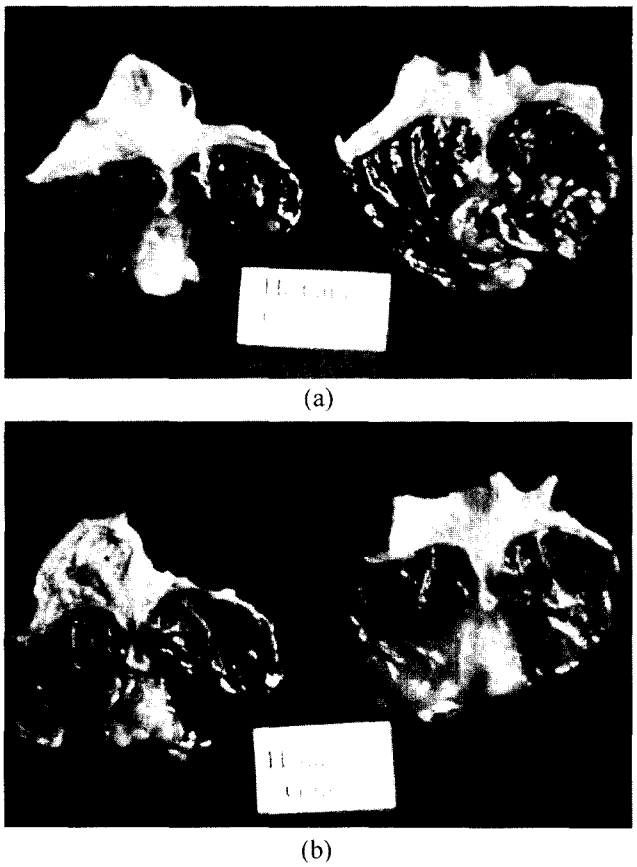

Fig. 3. **A & B.** Gross appearance of the rat stomach showing the protective effect of *Panax ginseng* (25 mg/ml) on the gastric mucosal damage evoked by i.p. histamine. Histamine dihydrochloride was given in a single dose of 150 mg/kg to pylorus-ligated rats and immediately thereafter, rats i.g. received 1 ml of physiological saline (control group) (A) or (B) ginseng in 25 mg/ml (100 mg/kg). Rats were killed 3 hours after ligation and drug administration.

(2) Gastric acid secretion in indomethacin-treated rats

Effect of indomethacin on gastric acid secretion: Basal gastric acid secretion was 31.9± 3.1 μmol/15 min and 127.5± 20.6 μmol/60 min (n=6). Indomethacin given s.c.with pylorus-ligation in a dose of 20 mg/kg had no significant effect for the next 60 or 90 min on gastric acid secretion, which averaged 30.2± 3.7 and 26.9± 2 μmol/15 min in both time periods, respectively. The total acid response obtained after indomethacin with pylorus-ligation was 108.8± 16.7 μmol/60 min and 161.2± 23.4. μmol/90 min (Fig. 5A, B).

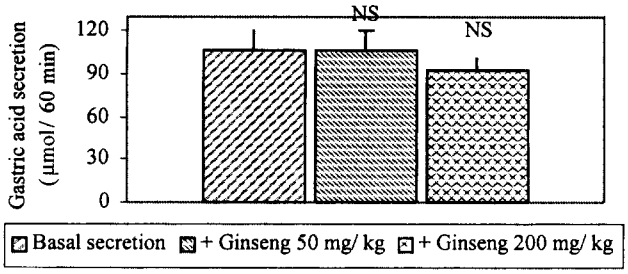

Fig. 4. The effect of i.p. ginseng (50 or 200 mg/kg) on basal gastric acid secretion in the urethane-anesthetized rat. Gastric acid secretion was measured by flushing of the gastric lumen with 5 ml saline every 15 min, through oesophageal cannula. Each column represents a mean ± SEM of 60 min collection of gastric acid secretion of 7 rats. NS=not significant compared with basal rate of secretion before ginseng administration.

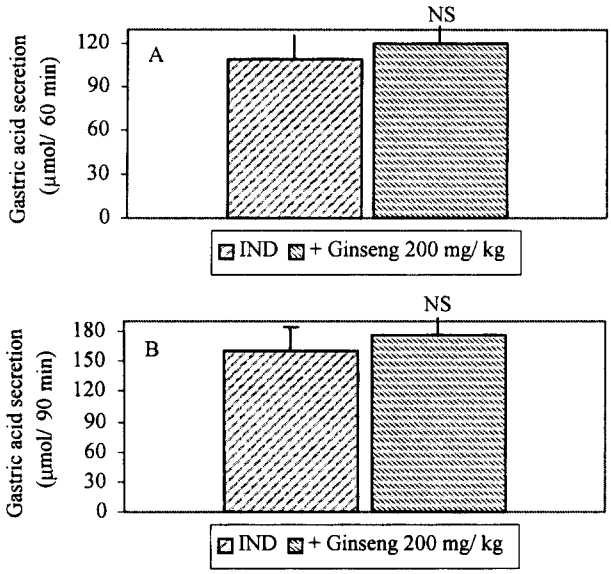

Fig. 5. The effect of i.p. ginseng (200 mg/kg) on gastric acid secretion in the indomethacin-treated urethane-anesthetized rat. Gastric acid secretion was measured by flushing of the gastric lumen with 5 ml saline every 15 min, through oesophageal cannula. Each column represents a mean ± SEM of 60 min (**A**) or 90 min (**B**) collection of gastric acid secretion of 6 rats. NS=not significant relative to the indomethacin-treated group.

Effect of ginseng on gastric acid secretion in the indomethacin-treated rats : Basal gastric acid secretion was 31.3± 3.3 μmol/15 min and 125± 13.6 μmol/60 min (n=6). Ginseng given in a dose of 200 mg/kg together with indomethacin did not modify the gastric acid secretory responses, which averaged 27.2± 2.8 and 29.4± 2.6 μmol/15 min in both time periods, respectively. The total acid response obtained after indomethacin with pylorus-ligation and ginseng was 120± 22.9 μmol/60 min and 176± 30 μmol/ 90 min. These responses were not significantly different from those values obtained after the administration of indomethacin with pylorus-ligation alone (Fig. 5A, B).

In anaesthetized rats, indomethacin with pylorus-ligation given for almost 2 hrs evoked a relatively minor degree of gastric injury with the number and severity of lesions being 2.0± 1.4 and 2.0± 1.4, respectively. This was not significantly different from the ginseng treated group, the number and severity of lesions being 1.5± 0.8 and 1.5± 0.8, respectively. The incidence of lesions was 50% in both groups.

DISCUSSION

The results of the present study provided evidence that i.g. but not i.p. administration of ginseng protects against the acute gastric mucosal lesions in two different models of experimental gastric ulceration, namely, the indomethacin and histamine-induced gastric mucosal ulceraction.

Indomethacin is a familiar non-sterodial anti-inflammatory drug, which is widely prescribed for the treatment of different rheumatic conditions. The drug is a potent ulcerogen and is well known for its ability to provoke gastric and intestinal mucosal damge in man and experimental animals. Thus the drug is widely used in experimental models of gastric mucosal damage to study the pathophysiologic mechanisms involving gastric mucoal injury and the effect of different compounds on it.[15-18] The indomethacin-induced gastric injury represents a vascular mediated one,[19] in which acid plays an important and facilitating role in intensifying the microvascular damage evoked by the drug. The intragastric administration of 0.15 N HCl to pylorus-ligated rats, although by itself caused a mild degree of mucosal injury in control rats, markedly potentiated the ulcerogenic effect of s.c. indomethacin.[20] Indomethacin is a potent inhibitor of prostaglandin synthesis.[21-23] The latter are powerful vasodilators in the gastric and other vascular beds [24,25] which has been shown to play an important role in modulating gastric mucosal defense mechanisms.[25] Indomethacin reduces gastric mucosal blood flow, as detected by various techniques for measuring gastric mucosal blood flow,[18,26,27] evokes vascular endothelial damage[19] and increases mucosal permeability to protons.[28] These, together with removal of prostaglandins-mediated protective mechanisms,[29] all contribute to the damaging effects evoked by indomethacin on the gastric

mucosa. Acid aggravates gastric injury by both a direct damaging effect on the vasulature[30] and by inducing a further reduction in gastric mucosal blood flow under such conditions.[31] It is not surprising therefore that prevention or protection against the indomethacin-induced gastric injury was obtained by vasodilator drugs such as prostaglandins,[32] capsaicin-type agents,[20] isoprenaline,[18] which prevent the early microvascular derangement evoked by the drug and maintain mucosal blood flow at appropriate levels, permitting thus a supply of oxygen and nutrients essential both for disposal of the hydrogen ions that might have permeated the gastric mucosa preventing the development of serious intramucosal acidosis and for the restitution process.[33] Prevention of the indomethacin-induced gastric injury was in addition accomplished by agents, which possess antisecretory activity such as cimetidine, atropine and omeprazole. These agents, while having no vasodilator effects and even were reported to reduce GMBF,[34,35] did alleviated injury by indomethacin or indomethacin plus acid.[20] The data in the present work indicate that the gastroprotective effect of i.g. ginseng against the indomethacin-induced gastric mucosal damage do not involve changes in gastric acid secretory responses. Ginseng did not modify gastric acid secretion in conscious pylorus-ligated and indomethacin-treated rats.

The present study has also provided evidence that ginseng given into the rat stomach is capable of protecting the rat gastric mucosa against the histamine-induced gastric mucoal damage. The histamine-evoked gastric mucosal injury has been markedly diminished in a concentration-dependent fashion by the co-administration of ginseng. In previous studies, histamine exacerbated lesions induced by intravenous aspirin[36] or s.c. indomethacin in the rat,[18,37] by virtue of its acid-stimulating action and the changes it evokes in vascular permeability.[38,39] The ulcers evoked thus involve increased acid secretion in addition to vascular changes. In this acid-dependent model of gastric injury, ginseng given into the rat stomach effected protection. Ginseng had no significant effect on gastric acid secretion in the histamine-treated rats. This suggests that the antiulcer effect of ginseng observed in this model of gastric mucosal damage is also independent of an effect on gastric acid secretion.

Experiments performed in anaesthetized rats further showed that ginseng given by i.p. route had no significant effect on basal gastric acid secretion or on gastric acid secretion in the indomethacin-treated rats. Findings in the present work thus indicated that neither orally given ginseng nor its intraperitoneal administration had any significant effect on gastric acid secretion in the conscious or in urethane-anaesthetized rats. It is clear therefore, that the protective effect of ginseng is independent of changes in gastric acid secretory responses.

Cytoprotection is the term introduced by Robert and coworkers[29] to denote the ability of prostaglandins given in non-antisecretory doses to prevent gastric mucosal damage, even mucosal necrosis evoked in the rat stomach by different necrotizing agents. By time, cytoprotection was found to be not confined to prostaglandins, but is also shared by other compounds such as sucralfate,[40] antacids,[41] vitamin A,[42] β-carotene,[42] by anticholinergic agents like atropine,[43] probanthine[30] and by H_2-receptor blockers like cimetidine[44] given in non-antisecretory doses. The essential point is that they all prevent gastric mucosal injury by mechanisms unrelated to changes in gastric acid secretory responses. In that sense, it can be concluded that ginseng exerts a cytoprotective effect in the rat stomach as shown in the present work.

Experimental evidence suggested that the gastric mucosa may be protected against the chemical-induced injury by maintain a pH gradient across an unstirred layer of mucus.[45] Gastric mucus exists as a water insoluble gel adherent to the mucosal surface and also as a viscous form that mixes with luminal juice. It is the adherent mucus that plays an important role in protecting the gastric mucosa by creating a stable unstirred layer at the mucosal surface. This acts as a mixing barrier, restricting the movement of the newly secreted bicarbonates and preventing it from being overwhelmed by the vast excess of acid in the lumen. It also prevents pepsin in the lumen from digesting the underlying epithelium.[46] Changes in the amount or quality of gastric mucus has been implicated in both the ability of some drugs to evoke gastric mucosal injury and in the protection provided by other drugs.[47-50] Thus, aspirin and indomethacin decrease gastric mucus gel, while topical 16, 16-dimethyl PGE_2 resulted in a dose-dependent increase in rat gastric mucus thickness measured up to 2 hours after administration *in vivo*.[47-50] In the present study, determination of the mucus content of the gastric mucosa, has shown that orally given ginseng in 100 mg/ml increases mucosal mucus content. In the present work, ginseng given p.o. at the concentration of 100 mg/ml increased gastric mucus output, both in the control and in the indomethacin-treated rats. Protection by topically applied ginseng against the indomethacin-evoked gastric mucosal injury, however, did not correlate with the effect

of the drug on gastric mucus. Ginseng at 25 mg/ml concentration had marked protective effect, despite no measurable influence on the amount of gastric mucus. In addition, the concentrations at which orally given ginseng prevented the histamine-mediated gastric mucosal damage did not cause a measurable increase in mucus secretion. Despite this it is still possible that changes in the quality or composition of gastric mucus plays a role in the gastroprotective effect of orally administered ginseng. These might precede the qualitative effect of the herb on gastric mucus. Work by several investigators has shown that the lipid component[51,52] enhance the ability of the mucus to retard hydrogen ions being diffused back through the mucus-bicarbonate layer overlying the gastric epithelial cells and thus protecting the gastric mucosa against the injurious effects of acid and other injurious agents in the gastric lumen.[46]

Panax ginseng root have been thoroughly studied by modern methods of analysis, and of the many compounds isolated, the medicinal activity appears to reside in a number of saponins termed ginsenosides by Japanese workers and panaxosides by Russian workers. However, the two series of compounds do not appear to be absolutely identical with respect to the sugar moieties. Ginseng root contains a mixture of both steroidal and pentacyclic triterpenoid saponins. Other compounds of the root having therapeutic activity are high-molecular-weight polysaccharides (glycans); for *P. ginseng* these are known as panaxans.[1] In the rat stomach, oral administration of a polysaccharide fraction, GL-4, from the leaves of *Panax ginseng*, has been reported to prevent ethanol and HCl-induced gastric injury.[53] Work by Sun *et al*[53] thus suggested that the polysaccharide content might have a role in the antiulcer effect of gensing.

In summary the present study has provided evidence for a cytoprotective action of orally administered ginseng on the indomethacin or histamine-induced gastric mucosal injury in the rat. The results strongly suggest a topical rather than a systemic action for ginseng on the gastric mucosa. We conclude that intragastrically administered ginseng possesses beneficial effect on the gastric mucosa. The mechanisms underlying the anti-ulcer effects of ginseng, however, needs to be elucidated.

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