Anti-ulcer Effect of Tea Catechin in Rats

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Oral administration of tea catechin dose-dependently prevented absolute ethanol-induced (50, 100, 200 mg/kg) or restraint plus water immersion stress-induced acute gastric mucosal injury (300, 400 mg/kg) in rats. When the effect of test compound was evaluated on the 15th day after acetic acid injection to rats, repeated oral administration of tea catechin (25, 50, 100 mg/kg twice daily) dose-dependently accelerated the healing of acetic acid-induced chronic gastric ulcers. Tea catechin (10^{-5}–10^{-4} g/100 ml) concentration-dependently scavenged superoxide anions in vitro. Tea catechin (100, 200 mg/kg orally) markedly inhibited the increase in thiobarbituric acid-reactive substances in the injured mucosa of rats treated with 50% ethanol. Tea catechin (50, 100 mg/kg twice orally, daily) markedly inhibited the increase in content of thiobarbituric acid-reactive substances in the ulcerated region of acetic acid-induced gastric ulcers on the 7th and 15th days. In addition, at 50, 100 and 200 mg/kg orally, it dose-dependently prevented the decrease in gastric mucosal hexosamine content induced by absolute ethanol, although it failed to inhibit the basal gastric acid secretion. These results suggest that tea catechin may primarily protect gastric mucosa from acute gastric mucosal injury and promote the healing of chronic gastric ulcers by its antioxidant activity and gastric mucus-increasing actions.

Key words tea catechin; anti-ulcer action; free radical; gastric mucus

Oxygen-derived free radicals have recently been postulated to play an important role in the pathogenesis of acute gastric mucosal injury induced by ischemia-reperfusion, stress, ethanol and anti-inflammatory drugs in rats. Furthermore, it has been suggested that free radicals generated by neutrophils may be important factors in delaying the healing of acetic acid-induced chronic gastric ulcers in these animals. It has been reported that polaprezinc, an anti-ulcer agent, probucol, a lipid-lowering agent, quercetin, a flavonoid, α-tocopherol, an antioxidant vitamin, nifedipine, Ca^{2+}-channel blocker, and tetracycline, an antibiotic, possess antioxidant actions and are effective on experimental acute and chronic gastric ulcers in rats.

Catechins are a main constituent of green tea and belong to polyphenols chemically. Green tea catechins consist primarily of four components: (−)-epicatechin (EC), (−)-epigallocatechin gallate (EGCg), (−)-epigallocatechin (EGC) and (−)-epicatechin gallate (EGCg). These catechins possess potent antioxidant activity. Therefore, catechins as well as the antioxidants mentioned above are expected to have the anti-ulcer action.

The present study was designed to clarify the effects of tea catechin (EGCg 50%, ECg 13%, 92% as polyphenols) in comparison with omeprazole or sucralfate on ethanol- or restraint plus water immersion stress-induced acute gastric mucosal injury and acetic acid-induced chronic gastric ulcers in rats. In a second study, in order to clarify whether or not it exerts an anti-ulcer action by means of its antioxidant activity, we examined the superoxide anion (O_2^-)-scavenging activity of tea catechin in vitro. We also examined the effect of this component on the content of thiobarbituric acid-reactive substances, an index of lipid peroxidation, in the injured or ulcerated mucosa in acute (ethanol) and chronic (acetic acid)-induced experimental models. As another mechanism for the anti-ulcer action of tea catechin, we examined the effects of this component on basal gastric acid secretion in normal rats and on the content of gastric mucosal hexosamine, an index of gastric mucus, after intragastric ethanol instillation in rats.

MATERIALS AND METHODS

Animals Male Sprague-Dawley strain SPF rats (Nippon SLC, Shizuoka) weighing 180–200 g were used in the experiment. The animals were housed in an air-conditioned room at 23±1 °C. All experimental procedures described were approved by the Experimental Animal Research Committee of Meijo University, Faculty of Pharmacy.

Materials The material used was tea catechin [EGCg 50%, ECg 13%, 92% as polyphenols (Teaflan 90S®)]. Tea catechin was supplied by Central Research Institute, ITO EN, Ltd. (Shizuoka), Omeprazole (Wako Pure Chemical Ind. Co., Ltd., Osaka) and sucralfate (Ulcemin®, Chugai Pharmaceutical Co., Ltd., Tokyo) were used as comparative anti-ulcer drugs. These test compounds were suspended in 1% gum arabic.

Measurement of Absolute Ethanol-Induced Gastric Mucosal Injury After rats were fasted for 24 h, absolute ethanol was administered in a volume of 1 ml per 100 g of body weight into the stomach of the animals. Each test compound was given orally in a volume of 1 ml per 100 g of body weight at 1 h prior to ethanol administration. As the control, vehicle (1% gum arabic) was given instead of each test compound. One hour after treatment with the necrotizing agent, the animals were killed under ether anesthesia, and then the stomach was removed and opened along the greater curvature. In order to evaluate the degree of gastric mucosal lesions, the length (mm) and width (mm) of hemorrhagic erosions in the gastric mucosa were measured under a stereoscopic microscope, and the area of each erosion (mm^2) was calculated. The total area of each erosion is expressed in terms of a lesion index (mm^2).

Measurement of Restraint Plus Water Immersion Stress-Induced Gastric Mucosal Injury After rats were fasted for 24 h, test compound or vehicle (1% gum arabic) as control was given orally in a volume of 1 ml per 100 g of...
body weight. One hour after the administration of test compound or the vehicle, these animals were restrained in a stress cage and immersed in 23 °C water. Six hours after the stress load, the animals were killed under ether anesthesia, and then the stomach was removed and opened along the greater curvature. The degree of gastric mucosal injury was expressed as the mucosal lesion index (mm²) as mentioned in measurement of ethanol-induced gastric mucosal injury.

**Measurement of Acetic Acid-Induced Gastric Ulcers**

The rats were allowed daily access to commercial food pellets between 10:00—11:00 a.m. and 6:00—7:00 p.m. throughout the experimental period from 3 d prior to the ulcer induction; however, tap water was always supplied ad libitum. Gastric ulcers were induced in these rats by the injection of 20% (v/v) acetic acid in a volume of 0.05 ml into the submucosal layer at the junction of the fundus and antrum in accordance with the method described by Takagi et al. Each test compound was given orally, daily (tea catechin and sucralfate: 9:30 a.m. and 5:30 p.m. twice; omeprazole: 11:30 a.m. once) for 14 consecutive days from the day (the 1st day) after acetic acid injection. Control animals were given the vehicle instead of a test compound. On the 15th day, the animals were killed by rapid decapitation. The stomachs were removed, filled with 5 ml of 10% formalin and allowed to stand for 5 min, then were cut open along the greater curvature. The longitudinal and abscissal lengths of the upper-opened part of the ulcer were measured with a micrometer which was set on a stereoscopic microscope, and the product of both lengths (mm²) was expressed in terms of the ulcer index. After the ulcer size was measured, the stomach tissue was again immersed in 10% formalin for 24 h. The formalin-fixed tissue was then cut so that a little of the normal tissue surrounding the ulcer remained. Thereafter, the central part of ulcer was cut vertically against the serosa along the long diameter. These tissues, cut in half, were embedded in paraffin and cut into 2- to 3-μm thick sections, which were stained with hematoxylin and eosin. Histological measurements were performed under light micrography of the stained preparations as shown in Fig. 2.

**Measurement of O₂⁻-Scavenging Activities in Vitro**

In order to examine the O₂⁻-scavenging activities of a test compound, each test compound was suspended in distilled water.
at concentrations of $10^{-6}$—$10^{-1}$ g/100 ml. Briefly, hydroxyl-o-sulfonic acid, xanthine oxidase, hypoxanthine, EDTA and the diluted samples were incubated at pH 8.2, 37°C for 30 min. After incubation, N-(1-naphthyl)ethylenediamine dihydrochloride was added to the incubated mixture. Absorption of the solution developed a pink color at 550 nm and was recorded on a spectrophotometer (Shimadzu UV-160, Tokyo). The $O_2^-$-scavenging activities of diluted suspensions of test compound were determined by the nitrite method of Oyanagi,15 and were calculated by the following formula: 

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(\text{OD of the diluted sample/OD of Blank}) \times 100
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**Measurement of 50% Ethanol-Induced Gastric Mucosal Injury and the Content of Thiobarbituric Acid-Reactive Substances in the Injured Mucosa** After a 24-h fast, 50% ethanol was instilled in a volume of 1 ml per 100 g of body weight to the stomach of rats. Test compound or vehicle was given orally in a volume of 1 ml per 100 g of body weight 1 h prior to ethanol treatment. One hour after ethanol administration, the effects of test compounds on gastric mucosal injury were evaluated as mentioned above. After the lesion index was measured, the mucosa of the glandular part of the stomach was removed by scraping and the content of thiobarbituric acid-reactive substances in the mucosa was determined by the method of Ohkawa et al.16

**Measurement of Acetic Acid-Induced Gastric Ulcers and the Content of Thiobarbituric Acid-Reactive Substances in the Ulcerated Region** Gastric ulcers were induced by acetic acid injection as mentioned above. Test compound or vehicle was given orally twice daily from the day after acetic acid injection. On the 7th and 15th days, the animals were killed with an overdose of ether, and the stomach was cut open along the greater curvature. Immediately after the ulcer size was measured for the ulcer index, the mucosa was collected from the ulcerated and unulcerated regions, and the content of thiobarbituric acid-reactive substances in these regions was determined.

**Measurement of Basal Gastric Acid Secretion** Rats were deprived of food but allowed free access to water for 24 h. After fasting, test compound was given orally. Control animals were orally given the vehicle only instead of test compound. One hour after this administration, the pylorus of each rat was ligated under ether anesthesia, the gastric contents were collected for 5 h thereafter. The volume of gastric juice was measured and the acidity was determined with an automatic titrator (ABT-104, Tohdenpa, Tokyo) and total acid output during a 1-h period was calculated.

**Measurement of Absolute Ethanol-Induced Gastric Mucosal Injury and Mucosal Hexosamine Content in the Glandular Stomach** After rats were fasted for 24 h, absolute ethanol was administered in a volume of 1 ml per 100 g of body weight into the stomach. Test compound was given orally in a volume of 1 ml per 100 g of body weight 1 h prior to ethanol administration. Control animals were orally given the vehicle instead of test compound. Three h after ethanol treatment, the animals were killed with an overdose of ether, and the stomach was removed by scraping, mixed, ground and defatted with 1:1 ether-acetone. The defatted mucosa was then dried under reduced pressure to a constant weight in a desiccator containing P$_2$O$_5$. The hexosamine content in the dry-defatted mucosa was determined in accordance with Blix's method17 after hydrolyzing 3N HCl at 100°C for 15 h. The hexosamine content was expressed as milligram per gram of dry-defatted tissue.

**Statistical Analysis** The results obtained are expressed as the mean±S.E.M. The data were analyzed by one-way analysis of variance, and the statistical significance among the groups was determined by Duncan’s multiple-range test.

**RESULTS**

**Effects of Tea Catechin, Omeprazole and Sucralfate on Absolute Ethanol-Induced Gastric Mucosal Injury** The effects of test compounds on absolute ethanol-induced gastric mucosal injury were evaluated 1 h after intragastric instillation of ethanol. Intragastric instillation of absolute ethanol to control rats produced large hemorrhagic injury in the glandular stomach. Tea catechin at oral doses of 50, 100 and 200 mg/kg prevented the gastric mucosal injury by 49, 70 and 100%, respectively (Fig. 3). Omeprazole at an oral dose of 50 mg/kg and sucralfate in an oral dose of 500 mg/kg, both comparative drugs, completely prevented the injury by 92 and 99%, respectively.

**Effects of Tea Catechin, Omeprazole and Sucralfate on Restraint Plus Water Immersion Stress-Induced Gastric Mucosal Injury** The restraint plus water immersion stress load for 4 h produced hemorrhagic erosion in the glandular stomach (Fig. 4). Tea catechin at oral doses of 300 and 400 mg/kg markedly prevented the stress-induced gastric mucosal injury by 80 and 93%, respectively. Omeprazole (50 mg/kg orally) also markedly prevented the stress-induced mucosal injury by 87%. However, sucralfate (500 mg/kg orally) was ineffective on such injury.

![Fig. 3. Effects of Tea Catechin, Omeprazole and Sucralfate on Absolute Ethanol-Induced Gastric Mucosal Injury in Rats](image1)

![Fig. 4. Effects of Tea Catechin, Omeprazole and Sucralfate on Restraint Plus Water-Immersion Stress-Induced Gastric Mucosal Injury in Rats](image2)
Effects of Tea Catechin, Omeprazole and Sucralfate on the Healing of Acetic Acid-Induced Gastric Ulcers

Repeated oral administration of tea catechin for 14 consecutive days accelerated the healing of gastric ulcers in a dose-dependent manner (Fig. 5). Namely, tea catechin given at 25, 50 and 100 mg/kg twice daily decreased the ulcer index by 17, 41 and 66%, respectively, and the defective area in the ulcerated region by 19, 46 and 63%, respectively. In addition, tea catechin at doses of 25, 50 and 100 mg/kg twice daily increased the index for the decrease in the exposed ulcer base by 18, 38 and 67%, respectively, and the index for mucosal regeneration by 23, 44 and 99%. Omeprazole (50 mg/kg twice daily orally) and sucralfate (500 mg/kg twice daily orally) decreased the ulcer index by 77 and 59%, respectively, and the defective area in the ulcerated region by 52 and 78%, respectively. In addition, omeprazole (50 mg/kg twice daily orally) and sucralfate (500 mg/kg twice daily orally) decreased the ulcer index by 77 and 59%, respectively, and the defective area in the ulcerated region by 52 and 78%, respectively. In addition, omeprazole (50 mg/kg twice daily orally) and sucralfate (500 mg/kg twice daily orally) increased the index for the decrease in the exposed ulcer base by 51 and 70%, respectively, and the index for mucosal regeneration by 91 and 55%.

Effects of Tea Catechin, Omeprazole and Sucralfate on the Healing of Acetic Acid-Induced Gastric Ulcers in Rats

Tea catechin or sucralfate was given orally, twice daily for 14 consecutive days, beginning the first day after acetic acid injection. Omeprazole was given orally, once daily for the same period. The effects of both agents were evaluated on the 15th day. Each column denotes the mean ± S.E.M. for 8 rats. Significantly different from respective control, *p < 0.05, **p < 0.01.

Effects of Tea Catechin and Omeprazole on 50% Ethanol-Induced Gastric Mucosal Injury and the Content of Thiobarbituric Acid-Reactive Substances in the Injured Mucosa

When the effects of test compounds on 50% ethanol-induced gastric mucosal injury were evaluated 1 h after ethanol treatment, tea catechin at oral doses of 100 and 200 mg/kg markedly prevented the mucosal injury 70 and 100%, respectively (Fig. 7, left). The content of thiobarbituric acid-reactive substances in the injured mucosa of ethanol-treated control rats was 3.3 times higher than in the mucosa of normal rats (Fig. 7, right). Tea catechin at oral doses of 100 and 200 mg/kg inhibited the increase in thiobarbituric acid-reactive substances in the injured mucosa by 60 and 94%, respectively. Omeprazole (50 mg/kg orally) markedly prevented the mucosal injury by 79% but failed to inhibit the increase in content of thiobarbituric acid-reactive substances in the injured mucosa.

Effects of Tea Catechin and Omeprazole on the Healing and Content of Thiobarbituric Acid-Reactive Substances in the Ulcerated Region of Acetic Acid-Induced Gastric Ulcers

Effects of Tea Catechin and Omeprazole on O$_2^*$-Scavenging Activities in Vitro

Tea catechin at $10^{-5}$—$10^{-1}$ g/100 ml inhibited O$_2^*$-scavenging activity in a concentration-dependent manner (Fig. 6). However, omeprazole ($10^{-6}$—$10^{-1}$ g/100 ml) and sucralfate ($10^{-6}$—$10^{-1}$ g/100 ml) failed to scavenge O$_2^*$.
Gastric Ulcers

The effects of test compounds on the healing and content of thiobarbituric acid-reactive substances in the ulcerated region of acetic acid-induced gastric ulcers were evaluated on the 7th and 15th days after acetic acid injection (Fig. 8). The content of these substances in the ulcerated region of the control rats was 8.3 and 2.7 times higher, respectively, than that in the respective unulcerated region on these days. Tea catechin (50, 100 mg/kg twice daily, orally) markedly inhibited the increase in thiobarbituric acid-reactive substances in the respective ulcerated region on the 7th and 15th days (Fig. 8, right). In addition, tea catechin (at both doses) significantly decreased the ulcer index on the 15th day, although it was ineffective on the 7th day (Fig. 8, left). On the other hand, omeprazole (50 mg/kg twice daily, orally) significantly decreased the ulcer index on the 15th day; however, this agent failed to inhibit the increase in content of thiobarbituric acid-reactive substances on both days.

Effects of Tea Catechin and Omeprazole on Basal Gastric Acid Secretion

A single oral administration of omeprazole (50 mg/kg) markedly decreased the volume of gastric juice by 42% and total acid output by 100% (Fig. 9). However, tea catechin at oral doses of 100 and 200 mg/kg was ineffective in decreasing either the volume or total acid output.

Effects of Tea Catechin and Sucralfate on Absolute Ethanol-Induced Gastric Mucosal Injury and Mucosal Hexosamine Content in the Injured Mucosa

The effects of test compounds on absolute ethanol-induced gastric mucosal injury and gastric mucosal hexosamine content were evaluated 3 h after intragastric instillation of ethanol. Tea catechin at oral doses of 50, 100 and 200 mg/kg dose-dependently prevented mucosal injury, although at 50 mg/kg it showed no significant effect (Fig. 10), while omeprazole (50 mg/kg orally) and sucralfate (500 mg/kg orally) markedly prevented mucosal injury. The gastric mucosal hexosamine content in ethanol-treated control rats was 52% lower than that in ethanol-untreated normal rats (Fig. 10). Tea catechin at oral doses of 50, 100 and 200 mg/kg dose-dependently in-

Fig. 7. Effects of Tea Catechin and Omeprazole on 50% Ethanol-Induced Gastric Mucosal Injury and the Content of Thiobarbituric Acid-Reactive Substances in the Injured Mucosa in Rats

Tea catechin or omeprazole was given orally 1 h prior to intragastric instillation of 50% ethanol. One hour after the ethanol instillation, the effects of both agents on gastric mucosal injury were evaluated and the content of thiobarbituric acid-reactive substances in the injured mucosa was then determined. Each column denotes the mean±S.E.M. for 6 rats. Significantly different from respective control, **p<0.01.

Fig. 8. Effects of Tea Catechin and Omeprazole on Ulcer Index and the Content of Thiobarbituric Acid-Reactive Substances in the Ulcerated Region of Acetic Acid-Induced Gastric Ulcers in Rats

Tea catechin was given twice daily for 6 or 14 consecutive days, beginning the first day after acetic acid injection; omeprazole was given orally, once daily for the same period. On the 7th and 15th days, the effects of both agents on the ulcer index were evaluated and the content of thiobarbituric acid-reactive substances in the ulcerated region was then determined. Each column denotes the mean±S.E.M. for 6 rats. Significantly different from respective control, *p<0.05, **p<0.01.
creased the gastric hexosamine content by 12% (not significantly), 44 and 73%, respectively, as compared with ethanol-treated control. Sucralfate (500 mg/kg orally) slightly but significantly increased the hexosamine content by 36%. However, omeprazole (50 mg/kg orally) showed no apparent increasing effect on this content.

**DISCUSSION**

Green tea has been widely consumed in Japan and China to maintain health and prevent disease. Catechins, its major component, have been demonstrated to have anticarcinogenic activities. Horie et al. reported a synergistic effect of green tea catechins on cell growth and apoptosis induction in gastric carcinoma cells. They suggest that the synergism may involve the extracellular production of reactive oxygen species. On the other hand, the undesirable action of catechins related to potential carcinogenicity has been reported in that they induce oxidative damage to cellular and isolated DNA through the generation of reactive oxygen species.

As mentioned in the Introduction, catechins possess potent antioxidant activity and are expected to possess anti- ulcer action by their free-radical-scavenging action. In the present study, we investigated whether or not tea catechin (EGCg 50%, ECg 13%, 92% polyphenols) has the anti-ulcer action using acute gastric mucosal injury and chronic gastric ulcer models in rats. The present results demonstrate that tea catechin protects gastric mucosa from acute gastric mucosal injury and promotes the healing of chronic ulcers probably by its potent antioxidant and gastric mucus-increasing actions.

In the present experiment, in order to determine oral doses of tea catechin to rats, we referred to a few references on tea catechins. Ryle et al. administered (−) epicatechin or (+) catechin to rats at 125 mg/kg i.p. twice daily for 21 d after alloxan administration to clarify the curative effects of both compounds against alloxan-induced diabetes. Sato et al. used the same tea catechin (EGCg 50%, ECg 13%, 92% as polyphenols, Teaflan 90S) in their experiments. They gave a 1% catechin solution in distilled water as drinking water to rats for 2 weeks before restraint plus immersion stress. If a rat weighing 200 g in their experiment drank 25 ml of 1% tea catechin solution per 24 h, the catechin dosage was 1000 mg/kg/d. In the present experiment, we gave tea catechin to rats at oral doses of 50—100, 200—400 mg/kg, respectively, in absolute ethanol- and restraint plus water immersion stress-induced acute gastric injury. We also administered it orally, twice daily for 2 weeks at doses of 25—100 mg/kg for acetic acid-induced chronic gastric ulcers.

In the first experiment, tea catechin (50, 100, 200 mg/kg orally) markedly prevented the induction of acute gastric mucosal injury induced by absolute ethanol. It has been demonstrated that oxygen-derived free radicals are involved in the pathogenesis of ethanol-induced gastric mucosal injury. Xanthine oxidase and neutrophils have been considered to be main sources of free radicals generated in such injury. As mentioned in the Introduction, we have earlier demonstrated that compounds such as probucol, quercetin, α-tocopherol, nifedipine and tetracycline with antioxidant activity possess...
gastric cytoprotective action against the HCl plus ethanol-induced acute gastric mucosal lesions in rats.\textsuperscript{6—9} In the present \textit{in vitro} experiment, tea catechin (10\textsuperscript{-5}—10\textsuperscript{-1} g/100 ml) concentration-dependently inhibited O\textsubscript{2}\textsuperscript{-}-scavenging activity, although omeprazole and sucralfate, comparative drugs, failed to scavenge this free radical. In addition, tea catechin (100, 200 mg/kg orally) markedly inhibited 50\% ethanol-induced gastric mucosal injury and the increase in thiobarbituric acid-reactive substances in the injured mucosa. These results suggest that the protective action of tea catechin against this injury may be due in part to the scavenging of free radicals produced in the injured mucosa. In this experiment, we used 50\% ethanol instead of absolute ethanol. When absolute ethanol was orally given to rats, severe, large hemorrhagic injury was produced in the glandular stomach and the red color of blood disturbed the determination of thiobarbituric acid-reactive substances. Therefore, we used 50\% ethanol which produced less bleeding.

Ethanol-induced gastric mucosal injury has also been indicated to be due to impairments in defensive factors such as mucus\textsuperscript{29} and mucosal microcirculation\textsuperscript{39} in addition to free radicals as mentioned above. In the present experiment, tea catechin (50, 100, 200 mg/kg, orally) dose-dependently prevented a marked decrease in gastric mucosal hexosamine content, an index of gastric mucus, produced by intragastric ethanol instillation. Therefore, tea catechin may also protect the mucosa against ethanol-induced damage by increasing mucosal defensive factors such as gastric mucus. In the present experiment, omeprazole (50 mg/kg, orally) and sucralfate (500 mg/kg, orally), comparative anti-ulcer drugs, also markedly protected rat gastric mucosa against absolute ethanol-induced damage. Omeprazole, unlike tea catechin (10\textsuperscript{-5}—10\textsuperscript{-1} g/100 ml), failed to scavenge O\textsubscript{2}\textsuperscript{-} \textit{in vitro}. In addition, omeprazole was ineffective in inhibiting the increase in the content of thiobarbituric acid-reactive substances in the injured mucosa of rats treated with 50\% ethanol. In our previous study, omeprazole (50 mg/kg, orally) markedly prevented HCl plus ethanol (150 m\textsuperscript{m} HCl in 60\% ethanol)-induced gastric mucosal injury in rats.\textsuperscript{8} This result indicates that omeprazole has gastric cytoprotective action, independent of its potent antisecretory activity. Chandranath et al.\textsuperscript{31} have reported that omeprazole may protect gastric mucosa in rats from acidified ethanol (150 m\textsuperscript{m} HCl in 60\% ethanol)-induced gastric mucosal injury by the increase in endogenous prostaglandins (PGs). On the other hand, Konturek et al.\textsuperscript{32} have reported that gastric cytoprotective action of omeprazole is not related to the biosynthesis of the mucosal PGs. Therefore, the exact mechanisms for the cytoprotective action of this agent are unclear. Sucrelrate also failed to scavenge O\textsubscript{2}\textsuperscript{-} \textit{in vitro}. Sucralfate has been demonstrated to have anti-ulcer action mainly by an adhesive action on gastric epithelial cells and H\textsuperscript{+}-neutralizing action.\textsuperscript{33} In the present experiment, when sucrelrate was given orally to fasted rats, the paste-like material of this agent was observed on gastric mucosa. Therefore, sucrelrate may locally exert the cytoprotective action mainly by coating the gastric mucosa. Sucralfate (500 mg/kg, orally) slightly but significantly prevented the decrease in hexosamine content in the injured mucosa, indicating that the gastric mucus-increasing action of sucralfate may also, at least in part, be related to the cytoprotective action of this agent.

In the second experiment, tea catechin (300, 400 mg/kg orally) markedly prevented the induction of acute gastric mucosal injury induced by restraint plus water immersion. The major factors implicated in the development of stress ulcers have been thought to be an increase in gastric acid secretion and a decrease in mucosal protection due to the reduction in mucus secretion, blood flow and PG biosynthesis. Furthermore, it has been indicated that oxygen-derived free radicals generated by ischemia-reperfusion play an important role in the pathogenesis of stress-induced gastric mucosal injury.\textsuperscript{34} It has been shown that proton pump inhibitors such as omeprazole prevent stress-induced gastric mucosal injury by strongly inhibiting gastric acid secretion.\textsuperscript{34} In the present experiment, tea catechin (100, 200 mg/kg orally) was ineffective in decreasing basal gastric acid secretion in pylorus-ligated rats. Therefore, the protective action of tea catechin on the stress-induced gastric mucosal injury may be mainly due to free radical-scavenging and gastric mucus-increasing actions.

In the third experiment, tea catechin (50, 100 mg/kg×2/d orally) markedly promoted the healing of chronic gastric ulcers induced by acetic acid. As mentioned in the Introduction, it has been demonstrated that oxygen-derived free radicals may play an important role in delaying the healing of acetic acid-induced chronic gastric ulcers in rats.\textsuperscript{35} In the present experiment, we evaluated the effects of daily repeated administration of tea catechin on gastric ulcer healing and the content of thiobarbituric acid-reactive substances in the ulcerated region on the 10th and 15th days after acetic acid injection to animals. Catechin (50, 100 mg/kg×2/d orally) had already inhibited increase in the content of thiobarbituric acid-reactive substances in the ulcerated region on the 10th day before the ulcer-healing effect of this compound was recognized. On the other hand, omeprazole, which is without antioxidant action, was ineffective in inhibiting the increase in lipid peroxidation. This result indicates that the ulcer healing-promoting action of tea catechin is, at least in part, due to the potent antioxidant action of this compound.

REFERENCES