

## Antigastritic and Antiulcerative Activities of Water Extracts Derived from *Scutellaria baicalensis*

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(Received 7 September, 2006; Accepted 21 September, 2006)

**Abstract** – Gastritis and gastric ulcer were known to be induced by gastric acid, stress, ethanol, *Helicobacter pylori* and free radical, etc. This study was performed for the development of a new drug or nutraceutical from medicinal plants or natural products with anti-gastritis, anti-ulcerative and gastroprotective activities. The water extract of *Scutellaria baicalensis* was exhibited potent inhibition in HCl-ethanol-induced gastric lesion, acetic acid-induced and Shay ulcers, indicating the effects on gastric lesion and ulcer in rats. The water extract of *Scutellaria baicalensis* significantly inhibited HCl-ethanol-induced gastric lesions at the oral dose of 300, 500 mg/kg. In pylorus ligated rats, the treatments of the water extract from *Scutellaria baicalensis* showed decrease in the volume of gastric secretion and acid output and increase pH at oral dose of 300, 500 mg/kg. And significantly reduced acetic acid-induced ulcer at the oral dose of 500 mg/kg for 12 days. In this study, we have found that the water extract from *Scutellaria baicalensis* had significant improvement in acute gastritis and ulcer at the dose of 300, 500 mg/kg and in chronic gastritis and ulcer at the dose of 500 mg/kg. Also we evaluated the antibacterial activity against *Helicobacter pylori* treated with *Scutellaria baicalensis*. *Scutellaria baicalensis* had a equivalent antibacterial activity with ampicillin against *H. pylori* at the dose of 100 µg/ml. In histological examination, the water extract of *Scutellaria baicalensis* drastically restored gastric damages induced by HCl-ethanol solution, pylorus- ligature and acetic acid. Therefore, we may use the water extract from *Scutellaria baicalensis* as anti-gastritic and antiulcerative agent for the purpose of the improvement or treatment of gastritis and gastric ulcer.

**Key words** □ *Scutellaria baicalensis*, Gastritis, Ulcer, *Helicobacter pylori*

### INTRODUCTION

*Scutellaria baicalensis* Georgi is one of the most widely used traditional Chinese herbal medicines. Its roots have been used for anti-inflammation, anticancer, antiviral and antibacterial infections of the respiratory and the gastrointestinal tract, cleaning away heat, moistening aridity, purging fire, detoxifying toxicosis, reducing the total cholesterol level and decreasing blood pressures (Li *et al.*, 2004). Furthermore, recent reports have demonstrated that extracts as well as major components from *Scutellaria baicalensis* have the various physiological activities such as anticancer, antiviral, antibacterial, antioxidant and anti-inflammatory effects (Bonham *et al.*,

2001; Lim, 2004).

Gastric ulcers affects a large portion of the world population and are induced by several factors, including stress, smoking, nutritional deficiencies, and ingestion of nonsteroidal anti-inflammatory drugs (Nash *et al.*, 1994). Stress-related gastric mucosal damage, nonsteroidal anti-inflammatory drug (NSAIDs)-induced gastric lesion and *Helicobacter pylori* (*H. pylori*)-mediated ulcers are quite common. Gastritis and gastric ulcers are pathological conditions caused by an imbalance between aggressive factors (i.e. gastric acid, pepsin, stimulation of the vagus nerves, secretion of gastrin, increase in the number of parietal cells) and protective factors (i.e. bicarbonate ion, mucus productivity, mucus secretion, prostaglandins) (Shay *et al.*, 1945). With the exception of the damaging role of gastric acid, reactive oxygen species (ROS), particularly hydroxyl radicals (OH), are a major cause of the oxidative damage of the mucosa in most types of gastric ulcers (Phull *et al.*, 1995).

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Protection of the gastric mucosa involves the factors such as acid-pepsin secretion, parietal cell activity, mucosal barrier, mucus secretion, blood flow, cell regeneration and the release of endogenous protective agents, especially prostaglandins and epidermal growth factors. Numerous approaches have been used to combat gastric ulcers, including the control of acid secretion, *H. pylori* level and  $H^+/K^+$ -ATPase activity, in attempt to reverse mucosal damage and inflammation (Woo *et al.*, 1998).

This research about *Scutellaria baicalensis* attempted because of its potential medicinal possibility in gastritis and gastric ulcer among the local folk medicines via previous documentary records and screening test. We evaluated the acute toxicity, antigastritis and antiulcerogenic effect of a water extract obtained from *Scutellaria baicalensis* *in vivo* and *in vitro*. In this study, we suggested that the water extract from *Scutellaria baicalensis* could be used as the source for the development of new drugs or nutraceuticals.

## MATERIALS AND METHODS

### Materials and chemicals

The *Scutellaria baicalensis* (1 kg) collected from the herbal market in Seoul, Korea was used after well-washed, dried and powdered. The water extracts solution were made by reflux with  $H_2O$  for 4 h five times at  $10^\circ C$  in a water bath and then the extracts were filtered and concentrated under decompression.

Bovine serum albumin, 1-diphenyl-2-picrylhydrazyl (DPPH), thiobarbituric acid, 1,1,3,3-tetraethoxypropane, L-ascorbic acid, Brucella, agar, horse serum, phosphoric acid, acetonitril, ampicillin, aspirin and dioctyl sodium sulfosuccinate were purchased from Sigma Chem. Co. and alcian blue (Janssen Chimica), sucrose (Shinyo Pure Chem. Co., Ltd.), carboxymethyl cellulose (Junsei Chem. Co.), cimetidine (Choongwea Pharm. Co., Ltd.), *Helicobacter pylori* (American Type Culture Collection, Rockville, MD, USA) were used. Other reagents and solvents for extraction were pharmaceutical or reagent grade for analysis.

### Animals

Male Sprague-Dawley rats weighing 180-200 g were purchased from Samyook Animal Laboratories, Kyunggi-do. Solid food and water were supplied *ad libitum*. All animals were housed and controlled on a 12 h light/dark cycle at  $60 \pm 1\%$  humidity and a temperature of  $23.5 \pm 1.5^\circ C$ . The samples dissolved in saline were administered in a volume of 0.5 ml per 100 g (body weight).

### Acid neutralizing activity

Activity was measured according to the modified acid neutralizing activity method of Korean Pharmacopoeia (K.P.VIII, 2003). Artificial gastric juice under the gastritis was prepared as adding 50 ml of 0.1N HCl to 50 ml of  $H_2O$ . Mixture with 1g of water extract in this solution was incubated for 1 h at the  $37^\circ C$  shaking incubator. The pH could be measured as the pH meter and talcid (1mg/mL) was used as positive control.

### HCl-ethanol-induced gastric lesion

Briefly, male rats, which were fasted for 24hr with free access to water prior to the experiment, were orally administered with 1mL of a HCl-ethanol (60% ethanol with 150 mM HCl) solution. One hour later, the animals were anesthetized with ether, and their stomachs were removed and fixed with 2% formalin for 30 min. The amount of hemorrhage on the glandular portion was measured by summing the total length (mm) of each lesion and expressed as a lesion index. The test substance was given orally 30 min prior to administration of HCl-ethanol solution (Mizui and Dodeuchi, 1983).

### Shay Ulcer and Gastric Secretion

The male rats, which were fasted for 24 h with free access to water, were immediately administered water extract from *Scutellaria baicalensis* and cimetidine intraduodenally after the pyloric ligation (Shay *et al.*, 1945).

**Shay Ulcer** Seventeen hours later, the animals were sacrificed and the excised stomachs were treated as described above. Gastric ulcers in the fore-stomach, which were induced by a pyloric ligation, were assessed by the ulcer index according to the severity of the ulcer: 1, no lesion; 2, bleeding or light; 3, moderate; 4, severe; 5, perforation.

**Gastric Secretion** Four hours after the pyloric ligation, the animals were sacrificed and the contents of the stomach were collected and centrifuged at 500 g for 10 min. The total gastric juice volume and pH were measured, and the acidity was determined by titrating of the gastric juice with 0.05 N NaOH using phenolphthalein as the indicator.

### Acetic acid-induced ulcer

According to the method of Takagi and Okabe (1968), male rats were fasted for 24 h before the experiment, the stomach was exposed under ether anesthesia, and 2  $\mu$ l of 20% acetic acid was injected in subserosal layer of forestomach and sutured. 50 mg/kg of ampicillin was orally administered for preventing infection. The test substance was orally adminis-

tered once a day from the 4th day to 11th day after surgery. On the 15th day after the surgery, animals were sacrificed and the excised stomach was treated as described above and the area ( $\text{mm}^2$ ) of each ulcer was measured and summed.

#### DPPH anti-oxidative assay

According to the partly modified method of Uchiyama *et al* (1968), radical scavenging activity ( $\text{IC}_{50}$ ) was determined. The test substance dissolved in MeOH was added to  $1.5 \times 10^{-4}$  M methanol solution of 1,1-diphenyl-2-picrylhydrazyl. Concentrations of the test substance and L-ascorbic acid were 240, 160, 80, 40, 5 and  $2.5 \mu\text{g/mL}$ . Then the solution with test substance was shook vigorously and kept in the dark for 30 min at  $25^\circ\text{C}$ . The absorbance of the test substance was measured on a spectrophotometer at 520 nm. L-ascorbic acid was used as a positive control.

#### Anti-*Helicobacter pylori* activity

*H. pylori* strain, HP ATCC43504 used throughout this study was obtained from ATCC (Rockville, MD, USA). The inhibitory effect of water extract from *Scutellaria baicalensis* on the growth of *H. pylori* was investigated. 600  $\mu\text{l}$  water extract samples of each concentration were injected to 5.4 ml of brucella agar medium contained 7% horse serum in the petri dish. *H. pylori* of  $5 \times 10^5$  CFU was seeded in this media and then incubated for 3 days at  $37^\circ\text{C}$  incubator (AnaeroPak Campylo : 85%  $\text{N}_2$ , 10%  $\text{CO}_2$ , 5%  $\text{O}_2$ ). Ampicillin was used as positive control.

#### Histological examination

The stomach fixed for 48 h with 10 % formalin was dehydrated by passing successively in different mixture of ethyl alcohol-water (50, 80, 95 % and finally in absolute alcohol), cleared in xylene and embedded in paraffin. Section (4-5  $\mu\text{m}$  thick) were prepared and then stained with hematoxylin-eosin dye for microscopic observation (40 $\times$ , 100 $\times$ ) of changes in stomach tissue.

#### Statistical analysis

All data represent means  $\pm$  S.E. Statistical analyses of the data were performed using analysis of variance followed by Student's *t*-test. All data were evaluated at the  $p < 0.05$  level of significance.

## RESULTS AND DISCUSSION

#### Acid neutralizing activity

To identified that 1g of water extract from *Scutellaria baicalensis* have the acid neutralizing activity that react with gastric acid under gastritis, the modified method of Korean Pharmacopoeia was used. As shown Table I, water extract from *Scutellaria baicalensis* had some acid neutralizing trend compared to the control. Antigastric activities seems to be another mechanism.

#### HCl-ethanol-induced gastric lesion

In the HCl ethanol-induced gastric ulcer model, water extract from *Scutellaria baicalensis* demonstrated significant inhibition of the ulcerative lesion index by 81.1% (300 mg/kg) and 99.6% (500 mg/kg), respectively, in relation to the control value (Fig. 1, 2, 3). This inhibition effects were dose dependent and the potent inhibition activity was shown in the treatment group at the dose of 500 mg/kg of water extract from *Scutellaria baicalensis*, especially when compared with the positive control, sucralfate (200 mg/kg, 94.7%). HCl ethanol induced lesion is known to be produced by direct irritation of gastric mucosal barrier (Seiki *et al.*, 1990). Thus the effectiveness of the test substance on HCl-ethanol-induced gastric lesion might be related to direct protection of the irritation and the gastric mucosal against injury.

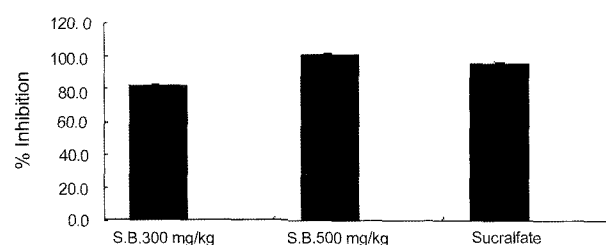
#### Shay Ulcer and Gastric Secretion

We showed the biochemical effects of water extract from *Scutellaria baicalensis* on gastric-juice parameters obtained after submitting the rats to pylorus ligation using all of the treat-

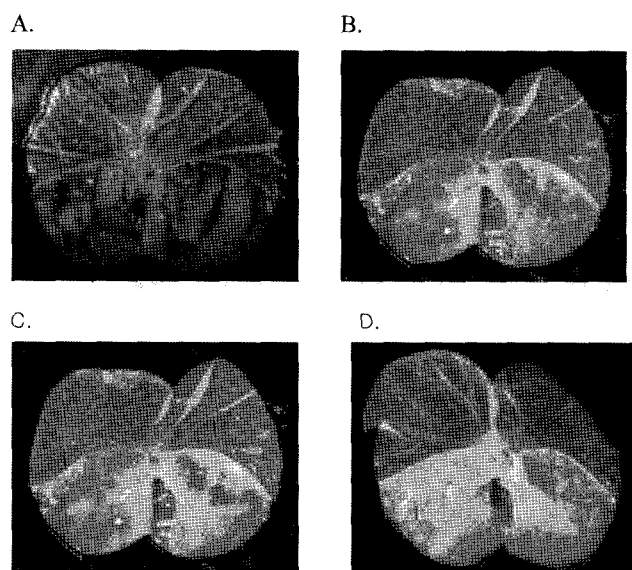
**Table I.** Acid neutralizing activity of water extract from *Scutellaria baicalensis*

Treatment	pH
Control	1.18
Water extract from <i>Scutellaria baicalensis</i> (1 g)	1.24
Talcid (1 mg/mL)	4.20

Control is the artificial gastric juice

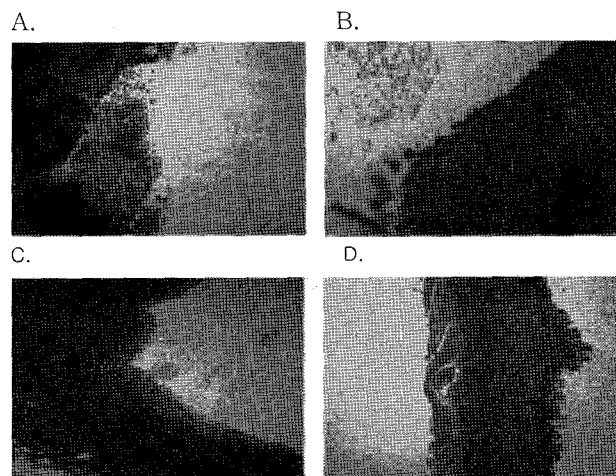


**Fig. 1.** Effects of the water extract from *Scutellaria baicalensis* (S.B) on HCl-ethanol-induced gastric lesions in rats. n=6.



**Fig. 2.** The effects of the water extract from *Scutellaria baicalensis* on HCl · ethanol induced in rats (macrography). The mucosal layer injury of the gastric tissue obtained from the rats treated with control(A), 300 mg/kg *Scutellaria baicalensis* (B), 500 mg/kg *Scutellaria baicalensis* (C) and Sucralfate (D). The mucosal layer injuries of (B) and (C) are dramatically reduced compared to that of (A).

ments, extracts and positive and negative control deministered intraduodenally. As shown in Table II, we observed that 300, 500 mg/kg of water extract as well as the sucralfate positive control, significantly decreased the gastric acid secretion ( $p < 0.05$ ), increased the pH values ( $p < 0.01$ ) and promoted reduced acid output. These data were consistent with previous result which showed the inhibition effect on HCl-ethanol-induced gastric lesion.



**Fig. 3.** The protective effect of the water extract from *Scutellaria baicalensis* on HCl · ethanol induced in rats (micrography  $\times 100$ ). The mucosal layer injury of the gastric tissue obtained from the rats treated with control(A), 300 mg/kg *Scutellaria baicalensis* (B), 500 mg/kg *Scutellaria baicalensis* (C) and sucralfate (D). The mucosal layer injuries of (B) and (C) are dramatically reduced compared to that of (A).

The test substance at an intraduodenal dose of 300, 500 mg/kg showed significant inhibition by 34.9, 60.5% respectively on Shay ulcer and decrease of ulcer index compared with negative control. Also positive control cimetidine significantly inhibited the ulcer by 37.2% and decrease of ulcer index at 150 mg/kg (Table III, Fig. 4, 5).

Shay ulcer is generated from over-secretion of gastric juice and the balance of defensive and aggressive factors is thought to be important in maintaining gastric mucosal integrity. The formation of gastric mucosal lesions by necrotizing agents such as HCl and ethanol has been reported to involve the depression

**Table II.** Effects of the water extract from *Scutellaria baicalensis* on gastric secretion in pylorus-ligated rats

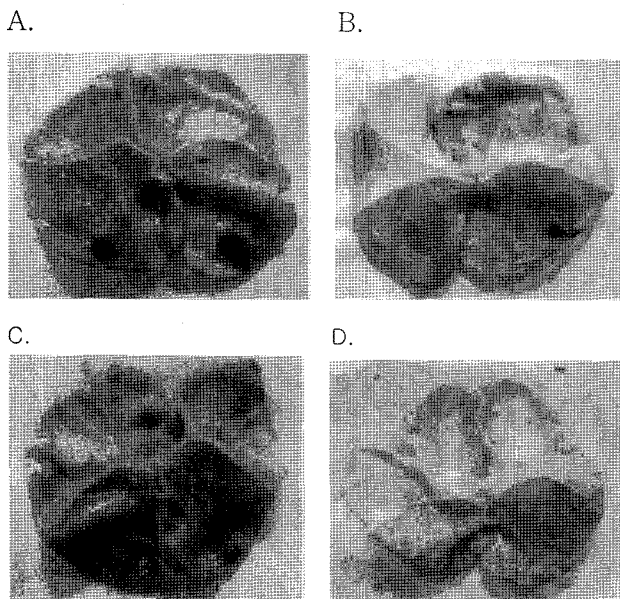
Treatments	Dose (mg/kg)	Volume of gastric juice (ml)	pH (units)	Total acid output (mEq/ml 4h)
Control	-	7.16 $\pm$ 1.14	0.98 $\pm$ 0.06	0.51 $\pm$ 0.14
Water extract from <i>Scutellaria baicalensis</i>	300	5.42 $\pm$ 1.39*	1.14 $\pm$ 0.08**	0.19 $\pm$ 0.10**
<i>Scutellaria baicalensis</i>	500	5.83 $\pm$ 1.34	1.15 $\pm$ 0.10**	0.23 $\pm$ 0.10**
Sucralfate	350	5.12 $\pm$ 1.08*	1.01 $\pm$ 0.06	0.29 $\pm$ 0.09*

\* $p < 0.05$ , \*\* $p < 0.01$  significantly different from the control group. n=6

**Table III.** The effect of the water extract from *Scutellaria baicalensis* on gastric ulcer in pylorus-ligated rats

Treatment	Dose (mg/kg)	Ulcer index (Mean $\pm$ S.E.) mm <sup>2</sup>	Inhibition (%)
Control		4.33 $\pm$ 2.07	-
Water extract from <i>Scutellaria baicalensis</i>	300	2.83 $\pm$ 1.17	34.9
<i>Scutellaria baicalensis</i>	500	1.67 $\pm$ 0.52	60.5*
Cimetidine	150	1.50 $\pm$ 0.33	37.2*

\* $p < 0.05$  significantly different from the control group. n=6

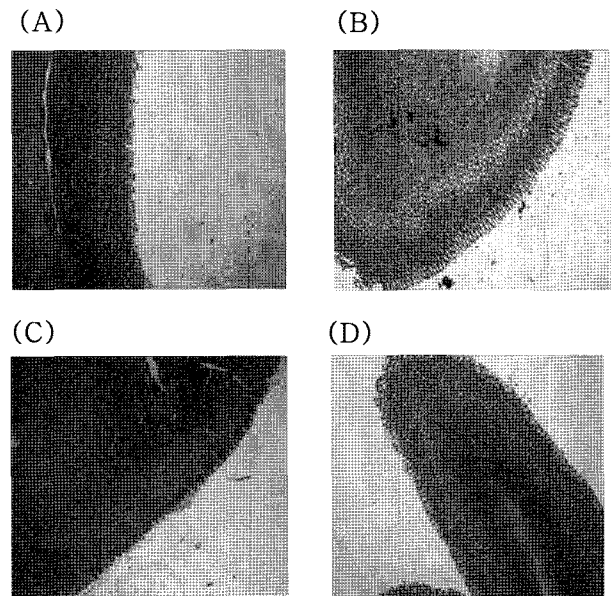


**Fig. 4.** The effects of the water extract from *Scutellaria baicalensis* on gastric ulcer in pylorus-ligated rats. The mucosal layer injury of the gastric tissue obtained from the rats treated with control(A), 350 mg/kg. Cimetidine (B), 300 mg/kg *Scutellaria baicalensis*(C) and 500 mg/kg (D).

of these gastric defensive mechanisms (Kinoshita M, *et al.*, 1995). It is generally believed that proton pump inhibitors accelerate the healing of gastric ulcers and gastritis by potent and long-lasting antisecretory actions. From these results, the water extract from *Scutellaria baicalensis* might be inhibited gastric ulcer and gastritis by similar mechanism as the gents that anti-secretory agents or proton pump inhibitors.

#### Acetic acid-induced ulcer

The test substance showed mild inhibition of acetic acid-induced ulcer at the doses of 500 mg/kg by 25.4%, but had no effect at the dose of 300 mg/kg. Sucralfate significantly inhibited the ulcer by 55.8% at 150 mg/kg p.o.(Table IV, Fig. 6, 7). Brzozowski *et al.* (2001) reported the natural healing of acetic acid-induced ulcer is originated from increase of PGE<sub>2</sub>. The test substance had mild effectiveness on acetic acid-induced



**Fig. 5.** The protective effect of the water extract from *Scutellaria radix* on gastric ulcer in pylorus-ligated rats(micrography×100). The mucosal layer injury of the gastric tissue obtained from the rats treated with control(A), 350 mg/kg cimetidine (B), 300 mg/kg *Scutellaria radix*(C) and 500 mg/kg *Scutellaria radix* (D). The mucosal layer injuries of (C) and (D)are reduced compared to that of (A)

ulcer likewise it was some effective on the aspirin-induced ulcer.

#### DPPH anti-oxidative assay

The test substance showed free radical-scavenging effect in dose dependent manner and exhibited the antioxidant activity (IC<sub>50</sub> = 71.8 µg/ml) in 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging assay (Table V). Although this free radical-scavenging effect of test substance was moderate compared with positive control L-ascorbic acid, it seems to be related to anti-oxidative activity on gastritis and gastric ulcer.

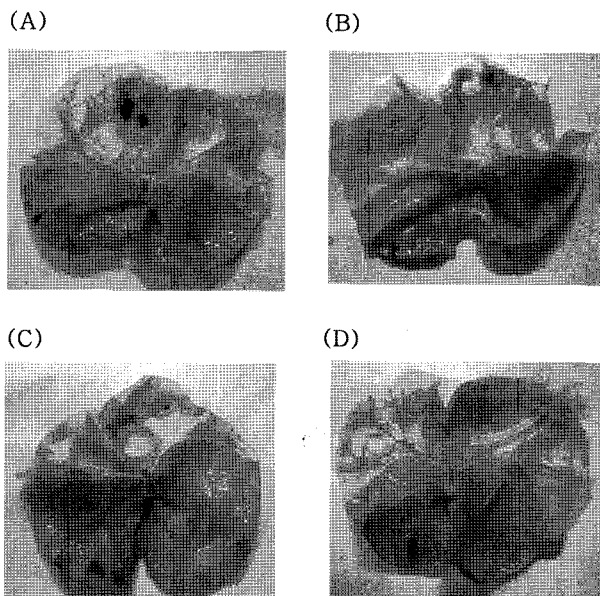
#### Anti-*Helicobacter pylori* activity

*H. pylori* is the major worldwide cause of bacterial gastrointestinal infections in adults and children. Antibiotic therapy and a

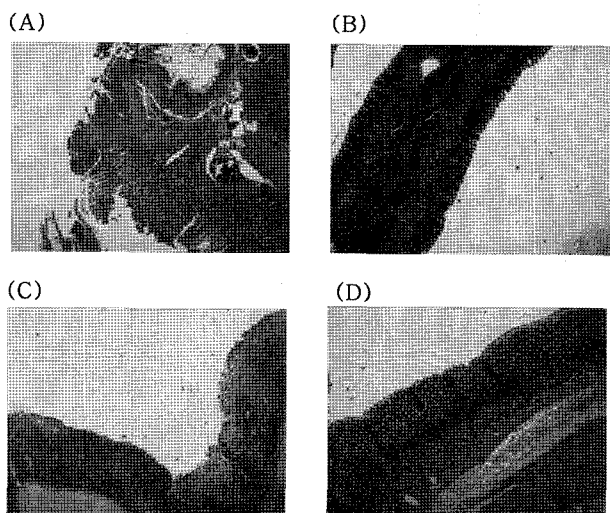
**Table IV.** The effect of water extract from *Scutellaria baicalensis* on acetic acid-induced ulcer in rats

Treatment	Dose (mg/kg)	Ulcer index (Mean ± S.E.) mm <sup>2</sup>	Inhibition (%)
Control		18.14 ± 5.76	-
Water extract from	300	22.00 ± 17.61	-
<i>Scutellaria baicalensis</i>	500	13.50 ± 4.80	25.4
Sucralfate	150	8.00 ± 1.41	55.8*

\*p<0.01 significantly different from the control group. n=6



**Fig. 6.** The effects of the water extract from *Scutellaria radix* on acetic acid-induced ulcer in rats. The mucosal layer injury of the gastric tissue obtained from the rats treated with control(A), 350 mg/kg Sucralfate(B), 300 mg/kg *Scutellaria radix* (C) and 500 mg/kg *Scutellaria radix*(D). The mucosal layer injuries of (C) and (D)are reduced compared to that of (A)



**Fig. 7.** The protective effect of the water extract from *Scutellaria radix* on acetic acid-induced ulcer in rats (micrography $\times 100$ ). The mucosal layer injury of the gastric tissue obtained from the rats treated with control(A), 350 mg/kg Sucralfate(B), 300 mg/kg *Scutellaria radix*(C) and 500 mg/kg *Scutellaria radix* (D). The mucosal layer injuries of (C) and (D)are reduced compared to that of (A)

combination of two or three drugs have been widely used to eradicate these infections. However, development of drug resistance in bacteria calls for new sources of drugs, and plants seem

**Table V.** Free radical scavenging effects of the water extract from *Scutellaria baicalensis*

Treatment	IC <sub>50</sub> ( $\mu\text{g/ml}$ )
Water extract from <i>Scutellaria baicalensis</i>	71.8
L-ascorbic acid	2.5

**Table VI.** Inhibitory effects of the water extract from *Scutellaria baicalensis* on growth of *H. pylori*

Control	Water extract from <i>Scutellaria baicalensis</i>		Ampicillin (100 $\mu\text{g/ml}$ )
	100 $\mu\text{g/kg}$	1 mg/kg	
Colonization	+++	-	-

+++ : colonies (over 5), ++ : colonies(3-4), + : colonies(1-2), - : none

to be a logical source of new antibacterial compounds. Due to the rise in antibiotic resistance, new sources of anti-*H. pylori* drugs are needed. The use of medicinal plants and/or their chemical components may have potential benefit in eradicating such problems (Nostro *et al.*, 2005). Many studies have been reported medicinal plants with anti-*H. pylori* activity and demonstrated these mechanisms. The water extract from *Scutellaria baicalensis* was quite effective in inhibiting the *H. pylori* growth over the dose of 100  $\mu\text{g}$ . *Scutellaria baicalensis* had a equivalent antibacterial activity with ampicillin against *H. pylori* at the dose of 100  $\mu\text{g/mL}$ .

#### Histological examination

In histological examination, hemorrhages induced by HCl-ethanol solution, pylorus-ligature and acetic acid are markedly reduced, and mucosal layer which is peeled off with lesions is recovered almost to the normal condition in the treatment group. The gastric damages in rats was effectively reduced when compared with the control group.

The water extract from *Scutellaria baicalensis* significantly protected the gastric mucosa against injury induced by HCl-ethanol and reduced gastric secretion and acid output for acute gastritis. And the water extract from *Scutellaria baicalensis* significantly protected shay ulcer and acetic acid induced ulcer for chronic gastritis and ulcer. In conclusion, these results indicate that gastric mucosal protective effect of the water extract from *Scutellaria baicalensis* resulted from increase of mucus secretion and reduction of acid secretion. Also due to the prevention of bacterial infection of the stomach as well as anti-oxidant activity, the water extract from *Scutellaria baicalensis* can expected to use the source for development of new anti-gastritis

and anti-ulcerative agents. Also it needs to isolate the original ingredient and further study for the clarification of mechanism and the biological basis on the anti-gastritis and anti-ulcerative activity.

### ACKNOWLEDGEMENTS

This work was supported by the Korea Research Foundation Grant funded by Korean Government(MOEHRD) (KRF-2005-005-J13000)

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