Features of the Anti-Ulcer Effects of Oren-Gedoku-To (a Traditional Chinese Medicine) and Its Component Herb Drugs

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Abstract—This report describes the features of the anti-ulcer effect of Oren-gedoku-to (OGT, a traditional Chinese medicine) and its component herb drugs. Coptidis rhizoma and Phellodendri cortex given orally dose-dependently inhibited the appearance of ethanol-induced gastric hemorrhagic lesions in a dose range of 25–100 mg/kg, but the formation of the lesions was not prevented by Scutellariae radix or Gardeniae fructus at the same doses. Coptidis rhizoma, Phellodendri cortex and Gardeniae fructus inhibited the gastric potential difference (PD) reduction induced by ethanol, whereas Scutellariae radix did not prevent the decrease in the PD reduction caused by ethanol. Phellodendri cortex, Scutellariae radix and Gardeniae fructus had no significant influence on the basal PD, while Coptidis rhizoma increased the basal PD. The four herb drugs prevented gastric acid secretion induced by 2-deoxy-D-glucose, but the three drugs except for Phellodendri cortex showed little effect on pentagastrin-stimulation. These results suggest that the gastric mucosal protection by OGT is ascribed to Coptidis rhizoma and Phellodendri cortex, and its antisecretory effect is due to the four drugs.

Oren-gedoku-to (OGT) is composed of four herbal drugs: Coptidis rhizoma, Phellodendri cortex, Scutellariae radix and Gardeniae fructus. We found that OGT prevented the development of experimental ulcers (1) and that cytoprotective effect of OGT against ethanol-induced gastric lesions was superior to that of other traditional Chinese medicines (2). Moreover, OGT may have an antisecretory effect through the central nervous system (3). The main mechanism by which OGT prevents the formation of lesions appears to be related to increased mucosal resistance, since the inhibitory potency of OGT on ethanol damage was consistent with its potency to prevent ethanol-induced PD reduction.

Robert et al. (4) have shown that prostaglandin (PGs) and PG derivatives protect the gastric mucosa against necrotizing agents by a mechanism independent of their antisecretory activities. The mechanisms of cytoprotection have not been fully elucidated, although stimulation of gastric mucus secretion (5), mucosal blood flow (6), alkali secretion (7) and mucosal barrier (8) have been suggested as possible contributing factors.

The purpose of the present study was to examine cytoprotective activity of four herbal medicines composing OGT in ethanol-induced gastric lesions or potential difference (PD) reduction and inhibitory activities in gastric acid secretion in rats.

Materials and Methods

Animals and drugs: Male Wistar rats (ST, substrain from Shizuoka Lab. Co., Ltd.), weighing 170–260 g, were used. The animals were fasted overnight, but allowed free access to water up to the beginning of the ex-
experiment. OGT (yield: 17.5%) was extracted with hot water from *Coptidis rhizoma* (Shibata), *Scutellariae radix* (Shibata), *Phellodendri cortex* (Shibata) and *Gardeniae fructus* (Sainogi) combined in the ratio of 1.5:3:1.5:2, and the aqueous extract was concentrated under reduced pressure and spray-dried. The component herb drugs were extracted with hot water, and the aqueous extract was concentrated and freeze-dried. The yields of the extracts of the component herb drugs were as follows: *Coptidis rhizoma* (13.2%), *Scutellariae radix* (22.8%), *Phellodendri cortex* (8.8%) and *Gardeniae fructus* (13.4%). One gram of OGT extract consists of 154 mg of *Coptidis rhizoma*, 534 mg of *Scutellariae radix*, 103 mg of *Phellodendri cortex* and 209 mg of *Gardeniae fructus*. This is equivalent to two-thirds the human daily dose. The drugs used are as follows: ethanol (Wako), pentagastrin (ICI), 2-deoxy-D-glucose (2-DG) (Wako), berberine chloride (Kanebo), (±)-isoproterenol HCl (Sigma) and cetrazate (Daichi). OGT, each component herb drug, pentagastrin, 2-DG, berberine, isoproterenol and cetrazate were dissolved in saline and given in a volume of 5 ml/kg of body weight, respectively.

**Ethanol-induced gastric lesions**: Gastric mucosal lesions were produced according to the method of Robert et al. (4). Each drug or saline vehicle was given to rats orally 30 min prior to oral administration of 1 ml of 99.5% ethanol. One hr after ethanol treatment, the animals were killed. The stomach was removed and inflated by injecting 10 ml of 1% formalin to the gastric lumen for 10 min. Subsequently, the stomach was incised along the greater curvature and examined for lesions. The length (mm) of each lesion was measured under a dissecting microscope (×10) with a square grid and the sum per stomach was used as the lesion index.

**Gastric potential difference (PD)**: The experimental procedure was essentially the same as that described by Nagashima et al. (9). After anesthesia with urethane (1.25 g/kg, i.p.), the trachea of the rat was cannulated. A polyethylene gastric cannula was introduced into the gastric lumen through a slit in the duodenum and was held in place by a ligature around the pylorus. The inlet and outlet tubes of the cannula were connected to a saline reservoir and the stomach was continuously perfused with saline solution (adjusted to pH 4 with HCl) at the rate of 5 ml/min through the gastric cannula by means of a perfusion pump. The perfusate was titrated in the reservoir with 0.01 N NaOH at pH 4 using an automatic titrator (HSM-10A, TOA Electronics Ltd., Japan) with a recorder. The acid output during a 2 min period in the perfusate was continuously recorded by use of a zero suppression adaptor (TOA Electronics Ltd., Japan). Each drug was given intraperitoneally 20 min before pentagastrin or 60 min after 2-DG injection.

**Statistics**: Data are expressed as mean± S.E. The statistical significance of the dif-
ference between two groups was determined by means of Student's t-test.

**Results**

**Ethanol-induced gastric lesions:** *Coptidis rhizoma* and *Phellodendri cortex* at doses ranging from 25 to 100 mg/kg inhibited the formation of gastric lesions induced by ethanol in a dose-dependent manner (Table 1). *Scutellariae radix* and *Gardeniae fructus* failed to inhibit the lesion formation at the same doses, but inhibited that induced by ethanol at 250 mg/kg. Berberine at 1–100 mg/kg did not prevent the lesions induced by ethanol. On the other hand, cetraxate showed a significant inhibition against ethanol-induced lesions at 100–250 mg/kg.

**Ethanol-induced PD reduction:** Intragastrical administration of *Phellodendri cortex* at doses of 25–100 mg/kg showed a dose-dependent inhibition against ethanol-induced PD reduction (Table 2). *Gardeniae fructus* at 50–100 mg/kg and *Coptidis rhizoma* at 100 mg/kg significantly inhibited ethanol-induced PD reduction.

### Table 1. Effects of oral administration of Oren-gedoku-to (OGT), *Coptidis rhizoma*, *Scutellariae radix*, *Phellodendri cortex*, *Gardeniae fructus*, berberine and cetraxate on ethanol-induced gastric lesions in rats

| Drug                  | Dose (mg/kg, p.o.) | No. of rats | Ulcer index (mm) | Inhibition (%) |
|-----------------------|--------------------|-------------|------------------|----------------|
| Control 1)            | —                  | 10          | 52.2±7.2         | —              |
| OGT                   | 25                 | 7           | 24.7±5.1*        | 53             |
|                       | 50                 | 8           | 28.8±6.5*        | 45             |
|                       | 100                | 7           | 15.9±3.9**       | 70             |
|                       | 250                | 7           | 7.3±2.0***       | 86             |
| Control               | —                  | 10          | 43.7±6.6         | —              |
| *Coptidis rhizoma*    | 10                 | 6           | 31.9±4.3         | 27             |
|                       | 25                 | 8           | 20.4±4.0*        | 53             |
|                       | 50                 | 6           | 10.7±2.5***      | 76             |
|                       | 100                | 7           | 6.7±2.2***       | 85             |
| *Scutellariae radix*  | 25                 | 8           | 44.7±5.3         | -2             |
|                       | 100                | 6           | 34.4±8.6         | 21             |
|                       | 250                | 6           | 21.9±7.0*        | 50             |
| Control               | —                  | 10          | 54.1±11.2        | —              |
| *Phellodendri cortex* | 25                 | 7           | 35.5±7.4         | 34             |
|                       | 50                 | 7           | 17.5±3.4**       | 68             |
|                       | 100                | 7           | 14.1±4.9**       | 74             |
| *Gardeniae fructus*   | 25                 | 7           | 30.1±8.1         | 44             |
|                       | 100                | 7           | 45.1±10.8        | 17             |
|                       | 250                | 7           | 25.1±5.1*        | 54             |
| Control               | —                  | 7           | 40.7±14.7        | —              |
| Berberine             | 1                  | 7           | 34.9±10.0        | 14             |
|                       | 5                  | 7           | 30.9±9.2         | 24             |
| Control               | —                  | 11          | 39.3±4.0         | —              |
| Berberine             | 25                 | 9           | 31.4±7.6         | 20             |
|                       | 100                | 10          | 34.0±6.2         | 14             |
| Control               | —                  | 12          | 47.6±9.3         | —              |
| Cetraxate             | 100                | 9           | 19.0±2.9*        | 60             |
|                       | 250                | 9           | 12.6±1.7**       | 74             |

*aEach value represents the mean±S.E. of the number of experiments. Gastric lesions were produced by ethanol (99.5%, 1 ml/rat, p.o.) to 24 hr-fasted rats. Each drug was given 30 min orally before ethanol administration. Animals were killed 1 hr after ethanol treatment. 1) cited from Takase et al., ref. 1. *P<0.05, **P<0.01, ***P<0.001, statistical significance of difference from each control (Student's t-test).*
PD reduction, respectively. Scutellariae radix did not prevent the PD reduction induced by ethanol at 50-100 mg/kg. Berberine showed no effect against PD reduction induced by ethanol at 50 mg/kg, although it showed a significant effect at 100 mg/kg. On the other hand, cetraxate aggravated ethanol-induced PD reduction at 100 mg/kg.

Table 2. Effects of Oren-gedoku-to (OGT), Coptidis rhizoma, Scutellariae radix, Phellodendri cortex, Gardeniae fructus, berberine and cetraxate on ethanol-induced PD reduction in anesthetized rats

| Drug                  | Dose (mg/kg) | No. of rats | Gastric potential difference (mV) | JPD   |
|-----------------------|--------------|-------------|-----------------------------------|-------|
| Control               | —            | 10          | 35.9±1.5                          | 19.6±1.9 | 16.5±1.3 |
| OGT                   | 50           | 5           | 35.4±1.6                          | 23.6±2.7 | 11.2±1.9 |
|                       | 100          | 5           | 34.0±1.1                          | 25.2±2.7 | 8.8±2.5** |
| Coptidis rhizoma      | 50           | 5           | 33.0±1.1                          | 20.0±2.4 | 13.0±2.3 |
|                       | 100          | 5           | 32.6±2.0                          | 23.4±2.4 | 10.2±0.6*** |
| Scutellariae radix    | 50           | 4           | 34.3±3.0                          | 18.0±4.7 | 17.0±2.6 |
|                       | 100          | 4           | 35.0±1.5                          | 21.0±1.8 | 14.0±2.0 |
| Phellodendri cortex   | 10           | 5           | 36.6±4.2                          | 20.6±2.2 | 16.0±1.1 |
|                       | 25           | 5           | 33.0±0.3                          | 22.4±1.4 | 10.6±1.4* |
|                       | 50           | 5           | 33.0±2.5                          | 22.8±1.7 | 10.2±1.7* |
|                       | 100          | 5           | 33.8±1.1                          | 28.3±2.2* | 6.5±1.6*** |
| Gardeniae fructus     | 25           | 5           | 36.8±2.6                          | 21.0±3.7 | 15.8±2.8 |
|                       | 50           | 5           | 33.6±1.1                          | 24.0±1.9 | 9.6±1.6** |
|                       | 100          | 6           | 33.5±1.2                          | 23.7±1.8 | 9.8±1.8** |
| Berberine             | 50           | 4           | 36.5±0.9                          | 23.5±0.6 | 13.0±0.8 |
|                       | 100          | 4           | 35.5±1.8                          | 24.8±2.7 | 10.8±0.9* |
| Cetraxate             | 100          | 4           | 35.0±1.6                          | 11.3±1.3* | 23.8±1.8** |

Each value represents the mean±S.E. of the number of experiments. Each drug was intragastrically administered prior to treatment with 40% ethanol. *P<0.05, **P<0.01, ***P<0.001, significantly different from the control (Student's t-test).

Table 3. Effects of Coptidis rhizoma, Scutellariae radix, Phellodendri cortex, Gardeniae fructus and cetraxate on gastric PD in anesthetized rats

| Drug                  | Dose (mg/kg) | No. of rats | Gastric potential difference (mV) | JPD   |
|-----------------------|--------------|-------------|-----------------------------------|-------|
| Control               | —            | 5           | 35.0±3.0                          | 33.6±2.0 | 0.0±2.5 |
| Coptidis rhizoma      | 100          | 4           | 39.0±2.9                          | 47.5±2.9 | 8.3±1.9* |
| Scutellariae radix    | 100          | 4           | 42.0±2.4                          | 45.3±2.6 | 3.5±0.6 |
| Phellodendri cortex   | 100          | 5           | 38.8±3.0                          | 36.0±1.8 | -2.0±2.3 |
| Gardeniae fructus     | 100          | 4           | 41.3±0.6                          | 44.8±2.3 | 3.3±2.7 |
| Cetraxate             | 250          | 5           | 33.2±1.7                          | 28.0±2.3 | -5.8±1.0 |

Each value represents the mean±S.E. of the number of experiments. Each drug was intragastrically instilled for 30 min. *P<0.05, significantly different from the control (Student's t-test).

PD reduction, respectively. Scutellariae radix did not prevent the PD reduction induced by ethanol at 50-100 mg/kg. Berberine showed no effect against PD reduction induced by ethanol at 50 mg/kg, although it showed a significant effect at 100 mg/kg. On the other hand, cetraxate aggravated ethanol-induced PD reduction at 100 mg/kg.

The basal PD: When the stomach was exposed to Coptidis rhizoma at 100 mg/kg, the PD significantly increased (Table 3). Intragastric administration of Phellodendri
Table 4. Effects of *Coptidis rhizoma*, *Scutellariae radix*, *Phellodendri cortex*, *Gardeniae fructus* and isoproterenol on pentagastrin-induced gastric acid secretion in anesthetized rats

| Drug               | Dose (mg/kg) | No. of rats | Acid output (µEq/30 min)* | Total acid after drug | Inhibition (%) |
|--------------------|--------------|-------------|---------------------------|-----------------------|----------------|
|                    |              |             | 0–30 min                  | 30–60 min             | 60–90 min       |
| Control            | —            | 7           | 29.3±2.3                  | 29.9±1.1              | 10.2±1.6        | 69.5±2.6       | —             |
| *Coptidis rhizoma* | 100          | 4           | 27.2±4.4                  | 27.2±4.2              | 9.6±4.4         | 63.9±8.8       | 8             |
| *Scutellariae radix* | 100         | 4           | 36.6±6.1                  | 36.0±6.5              | 16.8±4.0        | 89.3±15.0      | −28           |
| *Phellodendri cortex* | 100         | 4           | 19.8±3.9*                 | 27.9±4.8              | 14.0±2.5        | 61.7±8.8       | 11            |
| *Gardeniae fructus* | 100          | 4           | 29.1±4.1                  | 36.2±5.7              | 16.1±4.3        | 81.3±13.5      | −17           |
| Isoproterenol      | 10           | 4           | 13.2±4.7**                | 14.3±3.8*             | 3.9±1.7*        | 31.4±9.1*      | 56            |

*Each value represents the mean±S.E. of the number of experiments. Each drug was given intraperitoneally 20 min before pentagastrin injection. *P<0.05, **P<0.01, significantly different from the control (Student’s t-test).

Table 5. Effects of *Coptidis rhizoma*, *Scutellariae radix*, *Phellodendri cortex*, *Gardeniae fructus* and isoproterenol on 2-DG-induced acid secretion in anesthetized rats

| Drug               | Dose (mg/kg) | No. of rats | Acid output (µEq/30 min)* | Total acid after drug | Inhibition (%) |
|--------------------|--------------|-------------|---------------------------|-----------------------|----------------|
|                    |              |             | 0–30 min                  | 30–60 min             | 60–90 min       | 90–120 min     |                         |
| Control            | —            | 9           | 9.6±0.9                   | 28.8±4.6              | 40.4±5.9        | 48.3±7.8       | 88.6±13.4       | —             |
| *Coptidis rhizoma* | 100          | 5           | 15.3±5.6                  | 41.3±8.5              | 25.8±6.4        | 4.7±2.0**      | 30.4±7.5*      | 66            |
| *Scutellariae radix* | 100         | 5           | 12.8±3.4                  | 32.8±4.5              | 28.4±3.7        | 18.2±6.3*      | 46.6±8.8       | 47            |
| *Phellodendri cortex* | 100         | 5           | 10.3±2.9                  | 30.4±4.4              | 27.6±4.6        | 17.5±4.6*      | 45.0±8.8*      | 49            |
| *Gardeniae fructus* | 100          | 6           | 17.1±3.2                  | 27.1±3.9              | 13.3±2.8**      | 14.4±4.3**     | 27.8±6.0**     | 69            |
| Isoproterenol      | 10           | 5           | 17.7±5.0                  | 36.5±6.9              | 24.0±6.0        | 3.5±1.2***     | 27.5±6.2**     | 69            |

*Each value represents the mean±S.E. of the number of experiments. Each drug was given intraperitoneally 60 min after 2-DG injection. *P<0.05, **P<0.01, ***P<0.001, significantly different from the control (Student’s t-test).
cortex, Scutellariae radix and Gardeniae fructus had no effect on the basal PD. On the other hand, topical application of cetraxate (250 mg/kg) caused a decrease in the basal PD.

Pentagastrin- or 2-DG-induced gastric acid secretion: Coptidis rhizoma, Scutellariae radix and Gardeniae fructus had little effect on pentagastrin-induced gastric acid secretion, whereas Phellodendri cortex showed a moderate inhibition against pentagastrin response. The four drugs significantly inhibited gastric acid secretion induced by 2-DG (Tables 4 and 5). Isoproterenol exhibitory effects on pentagastrin- and 2-DG-induced gastric acid secretion.

Discussion

The present results have shown that the degrees of the inhibitory effects of Coptidis rhizoma and Phellodendri cortex against ethanol damage was superior to those of OGT, Gardeniae fructus and Scutellariae radix in the dose range tested, thereby suggesting that the mucosal protective effect of OGT was ascribed mainly to the component derived from Coptidis rhizoma and Phellodendri cortex.

Although berberine, a main constituent common to Phellodendri cortex and Coptidis rhizoma, is reported to exhibit an antisecretory effect (11), it failed to prevent ethanol-induced lesions even at a dose (100 mg/kg) much higher than clinical ones. Thus, berberine seems to be indifferent to the cytoprotective effect of Phellodendri cortex and Coptidis rhizoma.

Mild irritants such as dilute ethanol, acetic acid and NaCl are reported to produce a fall in the basal PD (12, 13) as a result of barrier disruption owing to damage in the gastric mucosa. The cytoprotective effect of Phellodendri cortex and Coptidis rhizoma seemed to be different from that of a mild irritant, since Coptidis rhizoma and Phellodendri cortex did not cause a fall in the basal PD.

The gastric PD, which represents the integrity of the gastric mucosal barrier, is considered to be closely related to cytoprotective functions. Our previous results have shown that the cytoprotective activity of OGT can be ascribed to maintenance of the mucosal barrier integrity (2). Phellodendri cortex inhibited the PD reduction induced by ethanol, at a dose range where the formation of ethanol-induced lesions was inhibited. The present results suggest that Phellodendri cortex exerts the cytoprotective activity mostly by maintaining the mucosal barrier. However, the preventive effect of Coptidis rhizoma on ethanol-induced PD reduction was inferior to that of Phellodendri cortex, though the inhibitory activity of the former on ethanol-induced lesions was equal to or stronger than that of the latter. Therefore, we cannot rule out the possibility that there is an involvement of a mechanism other than maintenance of the gastric mucosal barrier in the cytoprotective effect of Coptidis rhizoma. In addition, although Gardeniae fructus showed a protective effect on the gastric mucosal barrier, it did not prevent the ethanol-induced lesions at the same doses. This result may mean probably that Gardeniae fructus affords local protection, but has no parenteral activity.

Thus, there were differences of effects among the extracts of each component drug of OGT. However, 100 mg of OGT extract consists of 15.4 mg of Coptidis rhizoma, 53.4 mg of Scutellariae radix, 10.3 mg of Phellodendri cortex and 20.9 mg of Gardeniae fructus. OGT showed significant protective effects at 100 mg/kg, whereas each component drug exhibited significant preventive effects on ethanol-induced gastric lesions and PD reduction at doses higher than those included in the formulation of 100 mg of OGT. These findings suggest that the mucosal protective effect of OGT is due to the potencies of these component drugs.

Cetraxate, which is considered to show an anti-ulcer effect by increasing mucosal blood flow (14), inhibited the ethanol-induced lesions, while the effect on the PD reduction caused by ethanol was not prominent. Thus, the inhibitory effect of cetraxate on ethanol-induced lesions appears to be essentially different from that of Coptidis rhizoma or Phellodendri cortex.

We have previously shown that OGT produces a significant inhibition against gastric acid secretion induced by 2-deoxy-D-glucose (2-DG) (3). Further, it has been reported that OGT has a beta adrenergic activity (15) and
isoproterenol, a beta agonist, inhibits gastric acid secretion by activating beta-adrenoceptors (16–18). In the present study, Gardeniae fructus, Coptidis rhizoma, Phellodendri cortex and Scutellariae radix showed inhibitory effects on gastric acid secretion induced by 2-DG, but not on pentagastrin-induced acid secretion. On the other hand, isoproterenol inhibited pentagastrin- and 2-DG-stimulated acid secretion. Thus, the antisecretory effects of OGT and the component herb drugs appear to be different from that of isoproterenol and mediated through the vagal nerve system. Moreover, the degree of antisecretory activity of these drugs did not correspond to the potency of inhibition of ethanol-induced lesions, thereby suggesting that the preventive mechanism of OGT against ethanol-induced ulcer is not due to the antisecretory activity of these drugs.

In conclusion, the cytoprotective effect of OGT may be ascribed to the poteniations of each component drug. The antisecretory effect of these four drugs is considered to take a minor part in the cytoprotective activity of OGT.

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