Pharmacological Evaluation of Shokyo and Kankyo (1)

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Zingiberis Rhizoma (Shokyo, 生姜) showed significant ameliorative effect on the BaCl₂-induced delay of gastric emptying in rat. Bioassay-guided fractionation of the aqueous extract of Shokyo resulted in isolation of 6-gingesulfonic acid (1) and shogasulfonic acid A (3). These compounds significantly improved the delay of gastric emptying on both BaCl₂-induced and N^G-nitro-L-arginine (L-NNA)-induced model in rat.

Zingiberis Siccum Rhizoma (Kankyo, 乾姜) had significant efficacy against castor oil-induced diarrhea. In addition, Kankyo showed the activity increasing intestinal blood flow in normal rat.

Key words *Zingiber officinale*; gastric emptying; intestinal blood flow; *Zingiberis Rhizoma*; *Zingiberis Siccum Rhizoma*; shogasulfonic acid A

Ginger, *i.e.*, *Zingiber officinale* ROSCOE (Zingiberaceae), is a perennial plant of Southeast Asian origin. Since ancient times, it has been used as food and medicine in many countries. Its use as medicine was already written in the Sinnouhonzou-kyo (《神農本草經》), under the name of Kankyo. In this monograph, both raw and processed ginger were described. The Meii-betsuroku (《名醫別錄》) distinguishes Shokyo from Kankyo. In the subsequently written Honzou-koumoku (《本草綱目》), the term Kan-shokyo was also used to indicate ginger, in addition to the conventional names Shokyo and Kankyo, and it discussed how to distinguish among these three when used as medicine.

At present, Shokyo and Kankyo on the Japanese market are prepared by methods developed in Japan, on the basis of ideas specific to Japan. Dried ginger rhizoma is sold as Shokyo or Kan-shokyo, while steamed and dried ginger is sold as Kankyo. In Chinese pharmaceutical monograph, on the other hand, the term Shokyo is used to indicate fresh rhizoma of ginger, and Kankyo is used to indicate dried ginger, corresponding to Japanese Shokyo and/or Kan-Shokyo. Thus, even at present, nomenclature of ginger products differs between Japan and China. If we interpret the descriptions of classical monographs about the objectives of the use of Shokyo and Kankyo from the standpoint of modern medicine, it appears that Shokyo is used to treat vomiting and to promote sputum elimination, cough control, fever reduction and digestive function, while Kankyo is used to regulate gastrointestinal vermiculation, improve water and food retention, and treat abdominal (cold-related) pain, diarrhea, vomiting and cough. Several reports have been published concerning pharmacological effects of Shokyo and Kankyo, including reports that demonstrated the antiemetic effects,^{1–3)} stomach-protecting effects,^{4,5)} and effects on intestinal function,^{6–9)} of their components. Some of these reports suggest that distinction between Shokyo and Kankyo is clinically significant, but the discussion in these reports was not clear.

The present study was undertaken to examine the pharmacological effects of Shokyo and Kankyo on the digestive system and to evaluate the significance of distinction between these two.

MATERIAL AND METHODS

Materials Before selecting experimental materials, several Shokyo and Kankyo products, purchased in Japan were subjected to physicochemical tests. On the basis of pharmacognosic evaluation of these products, one Shokyo product (No. 13201240) and one Kankyo product (No. 12209270) were selected for the study.

Castor Oil-Induced Diarrhea Test Conducted according to the method reported elsewhere.¹⁰⁾ Statistical analysis: The statistical significance of value for diarrhoeal incidence was determined by the χ^2 test.

Cholera Toxin-Induced Intestinal Juice Secretion Stimulation Test Experimental animals: Male Wistar rats (8-weeks old, SLC Japan) were used after 1-week acclimation. Methods: The experiment was conducted according to the method reported by Beubler *et al.*¹¹⁾ The test drug was administered orally to the animals 1 h before anesthesia. Under urethane anesthesia (1.25 g/kg, *i.p.*), the abdomen was opened, and the small intestine was ligated for about 5 cm from the flexura duodenojejunalis. The small intestine was ligated again at a point 20 cm distal from the first point of ligation. In this way, a small intestinal loop was created. Two mL of Cholera toxin (1 μ g/mL), dissolved in Tyrode solution, was injected with a 27G syringe into the loop. The normal control group was given an injection of 2 mL Tyrode solution (the same solution, 2 mL, was injected again 30 min before the control animals were sacrificed). The abdomen of each animal was opened after administering cholera toxin. Four hours later, each animal was sacrificed, and the loop was removed for measurement of the total loop weight and the wet tissue weight. The difference between them was expressed as the amount of water absorbed. Statistical analysis: Results were expressed as the mean $\pm$ S.E. and analyzed by one-way analysis of variance (ANOVA) followed by Fisher's least significant difference procedure.

Gastric Emptying Test (on the Normal Condition or on the Delay of Gastric Emptying with BaCl₂) Experimental animals: Male Wistar rats (7 weeks old, SLC Japan) were used after one-week acclimation. Methods: The experiment was conducted according to the method reported by Yokochi *et al.*¹²⁾ Rats, fasted for 24 h, were orally treated with the drug. Thirty minutes later, phenol red (100 μ g/mL/rat) was

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orally administered. Fifteen minutes later, each animal was sacrificed, to measure the amount of phenol red retained in the stomach, with the goal of evaluating the effects of the test drug on gastric emptying.

A group of animals received an intraperitoneal injection of BaCl_2 (3.5 mg/kg) 5 min prior to the dose of phenol red, to evaluate the effects of the test drug on BaCl_2 -induced gastric emptying. Statistical analysis: Results were expressed as the mean $\pm$ S.E. and analyzed by one-way ANOVA followed by Fisher's least significant difference procedure.

NG -Nitro-L-arginine (L-NNA) Induced Gastric Emptying Test Experimental animals: Male Wistar rats (7 weeks old, SLC Japan) were used after one-week acclimation. Methods: Rats were orally treated with L-NNA (10 mg/kg). Eight and 22 hours later, the test drug was administered. Two hours after the last dose, phenol red (100 μg) was administered orally. Fifteen minutes later, each animal was sacrificed to measure the amount of phenol red retained in the stomach. Statistical analysis: Results were expressed as the mean $\pm$ S.E. and analyzed by one-way ANOVA followed by Fisher's least significant difference procedure.

Intestinal Blood Flow Test Conducted according to the method reported elsewhere.¹³⁾ Male Sprague-Dawley rats (Charles River Japan Inc., Japan) weighing 230–270 g were fasted overnight but given free access to water. After urethane (900 mg/kg, i.v.) and α -chloralose (45 mg/kg, i.v.) anesthesia, a tracheal cannula was inserted to facilitate spontaneous respiration. The cannula was inserted into the duodenum to facilitate injection of the test drugs. Body temperature was maintained at $37 \pm 0.5^\circ\text{C}$ by a warming plate. After exposing the intestine by a midline laparotomy, the part of the jejunum was placed on wet absorbent cotton and filled with warmed physiological saline, then covered with saran wrap to prevent movement, and the tissue from becoming dehydrated. Intestinal blood flow was measured by laser Doppler flowmetry (Omega Flow FLO-N1, Omega Wave, Japan). A pencil probe (CS-N, Omega Wave) was placed over the midjejunum and the position of the probe was not altered during the course of the experiments. The penetration depth of the laser Doppler flowmetry system used was 1 mm. Blood flow was measured on a polygraph system (8MI4, Nippon Denki Sanei Co., Japan) and recorded on a computer (Apple, Macintosh) through MP100 (Biopac Systems, U.S.A.). The data were analyzed using Acknowledge III (Biopac Systems). Blood flow was expressed as milliliters per minute per 100 g. Statistical analysis: Results were expressed as the mean $\pm$ S.E. Comparisons between multiple groups were made by one-way ANOVA followed by Dunnett's test.

Instrumental Analysis The isolated compounds were analyzed using the instruments and methods reported elsewhere.¹⁴⁾

Extraction, Fractionation and Isolation One kilogram of Shokyo was crushed into pieces and subjected to perfusion extraction in water (10 l) for 2 h, to yield aqueous extract (138.0 g). The extract was dissolved in water (3 l) and chromatographed on Diaion HP-20 (6 l, Mitsubishi Kasei, Japan) column, eluting with water (30 l), 50 % MeOH (30 l), MeOH (30 l) and then acetone (30 l), to yield fractions (water eluate: 113.92 g, 50% MeOH eluate: 11.02 g, MeOH eluate: 9.79 g, acetone eluate: 2.27 g). A portion (4.0 g) of the 50% MeOH

eluate was found to be pharmacologically active and was subjected to reverse phase column chromatography (Cosmosil 140 C_{18} -OPN, Nakarai, Japan) to yield fractions (water eluate: 1.47 g, 20% MeOH eluate: 1.13 g, MeOH eluate: 1.15 g). The MeOH eluate was found to be active, and was subjected to purification in H_2O –MeOH system by reverse phase column chromatography, which allowed isolation of 6-gingesulfonic acid (**1**; 127 mg), (+)-angelicoidenol-2- O - β -D-glucopyranoside (**2**; 74 mg) and shogasulfonic acid A (**3**; 21 mg).

Kankyo (1 kg) was also subjected to extraction procedure, similar to that for Shokyo, to yield fractions (water eluate: 105.07 g, 50% MeOH eluate: 24.52 g, MeOH eluate: 6.45 g, acetone eluate: 0.4 g). The MeOH eluate was subjected to repeated purification in H_2O – CH_3CN system by reverse phase column chromatography, leading to isolation of 6-gingerol (**4**; 1.872 g), 8-gingerol (**5**; 326 mg), 10-gingerol (**6**; 220 mg), 6-shogaol (**7**; 1.691 g), 8-shogaol (**8**; 236 mg), 10-gingerdione (**9**; 210 mg) and 10-dehydrogingerdione (**10**; 95 mg). From the MeOH eluate which was found to be pharmacologically active, we could collect large amounts of 6-gingerol (**4**) and 6-shogaol (**7**), and these two compounds were further evaluated. Of the above-mentioned compounds isolated from Shokyo and Kankyo were previously known compounds and were identified by referring to published data.^{15–19)}

Heat Treatment of Substances Stimulating Gastric Emptying Aqueous solution of 6-gingesulfonic acid (**1**) (0.1 mg/ml) was poured into each of the 6-chained extractors in a volume of 25 ml/extractor. It was then subjected to heated perfusion for a certain period of time. The reaction system was harvested every 2 h during the first 12 h period and was combined with methanol to yield a 50 ml solution for analysis. The decrease in the amount of 6-gingesulfonic acid (**1**) and the amount of 6-shogaol (**7**) produced were analyzed under the following conditions: column; Deverosil C_8 (4.6 mm I.D. $\times$ 150 mm), mobile phase; 50 mM ammonium acetate (pH 3.6)/acetonitrile (6 : 4), flow rate; 1.0 ml/min, detection wavelength; 280 nm, temperature: 50°C . Similar heat treatment was conducted of shogasulfonic acid A (**3**), and the decrease in its amount and the amount of gingerenone A formed were analyzed under the similar conditions.

Analysis of Shokyo Using Gastric Emptying Stimulating Factors as an Indicator Seventeen Shokyo products, manufactured in China and purchased in Japan, were subjected to quantification of 6-gingesulfonic acid (**1**) and shogasulfonic acid A (**3**). Samples: No. 6344, 7319, 8622, 8623, 8933, 10254, 10255, 12169, 12903, 14543, 15224, 16744, 13201240, 17203810, 17204010, 17204810 and 17204850. Sample treatment: Powdered Shokyo (1.0 g) was subjected to 30 min of ultrasonic extraction in water (30 ml). After centrifugation, the residue was extracted in water (15 ml). The two extracts were combined to a volume of 50 ml, to yield a sample for analysis. Analysis was conducted under the following conditions: column; Deverosil C_8 (4.6 mm I.D. $\times$ 150 mm), mobile phase; 50 mM ammonium acetate (pH

Chart 1. Structure of Shogasulfonic Acid A (**3**)

3.6)/acetonitrile (82:18), flow rate; 1.0 ml/min, detection wavelength; 280 nm, temperature; 50 °C.

RESULTS AND DISCUSSION

Effects on Castor Oil-Induced Diarrhea The effects of a combined Kankyo preparation (K), a combined Shokyo preparation (S) and Shokyo-free or Kankyo-free preparation (N) were evaluated, referring to published data concerning the efficacy of Hange-shashin-to (半夏瀉心湯) on castor oil-induced diarrhea.¹⁰⁾ None of the products tested exacerbated diarrhea. Only product K had significant efficacy vs. control on castor oil-induced diarrhea. Next, when Shokyo extract and Kankyo extract were tested, only the Kankyo extract showed significant effects vs. control (Table 1). Thus, Kankyo was found to be effective against castor oil-induced diarrhea. Shokyo has been reported to be effective against serotonin-induced diarrhea,⁹⁾ but this efficacy was observed in an experiment using a model of diarrhea induced by the action of serotonin on the nervous system (serotonin does not injure the intestinal mucosa). On the other hand, castor oil stimulates and injures the intestinal mucosa, resulting in induction of diarrhea. The mechanism of diarrhea is diverse and complex. Simply saying, diarrhea represents the transfer of excessive water into feces following failure of adequate absorption of water and electrolytes through the intestine. The results of the present study suggest that Kankyo is useful for treating diarrhea. When the effects of 6-gingerol (4) and 6-shogaol (7), which are major active components of the active fraction of Kankyo, were evaluated, both compounds exhibited similar activity (Table 1).

Effects on Cholera Toxin-Induced Intestinal Juice Hypersecretion To examine the effectiveness of Kankyo against castor oil-induced diarrhea, the effects of Shokyo and Kankyo on intestinal juice secretion were evaluated. Our experiment using a model of cholera toxin-induced intestinal juice hypersecretion revealed significant suppression of intestinal juice secretion by Kankyo. Thus, we obtained evidence for the effectiveness of Kankyo against diarrhea (Table 2). Cholera toxin used in this experiment is known to act directly on the intestinal mucosa to stimulate intestinal juice secretion. Prostaglandin production inhibitors and serotonin receptor antagonist are known to suppress this action of cholera toxin.

Effects on Gastric Emptying We attempted to explain why Shokyo was not effective against castor oil-induced diarrhea, from the viewpoint of effects on gastric motility. Stimulation of gastric emptying is not favorable in the presence of diarrhea. Since Shokyo is thought to improve digestive function, it is expected to stimulate gastric emptying. Therefore, we evaluated the effects of Shokyo and Kankyo on gastric emptying.

In the presence of BaCl₂-induced delay of gastric emptying, only Shokyo was found to improve gastric emptying significantly vs. control (Table 3). This result suggests that Shokyo may adversely affect intestinal motility in the presence of diarrhea. This seems to provide partial support to the finding that Shokyo was not effective against diarrhea. At the same time, it is suggested that the effect of Shokyo in stimulating gastric emptying is not always an unfavorable action and that this action explains why Shokyo stimulate digestive

Table 1. Effects of Hange-shashin-to, Kankyo, Shokyo and Its Compounds on Castor Oil-Induced Diarrhoea in Mice

Samples	Dose (mg/kg)	n	Incidence of diarrhoea
Control		10	10/10
Hange-shashin-to (K)	500	10	5/10*
	1000	11	4/11**
Hange-shashin-to (S)	500	10	8/10
	1000	10	10/11
Hange-shashin-to (N)	500	10	7/10
	1000	10	8/11
Kankyo	500	8	6/8
	1000	8	4/8**
Shokyo	500	11	10/11
	1000	11	8/11
6-Gingerol (4)	62.5	11	5/11*
	125	11	6/11*
6-Shogaol (7)	62.5	11	8/11
	125	11	4/11**
Loperamide	5	11	1/11**

Diarrhoea was induced by giving castor oil (0.01 ml/g, *p.o.*). The condition of faeces was checked for 2 h after the castor oil administration. Each drug was given orally 60 min before the oral administration of castor oil. Significantly different from the control at **p*<0.05 and ***p*<0.01, respectively.

Table 2. Effects of Kankyo and Shokyo on Cholera Toxin-Induced Secretion in the Jejunum of Anesthetized Rat

Samples	Dose (mg/kg)	n	Mean ± S.E.
Control		7	666.8 ± 48.3
Kankyo	500	7	526.7 ± 75.3
	1000	7	442.8 ± 62.4**
Shokyo	500	7	533.5 ± 73.0
	1000	7	516.6 ± 48.2
Indomethacin	10	7	314.1 ± 28.6***

Significantly different from the control at ***p*<0.01 and ****p*<0.001, respectively.

Table 3. Effects of Kankyo and Shokyo on BaCl₂-Induced Delay of Gastric Emptying in Rat

Samples	Dose (mg/kg)	Mean ± S.E.
Normal		76.3 ± 2.7***
Control (+BaCl ₂)		18.5 ± 7.7
Kankyo	30	17.7 ± 6.4
	100	26.3 ± 8.9
	300	16.6 ± 6.7
Shokyo	30	34.6 ± 8.8
	100	33.9 ± 6.6
	300	40.8 ± 4.7*
Metoclopramide	3	65.5 ± 8.5***

Significantly different from the control at **p*<0.05 and ****p*<0.001, respectively. *n*=8.

function and is useful in improving or preventing vomiting. This probably explains why Shokyo has been regarded as a major herb to be used to control vomiting.

Thus, to clarify which component of Shokyo stimulates gastric emptying, we attempted to identify active fractions that improve the delay of gastric emptying induced by BaCl₂. Significant activity was noted in the MeOH eluate (secondary fraction) originating from 50% MeOH eluate (primary fraction) in aqueous extract of Shokyo. We then examined the effects of 6-gingerol (4) and 6-shogaol (7) previously reported to suppress gastric motility,²⁰⁾ in comparison to three compounds (1—3) isolated as major components of

Table 4. Effects of Compounds **1**, **2**, **3**, **4** and **7** on BaCl₂-Induced Delay of Gastric Emptying in Rat

Samples	Dose (mg/kg)	Mean±S.E.
Normal		71.1±2.7***
Control (+BaCl ₂)		20.8±3.9
1	1	43.6±4.7***
	3	49.7±5.2***
2	1	30.5±3.8
	3	26.6±6.2
3	1	41.7±3.8**
	3	53.1±4.1***
4	1	16.3±4.0
	3	15.3±2.8
7	1	19.0±3.9
	3	22.8±6.0
Metoclopramide	3	63.3±5.2***

Significantly different from the control at ** $p<0.01$ and *** $p<0.001$, respectively. $n=8$.

Table 5. Effects of Compounds **1** and **3** on L-NNA-Induced Delay of Gastric Emptying in Rat

Samples	Dose (mg/kg)	Mean±S.E.
Normal		76.9±4.2***
Control (+L-NNA)		51.4±4.5
1	0.3	61.0±2.7
	1	69.8±4.9***
	3	73.3±3.4***
3	0.3	62.8±4.2*
	1	77.6±2.2**
	3	80.0±3.6***
Metoclopramide	3	84.3±3.2***

Significantly different from the control at * $p<0.05$ and *** $p<0.001$, respectively. $n=8-10$.

this active fraction. We thus found significant stimulation of gastric emptying by 6-gingesulfonic acid (**1**) and shogasulfonic acid A (**3**). Both 6-gingesulfonic acid (**1**) and shogasulfonic acid A (**3**), which were found to stimulate gastric emptying, have a sulfonyl group. We confirmed that neither 6-gingerol (**4**) nor 6-shogaol (**7**) improves the delay of gastric emptying induced by BaCl₂ (Table 4).

6-Gingesulfonic acid (**1**) and shogasulfonic acid A (**3**) significantly improved gastric emptying also in an experiment using a model of L-NNA induced delay of gastric emptying^{21,22)} (a model involving NO-mediated disturbance of the nervous system), as shown in Table 5. Furthermore, both compounds **1** and **3** significantly enhanced gastric emptying in normal condition, as is the case with the Shokyo-treated group (Table 6). 6-Gingesulfonic acid (**1**) is reported to have anti-ulcer effect⁵⁾ and seems to have physiological activity that has organic and functional effects on the stomach.

Fate of Gastric Emptying Stimulators Following Heat Treatment Following the finding that only Shokyo significantly stimulated gastric emptying, we examined the fate of Shokyo's active components (**1**, **3**) and the effects of the heat treatment products on gastric emptying. Kano *et al.*²³⁾ reported that 6-gingerol (**4**) is converted into 6-shogaol (**7**) when Kankyo is prepared. We have also obtained a similar finding in our evaluation at a commercial production level.²⁴⁾ Structurally, 6-gingesulfonic acid (**1**) can be deemed as a compound yielded by replacement of the hydroxyl group of 6-gingerol (**4**) with the sulfonyl group. We therefore examined

Table 6. Effects of Shokyo and Its Compounds on Gastric Emptying in Rat

Samples	Dose (mg/kg)	Mean±S.E.
Control		64.8±2.6
Shokyo	100	73.8±3.4*
1	1	74.4±3.1*
	3	78.4±3.7**
3	1	63.7±4.6
	3	76.1±3.7*
Gingerenone A	1	66.4±4.7
	3	57.8±2.4
Metoclopramide	3	86.1±2.5***
Control		61.9±4.1
Shokyo (L)	100	58.5±3.2
Shokyo (H)	100	68.7±3.7**

Significantly different from the control at * $p<0.05$, ** $p<0.01$ and *** $p<0.001$, respectively. $n=8$.

chemical conversion of 6-gingesulfonic acid (**1**) into 6-shogaol (**7**) caused by heat treatment. HPLC analysis revealed that heat treatment and perfusion of aqueous solution of 6-gingesulfonic acid (**1**) resulted in a progressive decrease of 6-gingesulfonic acid (decrease by 1.3% at 2 h, 5.2% at 4 h, 7.4% at 6 h, 10.0% at 8 h, 12.7% at 10 h and 15.3% at 12 h), accompanied by progressive formation of 6-shogaol (**7**).

Similar heat treatment was conducted of shogasulfonic acid A (**3**) to examine its chemical conversion. This revealed a progressive decrease of shogasulfonic acid A (**3**) and formation of gingerone A which is equivalent to desulfonylation product of this compound. The decrease in shogasulfonic acid A (**3**), as measured in the reaction system, was 2.8% at 2 h, 5.5% at 4 h, 8.3% at 6 h, 9.9% at 8 h, 12.6% at 10 h and 14.6% at 12 h. As stated above, 6-shogaol (**7**) does not improve gastric emptying. We examined the effects of gingerone A, another compound yielded from heat treatment. Gingerone A did not affect gastric emptying at a dose level equal to that of pre-conversion compound, *i.e.*, shogasulfonic acid A (**3**), as shown in Table 6. Thus, 6-gingesulfonic acid (**1**) and shogasulfonic acid A (**3**), which are involved in the Shokyo's effect in stimulating gastric emptying, were partially converted by heat treatment into compounds that do not affect gastric emptying. This finding provides evidence supporting the results that Kankyo did not stimulate gastric emptying.

Components Affecting the Quality of Shokyo To clarify the possibility of using 6-gingesulfonic acid (**1**) and shogasulfonic acid A (**3**) as components determining the quality of Shokyo used for stimulation of gastric emptying, we evaluated the effects of Shokyo products, selected on the basis of above-mentioned data, on gastric emptying. First, 17 commercially available Shokyo products were subjected to quantification using 6-gingesulfonic acid (**1**) and shogasulfonic acid A (**3**) as indicators. One sample (L) was found to contain both compounds in only trace amounts (below 0.001%), while the remaining 16 products contained more 6-gingesulfonic acid (**1**) (0.015–0.041%; mean=0.025%) and shogasulfonic acid A (**3**) (0.004–0.012%; mean=0.007%).

The effects on gastric emptying were compared between the sample containing the largest amounts of both compounds (sample H, containing 0.041% of compound **1** and 0.010% of compound **3**) and sample L. Significant stimulation of gastric emptying was effected only by sample H

Fig. 1. Effects of Kankyo (150 mg/kg) and Shokyo (150 mg/kg) on Intestinal Blood Flow (IBF) in Normal Rat

Percent change in IBF from basal was calculated every 30 min after administration of the test drugs. Data are mean $\pm$ S.E.M. Significantly different from the control (Water) at * $p < 0.05$ and ** $p < 0.01$, respectively. $n = 7$.

(Table 6). These results suggest that compounds **1** and **3** are quality-determining components of Shokyo.

Effects on Intestinal Blood Flow Our previous study of the effects of Dai-kenchu-to (大建中湯) on intestinal blood flow revealed that it significantly increases intestinal blood flow at doses not affecting blood pressure or heart rate, and that this effect is primarily attributable to the ingredient Kankyo and involves Kankyo's vasodilative action mediated by CGRP (calcitonin gene-related peptide).¹³⁾ We identified 6-shogaol (**7**) as an active component of Kankyo and reported that 6-gingerol (**4**) has no such effect.¹³⁾

In the present study, we also compared the effects on intestinal blood flow between Shokyo and Kankyo. This study revealed that Shokyo increases intestinal blood flow although temporarily, and that Kankyo exerts this action more potently and for prolonged periods of time (Fig. 1). This difference between Shokyo and Kankyo is probably because chemical conversion of 6-gingerol (**4**) into 6-shogaol (**7**) during the course of manufacturing Kankyo preparations elevates the concentration of 6-shogaol (**7**) in the Kankyo preparation. The observed effect of Kankyo in increasing intestinal blood flow supported the empirical knowledge that Kankyo warms the abdomen.

CONCLUSIONS

We attempted to scientifically distinguish between Shokyo and Kankyo and obtained the following findings concerning the pharmacological action of these herbs on the digestive system. Shokyo was found to elevate gastric motility and to be useful in reducing and preventing dyspepsia and vomiting. Kankyo was found to have marked effects on the intestine and seemed to alleviate intestinal dysfunction. Thus, Shokyo and Kankyo, both of which originate from ginger, were found to have different pharmacological features due to the difference in the method of processing. We are greatly impressed by the wisdom of our predecessors who distinguished between them when used for herbal medicine. It also

seems significant that the present study demonstrated part of pharmacological and chemical characterization of Shokyo and Kankyo.

Since the methods used for preparing Shokyo and Kankyo are selected at the discretion of their manufacturers, we cannot rule out that poor quality preparations of these herbs are on the market. It is therefore essential to evaluate the properties of individual products before reaching conclusions concerning Shokyo and Kankyo.

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REFERENCES

- 1) Yamahara J., Rong H. Q., Naitoh Y., Kitani T., Fujimura H., *J. Ethnopharmacology*, **27**, 353–355 (1989).
- 2) Kawai T., Kinoshita K., Koyama K., Takahashi K., *Planta Med.*, **60**, 17–20 (1994).
- 3) Sharma S. S., Kochupillai V., Gupta S. K., Seth S. D., Gupta Y. K., *J. Ethnopharmacology*, **57**, 93–96 (1997).
- 4) Yamahara J., Mochizuki M., Rong H. Q., Matsuda H., Fujimura H., *J. Ethnopharmacology*, **23**, 299–304 (1988).
- 5) Yoshikawa M., Hatakeyama S., Taniguchi K., Matsuda H., Yamahara J., *Chem. Pharm. Bull.*, **40**, 2239–2241 (1992).
- 6) Yamahara J., Rong H. Q., Iwamoto M., Kobayashi G., Matsuda H., Fujimura H., *Phytother. Res.*, **3**, 70–71 (1989).
- 7) Huang Q., Iwamoto M., Aoki S., Tanaka N., Tajima K., Yamahara J., Takahashi Y., Yoshida M., Tomimatsu T., Tamai Y., *Chem. Pharm. Bull.*, **39**, 397–399 (1991).
- 8) Yamahara J., Huang Q., Li Y., Xu L., Fujimura H., *Chem. Pharm. Bull.*, **38**, 430–431 (1990).
- 9) Huang Q., Matsuda H., Sakai K., Yamahara J., Tamai Y., *Yakugaku Zasshi*, **110**, 936–942 (1990).
- 10) Kase Y., Saitoh K., Makino B., Hashimoto K., Ishige A., Komatsu Y., *Phytother. Res.*, **13**, 468–473 (1999).
- 11) Beubler E., Kollar G., Saria A., Bukhave K., Madsen J. R., *Gastroenterology*, **96**, 368–376 (1989).
- 12) Yokochi E., Kouno S., Oohata K., *Nippon Yakurigaku Zasshi*, **92**, 297–310 (1998).
- 13) Murata P., Kase Y., Ishige A., Sasaki H., Kurosawa S., Nakamura T., *Life Sciences*, **70**, 2061–2070 (2002).
- 14) Hashimoto K., Yanagisawa T., Okui Y., Ikeya Y., Maruno M., Fujita T., *Planta Med.*, **60**, 124–127 (1994).
- 15) Yoshikawa M., Yamaguchi S., Kunimi K., Matsuda H., Okuno Y., Yamahara J., Murakami N., *Chem. Pharm. Bull.*, **42**, 1226–1230 (1994).
- 16) Shoji N., Iwasa A., Takemoto T., Ishida Y., Ohizumi Y., *J. Pharm. Sci.*, **71**, 1174–1175 (1982).
- 17) Kiuchi F., Iwakami S., Shibuya M., Hanaoka F., Sankawa U., *Chem. Pharm. Bull.*, **40**, 387–391 (1992).
- 18) Hatanaka M., Himeda Y., Imashiro R., Tanaka Y., Ueda I., *J. Org. Chem.*, **59**, 111–119 (1994).
- 19) Hori Y., Miura T., Wakabayashi Y., Fujii M., Hirai Y., Nemoto Y., Toriizuka K., Ida Y., 122th Nihon Yakugakkai (Makuhari), 26[P] II-118, March 26, 2002.
- 20) Aburada M., *Gendai Toyo Igaku*, **8**, 45–50 (1987).
- 21) Anvari M., Raterson C. A., Daniel E. E., *Digestive Diseases and Sciences*, **43**, 506–512 (1998).
- 22) Mashimo H., Kjellin A., Goyal R. K., *Gastroenterology*, **119**, 766–773 (2000).
- 23) Kano Y., Saito K., Sakurai T., Kanemaki S., Tanabe M., Yasuda M., *Shoyakugaku Zasshi*, **40**, 333–339 (1986).
- 24) Hashimoto K., *Shoyaku-ni-kansuru-kondankai*, 14th, 15–23, 1998.