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Antispasmodic Activity of SJ-200 (Himcospaz): An Herbal Preparation

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Abstract

SJ-200 (Himcospaz), an herbal preparation, was investigated for antispasmodic activity on gastrointestinal smooth muscles of guinea pig, rats, rabbits and mice. SJ-200 dose-dependently inhibited acetylcholine, histamine and barium chloride-induced contraction of guinea pig ileum. It inhibited spontaneous contraction of rabbit and rat colon. Oxytocin-induced contraction of rat uterus was also inhibited. Oral administration of SJ-200 dose-dependently reduced gastric emptying in rats and intestinal transit in mice. All these findings suggest the non-specific antispasmodic activity of SJ-200 in experimental models.

Keywords: Antispasmodic, gastric emptying, intestinal transit, irritable bowel syndrome, SJ-200, Himcospaz.

Introduction

Functional gastrointestinal disorders (FGID) affect millions of people from all age groups (Loe et al., 1999). Irritable bowel syndrome (IBS), dyspepsia and inflammatory bowel disease (IBD) are the most common disorders of FGID. The symptoms of FGID can cause discomfort, ranging from inconvenience to deep personal distress (Koloski et al., 2000). Unfortunately no single drug has proven to be effective in treating FGID. In addition, the search for a truly effective and safe drug to control motility disturbances in FGID continues (Scapignato & Pelosini, 1999).

Ayurveda, an Indian system of medicine, cited several plants, which are useful against various gastrointestinal disorders without any side effects. SJ-200 (Himcospaz), a herbal preparation, contains *Zingiber officinale* Roscoe, Zingiberaceae (rhizome), *Apium graveolens* L., Apiaceae (fruit) and *Foeniculum vulgare* Mill., Apiaceae (fruit). All these plants have been used to treat various gastrointestinal disorders like abdominal pain, flatulence and colic (Satyavathi, 1976; Nadkarni, 1982; Vavier, 1996).

In the present study we have investigated the effect of SJ-200 on various smooth muscles *in vitro*, gastric emptying rate and intestinal transit rate *in vivo*.

Materials and methods

Plant materials

Apium graveolens, Foeniculum vulgare and *Zingiber officinale* were procured from a local supplier and identified by Dr. Kannan, Botanist, The Himalaya Drug Company, Bangalore. Samples were retained for reference purpose at the R & D herbarium.

Drugs

The drugs acetylcholine chloride (Ach) and histamine dihydrochloride were from Sigma Chemical Co., St. Louis. MO. Oxytocin was from Rathi Laboratories (Hindustan Pvt. Ltd., Patna, India). All other chemicals were purchased from Loba Chemie, Mumbai, India.

Preparation of physiological solutions

Tyrode solution composition (mM): NaCl, 137; KCl, 2.7; $CaCl_2$, 1.8; NaH_2PO_4, 0.4; $MgSO_4$ 0.25; $NaHCO_3$, 11.9; glucose, 11.1 de Jalon solution composition (mM): NaCl, 154; KCl, 5.6; $CaCl_2$, 0.55; $NaHCO_3$, 6.0; glucose 2.78.

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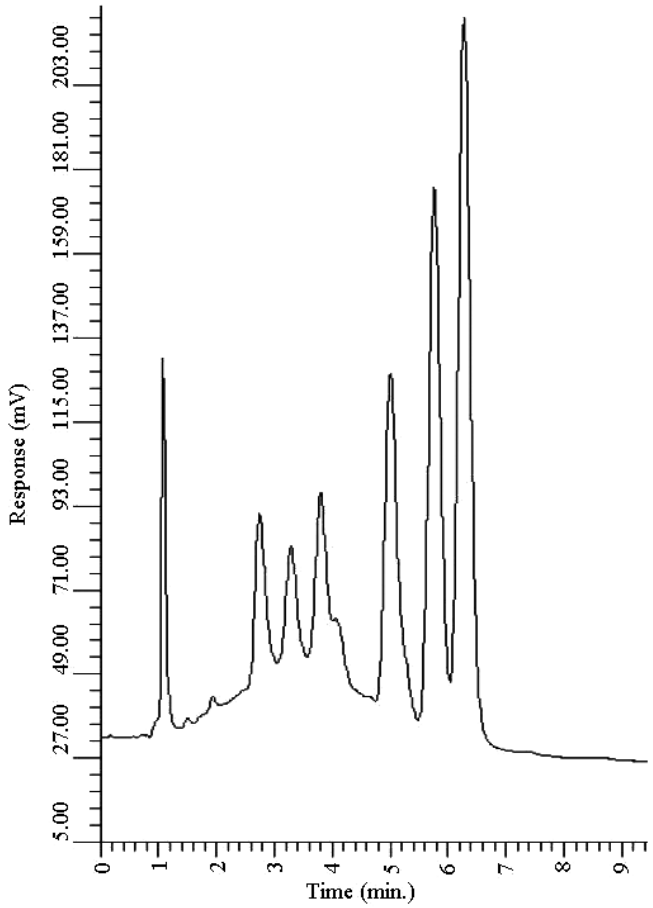

Figure 1. Gas chromatogram of SJ-200.

Preparation and standardization of SJ-200

Dried and powdered materials of *Zingiber officinale, Apium graveolens* and *Foeniculum vulgare* in the ratio of 1 : 1 : 1 were mixed and 100 g of powder was refluxed with 500 ml chloroform at 70 °C for 6 h. After filtration the chloroform was evaporated in a vacuum evaporator. The extract thus obtained was taken for the standardization and pharmacological studies. The yield of the extract was 10% of total dried material.

Ten microlitres of 1% v/v solution of SJ-200 in chloroform was injected into a 20 M stainless-steel column filled with 10% carbowax. Nitrogen was used as the carrier gas at 30 ml per min and a flame ionization detector was used. The temperature of the oven, injector and detector were 220, 230 and 250 °C, respectively. The chromatogram was recorded with the help of Aimil chromatography data station. A fingerprint chromatogram of SJ-200 is presented in Figure 1.

Experimental animals

Swiss albino mice, albino rats (Wistar strain), New Zealand white rabbits and guinea pigs were housed in an air-conditioned area at 25 ± 2 °C with 12 : 12 h light and dark cycle. They were maintained on synthetic pelleted feed (Lipton India Ltd., Mumbai, India) and water *ad libitum*.

Animals for organ bath studies

Male and female Wistar rats (160–200 g b.wt.) and male guinea pig (300–350 g b.wt.) after 24 h fasting were killed by stunning and bleeding. Ileum, colon or uterus were removed and suspended under a constant tension of 1 g in 15 ml organ baths containing Tyrode at 37 °C (Ulrike et al., 1997; Parry et al.,1996). Before the experimental procedures the organs were allowed a 30–40 min equilibration period with changes of medium at every 5 min. SJ-200 was dissolved in 0.5% DMSO. 200 µl diluted SJ-200 was used as the maximum volume in the baths, at which volume there was no solvent effect. During the experimental phase SJ-200 was added to the bath and after 1 min incubation period the agonist was added. Contractions were recorded using an isotonic transducer connected to a polyrite (Model 201, Recorders and Medicare, India).

Isolated rat colon and uterus

A portion (2.5 cm) of colon (n = 6) was washed and suspended in aerated tyrode solution at 37 °C. The uterus (n = 6) from an estradiol-treated female rat (10 µg/kg s.c. 48 h before experiment) was isolated and suspended in de Jalon solution (Blazquez et al., 1995).

Isolated guinea pig ileum and rabbit colon

A portion of 2.5 cm guinea pig ileum (n = 6) and rabbit colon (n = 3) was suspended in aerated Tyrode solution at 37 °C.

Effect of drugs

Dose-response curves or isolated concentrations were performed with Ach (10^{-8}–10^{-4} M), Oxytocin (2 mIU/ml) histamine 10^{-8}–10^{-4} M and barium chloride (10^{-3}–10^{-1} M) in the presence or absence of SJ-200. The effect of SJ-200 on normal motility of rat and rabbit colon was evaluated without agonists.

Effect of SJ-200 on gastric transit rate in rats

Wistar strain rats of either sex weighing between 180–200 b.wt. were used for the study. Twenty-four overnight fasted rats were divided into 4 groups of 6 each. Group I served as control and received vehicle alone. Group II, III and IV received SJ-200 at a dose of 50, 100 and 200 mg/kg p.o. in 0.5% DMSO. After 30 min all the rats received 1.5 ml of test meal/animal, which contains 50 mg of phenol red in 100 ml of 1.5% w/v aqueous methylcellulose. Twenty minutes after administration of the test meal, the rats were euthanised under ether anesthesia. The stomach was dissected out by opening the abdominal cavity after clamping the cardiac and

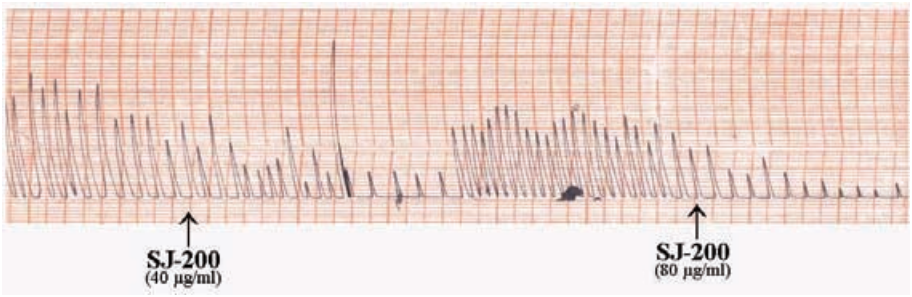

Figure 2. Effect of SJ-200 on normal motility of rat colon.

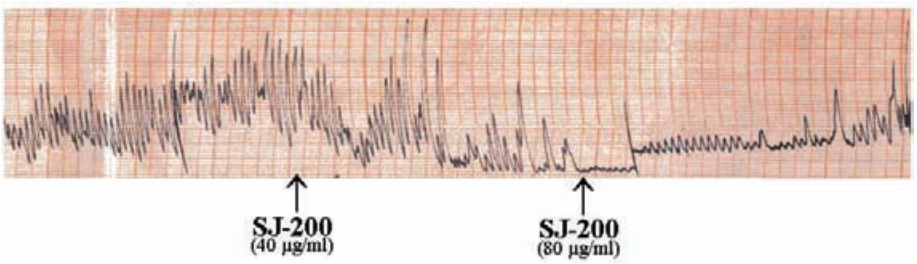

Figure 3. Effect of SJ-200 on normal motility of rabbit colon.

pyloric ends. The stomach was rinsed in physiological saline and placed into 100 ml 0.1 NaOH and cut into small pieces and then homogenized. The homogenized suspension was allowed to settle for 60 min at room temperature. Five milliliter of supernatant was pipetted out into a test tube to which 0.5 ml of 20% w/v trichloroacetic acid (TCA) was then added and centrifuged at 2800 rpm for 20 min. To the supernatant, 4 ml of 0.5 N NaOH was added and absorbance was measured spectrophotometrically at 560 nm. For the standard concentration, phenol red recovered from the stomach of rats sacrificed immediately following oral administration was considered (Tache et al., 1987).

Effect of SJ-200 in intestinal transit time in mice

Twenty-four Swiss albino mice weighing 25–28 g were fasted overnight and divided into four groups of 6 each. Group I served as control, which received vehicle alone. Group II, III and IV received SJ-200 at a dose of 50, 100 and 200 mg/kg p.o. in 0.5% DMSO. After 30 min all the mice received charcoal meal (1.0% charcoal in 1.5% tragacanth) at a dose of 0.1 ml/animal. Twenty minutes after administration of the charcoal meal, the intestine was removed. The total length of the intestine, from duodenal end to the cecum, and the distance travelled by the charcoal were recorded and the percentage of charcoal movement was calculated (Hamada et al., 1999).

Statistical analysis

Data were expressed as Mean ± SEM. Significance was assessed by Student's *t*-test or ANOVA followed by Dunnet's test. The minimum level of significance was fixed at $p < 0.05$.

Results

Effect of SJ-200 on spontaneous motility of rat and rabbit colon

SJ-200 at a concentration of 40–80 µg/ml dose-dependently inhibited spontaneous contraction of rat and rabbit colon. A dose of 80 µg/ml of bath concentration completely blocked spontaneous contraction (Figs. 2 and 3).

Effect of SJ-200 on agonist-induced contraction

Acetylcholine and histamine (10^{-8}–10^{-4} M) induced dose-dependent contraction of guinea pig ileum. Exposure (60 sec) of the ileum to SJ-200 (40–80 µg/ml) reduced the contractile response of acetylcholine and histamine (10^{-4} M) in a dose-dependent manner (Fig. 4). SJ-200 at a dose of 80 µg/ml almost completely blocked the barium chloride-induced contraction of guinea pig ileum (Fig. 5). The incubation of the isolated rat uterus with SJ-200 (80 µg/ml) resulted in significant inhibition of the oxytocin-induced contractile response (Fig. 6).

Effect of SJ-200 on gastric emptying rate (GER) and intestinal transit time (ITT)

SJ-200 (50–200 mg/kg b.wt) dose-dependently reduced gastric emptying and intestinal transit in rat and mice respectively. The effects on both parameters were signifi-

cant at a dose of 100 and 200 mg/kg b. wt. p.o. of SJ-200 (Fig. 7).

Discussion

The present study shows that SJ-200 reduces spontaneous motility of rat and rabbit colon. The absence of contractile activity of the drug itself on various smooth muscle preparations shows the lack of agonistic activity on muscaranic, histaminergic and oxytocin receptors. The results obtained on isolated smooth muscle show the inhibition of histamine, acetylcholine, oxytocin and barium chloride-induced contractions.

Binding of Ach to muscarinic receptors or histamine to H_1 receptor in smooth muscles results in opening of receptor operated channels, thereby allowing sodium influx, which causes a depolarization of the cell membrane. This depolarization opens voltage dependent calcium channels and calcium ions enter the cell to induce the release of calcium from the sarcoplasmic reticulum. The cytosolic calcium thus binds to calmodulin, which results in contraction (Balton, 1979; Rojas et al., 1996).

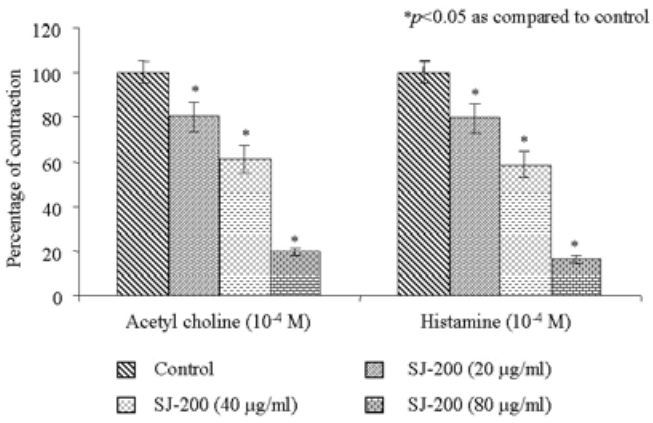

Figure 4. Effect of SJ-200 on acetylcholine- and histamine-induced contractions of guinea pig ileum.

Since these spasmogens have different modes of action, the antagonism elicited by SJ-200 indicates that it might be acting at a common step in the contraction mechanism elicited by these agonists. The antagonism displayed was concentration dependent. Since acetylcholine, histamine, oxytocin and barium chloride effects were altered by the SJ-200, it seems to be non-specific antagonism. Earlier research works on the extracts of individual ingredients of *Zingiber officinale, Apium graveolens* and *Foeniculum vulgare* were credited for their antispasmodic activity. *Zingiber officinale* is proven to be effective in inhibiting the gastric and intestinal motility in mice and also found to inhibit the colonic motility in rats (Tulimat et al., 2001; Wu et al., 1994). The spasmolytic activity of *Zingiber officinale* could be attributed to gingerol, an active constituent that was found to inhibit prostaglandin biosynthesis and serotonergic activity (Harborne et al., 1999). Apigenin, an active constituent of *Apium graveolens*, was reported to inhibit norepinephrine-induced contractions of rat aortic preparations in a dose-dependent manner (Ko et al., 1991). The essential oils of *Foeniculum vulgare* are reported to exhibit an antispasmodic effect in rat uterus preparation. (Ostad et al., 2001; Neuhas-Carlisle et al., 1993; Forster et al., 1980). The combination of these active constituents could be responsible for the observed antispasmodic effect of SJ-200.

Irritable bowel syndrome is the most common functional disorder, which is characterized by a combination of abdominal pain and altered bowel function affecting primarily the mid and lower gut (Vasllo et al., 1992). As a consequence, drugs affecting gastrointestinal motility have been widely

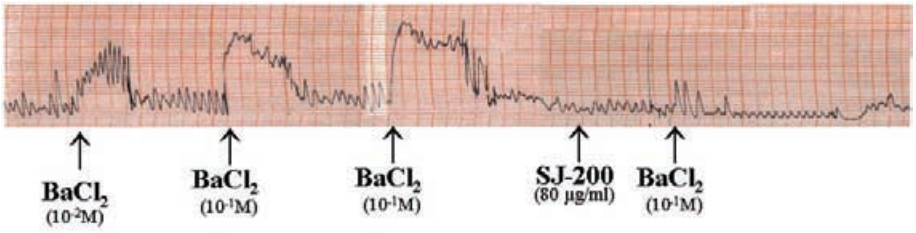

Figure 5. Effect of SJ-200 on barium chloride ($BaCl_2$)-induced contractions of guinea pig ileum.

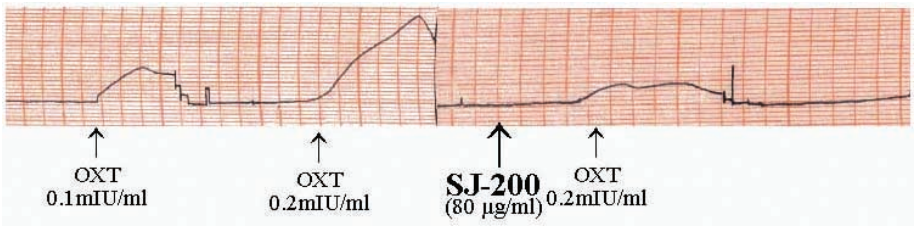

Figure 6. Effect of SJ-200 on oxytocin (OXT)-induced contractions of rat uterus.

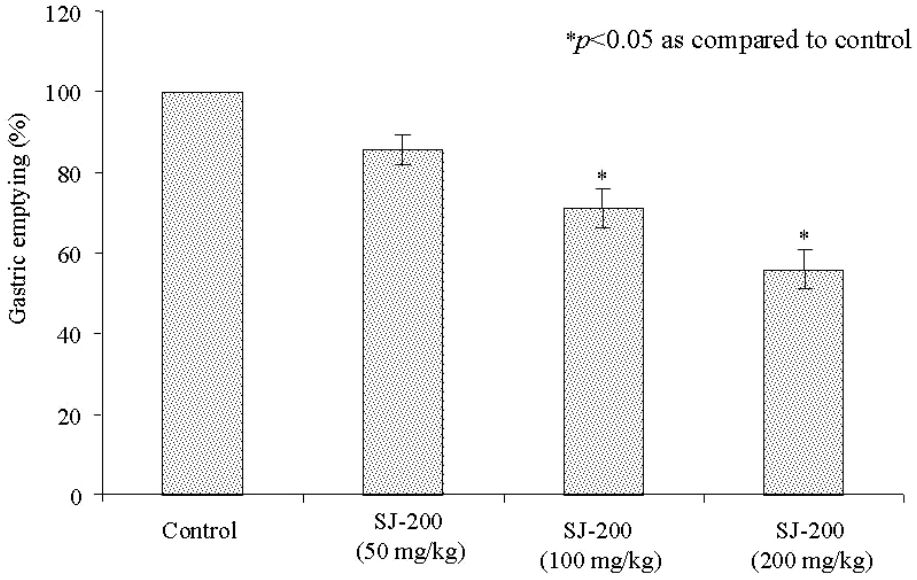

Figure 7. Effect of SJ-200 on gastric emptying in rats.

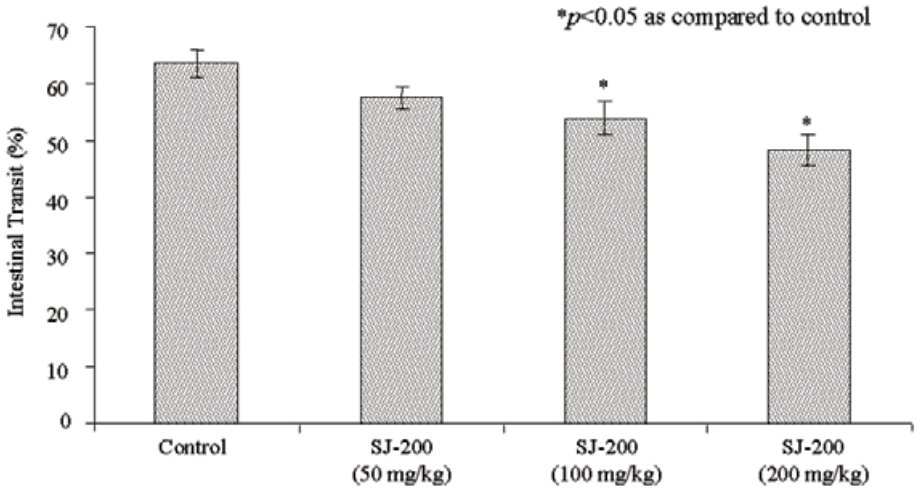

Figure 8. Effect of SJ-200 on intestinal transit in mice.

employed with the aim of correcting the major IBS manifestation, i.e., pain and altered bowel function (Scapignato & Pelosini, 1999). The present study reveals that SJ-200 dose-dependently decreased gastric emptying and intestinal transit, which indicates inhibition of gastrointestinal motility *in vivo*. The *in vivo* observations also correlated with *in vitro* studies. All these findings suggest that SJ-200 has non-specific antispasmodic activity, which can be used in the treatment of various non-specific spasm disorders.

References

Balton T (1979): Mechanism of action of transmitters and other substances on smooth muscle. *Physiological Rev 59*: 649–677.

Blazquez MA, Catret M, Zafra-Polo MC (1995): Effect on rat uterine and aorta strip smooth muscle of *Thymus leptophyllus* extract. *J Ethnopharmacol 45*: 59–66.

Forster HB, Nikias H, Lutz S (1980): Antispasmodic effects of some medicinal plants. *Planta Med 40*: 309–319.

Hamada S, Kawane T, Akeno N, Igarshi H, Horiuchi N (1999): Regulation of small intestinal transit by central nervous calcitonin receptors. *Horm Metab Res 31*: 499–504.

Harborne JB, Baxter H, Moss GP (1999): *Phytochemical dictionary–A handbook of bioactive compounds from plants*, 2nd Edition, Taylor & Francis Ltd, London, p. 528.

Ko FN, Huang TF, Teng CM (1991): Vasodilatory action mechanisms of apigenin isolated from *Apium graveolens* in rat thoracic aorta. *Biochim Biophys Acta 1115*: 69–74.

Koloski NA, Talley NJ, Boyce PM (2000): The impact of functional gastrointestinal disorders on quality of life. *Am J Gastroenterol 95*: 67–71.

Loe OY, Schamulson M, Mayer EA (1999): Common functional gastrointestinal disorders nonulcer dyspepsia and irritable bowel syndrome. *Clin Cornerstone 1*: 57–71.

Nadkarni KM (1982): Indian Materia Medica, Vol.1, 3rd Edition, Popular Prakashan, Mumbai, India, p. 558.

Neuhaus-Carlisle K, Vierling W, Wagner H (1993): Calcium-channel blocking activity of essential oils from *Petroselinum crisp*., *Apium graveolens* and isolated phenylpropane constituents. *Pharm Pharmacol Lett 33*: 77–79.

Ostad. SN, Soodi M, Shariffzadeh M, Khorshidi N, Marzban H (2001): The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea, pharmacology and toxicology study. *J Ethnopharmacol 76*: 299–304.

Parry O, Duri ZJ, Zinyama E (1996): The effect of *Heteromorpha trifoliata* on gastrointestinal smooth muscle of the guinea pig. *J Ethnopharmacol 54*: 13–17.

Rojas A, Cruz S, Ponce-Monter H, Mata R (1996): Smooth muscle relaxing compounds from *Dodenaea Viscosa*. *Planta Med 62*: 154–159.

Satyavathi GV (1976): *Medicinal Plants of India*, Vol. 1. Indian Council of Medical Research, New Delhi, p. 80.

Scarpignato G, Pelosini I (1999): Management of irritable bowel syndrome; novel approaches to the pharmacology of gut motility. *Can J Gastroenterol 13(Supp A)*: 50A–65A.

Tache Y, Hagiwara M, Turkelson CM (1987): Central nervous system action of corticotropin releasing factor to inhibit gastric emptying in rats. *Am J Physiol 253*: 241–245.

Tulimat MA, Ishiguchi T, Kurosawa S, Nakamura T, Takahashi T (2001): The inhibitory effect of herbal medicine Dai Kenchu To (DKT) on the colonic motility in rats in vitro. *Am J Chi Med 29*: 111–118.

Seitz U, Ameri A, Pelzer H, Gleitz J, Peters T (1997): Relaxation of evoked contractile activity of isolated guinea pig ileum by (±) – kavain. *Planta Med 63*: 303–306.

Vasallo M, Camilleri M, Phillips SF, Brown ML, et al. (1992): Transit through the proximal colon influences stool weight in the irritable bowel syndrome. *Gastroenterol 102*: 102–108.

Vavier, P.S. (1996): Indian Medicinal Plants, In: Warrier PK, Nambiar VPK, Ramankutty C, eds., *Orient Longman*, Chennai, India. Vol. 5, p. 431.

Wu H, Cai BC, Rong GX, Ye DG (1994): The effect of *Pinellia* processed by the ginger juice on the gastric and intestinal function of animals. *Zhongguo Zhong Yao Za Zhi 19*: 535–537.