Effects of Lizhong Tang on gastrointestinal motility in mice

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Abstract

AIM
To investigate the effects of Lizhong Tang, a traditional Chinese medicine formula, on gastrointestinal motility in mice.

METHODS
The in vivo effects of Lizhong Tang on GI motility were investigated by measuring the intestinal transit rates (ITRs) and gastric emptying (GE) values in normal mice and in mice with experimentally induced GI motility dysfunction (GMD).

RESULTS
In normal ICR mice, the ITR and GE values were significantly and dose-dependently increased by Lizhong Tang (ITR values: 54.4% ± 1.9% vs 65.2% ± 1.8%, P < 0.01 with 0.1 g/kg Lizhong Tang and 54.4% ± 1.9% vs 83.8% ± 1.9%, P < 0.01 with 1 g/kg Lizhong Tang; GE values: 60.7% ± 1.9% vs 66.8% ± 2.1%, P < 0.05 with 0.1 g/kg Lizhong Tang and 60.7% ± 1.9% vs 72.5% ± 1.7%, P < 0.01 with 1 g/kg Lizhong Tang). The ITRs of the GMD mice were significantly reduced compared with those of the normal mice, which were significantly and dose-dependently reversed by Lizhong Tang. Additionally, in loperamide- and cisplatin-induced
models of GE delay, Lizhong Tang administration reversed the GE deficits.

**CONCLUSION**
These results suggest that Lizhong Tang may be a novel candidate for development as a prokinetic treatment for the GI tract.

**Key words:** Lizhong Tang; Gastrointestinal disorders; Motility; Intestinal transit rate; Gastric emptying

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Core tip: Lizhong Tang, a traditional Chinese medicinal formula, has been widely used in China, Japan, and South Korea for many years to ameliorate gastrointestinal (GI) disorders. Our data suggest that Lizhong Tang is a novel candidate for development as a prokinetic agent for treatment of GI motility dysfunctions in man.

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**INTRODUCTION**
Lizhong Tang, also known as Yijung-tang or Richu-tang, is a traditional Chinese medicine (TCM) formula[1] and is composed of Radix Ginseng (*Panax ginseng* C.A. Meyer), Rhizoma Zingiberis (*Zingiber officinale* Roscoe), Rhizoma Atractylodis Macropodae (*Atractylodes macrocephala* Koidz.), and Radix Glycyrrhizae (*Glycyrrhiza uralensis* Fisch)[2]. Lizhong Tang is widely used in traditional medicine to treat gastrointestinal (GI) disorders, such as vomiting, diarrhea, stomach pain, chronic gastritis, stomach bleeding, and GI ulceration, in China, Japan, and South Korea[1-3]. However, no studies have been conducted to evaluate the effect of Lizhong Tang on GI motility.

Prokinetic agents are medications that enhance coordinated GI motility and the transit of content in the GI tract mainly by amplifying and coordinating the GI muscular contractions. In addition, prokinetic therapy should be considered as a means to improve gastric emptying and symptoms of gastroparesis, balancing the benefits and risks of treatment[4]. Recently, prokinetic therapy has been shown to improve the symptoms and quality of life in patients with GI motility disorders[5]. Therefore, there has been an increasing need to develop safer and more effective gastroprokinetic agents.

In our previous report, we investigated the effects of Lizhong Tang on mouse small intestine interstitial cells of Cajal (ICC)[6]. These cells are the pacemaker cells of GI muscles and generate rhythmic oscillations in membrane potentials known as slow waves[7-9] by activating $\text{Ca}^{2+}$ entry through L-type $\text{Ca}^{2+}$ channels in smooth muscles to initiate GI contractions[10,11]. In this report, we found that Lizhong Tang affected GI motility by modulating pacemaker activity in ICC through internal $\text{Ca}^{2+}$- and phospholipase (PLC)-dependent pathways[6]. However, despite the widespread use of Lizhong Tang to treat GI disorders, little is known about its regulatory effects on GI motility. Therefore, we performed this study to investigate the effects of Lizhong Tang on the mouse GI tract *in vivo*.

**MATERIALS AND METHODS**

**Preparation of the standard solutions and sample extracts**
Liquiritin, 6-gingerol, ononin, glycyrrhizin, ginsenoside Rg1, isoliquiritin, and atracylenolide III were accurately weighed and dissolved in methanol (all at 100 μg/mL) to prepare standard solutions. Lizhong Tang powder was dissolved in the water and then filtered through a 0.2 μm syringe filter (BioFACT™, South Korea) prior to injection in the high performance liquid chromatography (HPLC).

**Chromatographic conditions**
An Agilent 1200 (Agilent Technologies, Palo Alto, CA, United States) equipped with an autosampler, degasser, quaternary solvent pump, and diode array detector (DAD) was used for the analysis. The data were acquired using ChemStation software (Agilent Technologies, Palo Alto, CA, United States). Separation was performed on a Capcell Pak Mg II C18 column (4.6 mm × 250 mm, 5 μm; Shiseido, Tokyo, Japan) at 35 °C. The mobile phase consisted of water containing 0.1% trifluoroacetic acid (A) and acetonitrile (B), and gradient elution was conducted as follows: 5% (B) for 0-1 min; 5%-10% (B) for 1-5 min and held for 5 min; 10%-15% (B) for 10-12 min and held for 4 min; 15%-20% (B) for 16-18 min and held for 4 min; 20%-23% (B) for 22-25 min and held for 6 min; 23%-28% (B) for 31-32 min and held for 8 min; and 28%-65% (B) for 40-80 min and held for 2 min. The column was then re-equilibrated using 5% (B) for the subsequent analyses. The flow rate was set at 1.0 mL/min, and the detection wavelengths were 205, 230, 250, 280, and 360 nm.

**Animals**
Male ICR mice (Samtako BioKorea Co., Ltd., Osan, South Korea) weighing 23-30 g were used to investigate the effects of the Lizhong Tang extract on the GI tract *in vivo*. The animals were maintained under controlled conditions (21 °C ± 3 °C, relative humidity 50% ± 6%, lights on 6 a.m.-6 p.m.). The mice were allowed free access to a commercial diet and tap water, but were fasted for 24 h before the
experiments. All experiments were conducted between 10 a.m. and 6 p.m.

**Measurement of intestinal transit rate using Evans blue staining**

We used Evans blue solution [5%, w/v, in distilled water (DW)] to determine the intestinal transit rates (ITR) of the Lizhong Tang extract in vivo. The Evans blue solution was administered (0.1 mL/kg of body weight; i.g.) through an orogastric tube 30 min after the Lizhong Tang extract was intragastrically (i.g.) administered to the normal ICR mice. The animals were sacrificed 30 min after Evans blue administration, and the intestinal transit distances of the dye were determined by measuring the distance the Evans blue dye had migrated in the intestine from the pylorus to its most distal point. Intestinal transit was quantified using the ITRs (%), which were calculated by expressing the distance the Evans blue dye traveled in 30 min as a percentage of the total small intestine length (from the pylorus to the ileal terminus).

**Induction of GI motility dysfunction in mice**

Two experimental GI motility dysfunction models were used: an acetic acid (AA)-induced peritoneal irritation mouse model and a STZ-induced diabetic mouse model. For the AA model, peritoneal irritation was induced by administering AA to ICR mice 30 min after the i.g. administration of the Lizhong Tang extract (or DW as vehicle) by intraperitoneally (i.p.) injecting 10 mL/kg AA (0.6%, w/v, in saline) as previously described[12-14]. After injecting AA, the mice were placed in individual cages and allowed to recover for 30 min. Male ICR mice (aged 5 wk) were used for the STZ-induced diabetic mouse model. The mice were randomly allocated to two groups: a control group or an STZ (Sigma-Aldrich, St. Louis, MO, United States) solution was administered i.p. on the following day to produce diabetes. Fresh STZ was prepared in 0.1 mol/L ice-cold citrate buffer (pH 4.0) and administered at 200 mg/kg body weight[15]. The control mice were i.p. administered the same volume of 0.1 mol/L citrate buffer. The animals had free access to food and water and were maintained under standard conditions (24-27 °C, RH 60%-65%) under a 12 h light/dark cycle. Two months after the STZ injection, blood was sampled from the mice and the intestinal transit distances of the dye were determined by measuring the distance the Evans blue dye migrated in the intestine from the pylorus to its most distal point. Intestinal transit was quantified using the ITRs (%), which were calculated by expressing the distance the Evans blue dye traveled in 30 min as a percentage of the total small intestine length (from the pylorus to the ileal terminus).

**Evaluation of gastric emptying**

As previously described by Scarpignato et al[16], the mice were fasted for 24 h with free access to water[14]. Gastric emptying (GE) was performed by administering a 0.05% (w/v) phenol red solution (0.5 mL/mouse) 30 min after treatment with the Lizhong Tang extract. Twenty min later, the mice were sacrificed and the stomachs were immediately removed, cut into several pieces, placed into 5 mL of 0.01 N NaOH, and homogenized. The homogenates were treated with 0.2 mL of 20% trichloroacetic acid per mL of homogenate. The mixtures were centrifuged for 10 min at 1050 × g, and the supernatants (0.05 mL) were added to 0.5 N NaOH (0.2 mL). The absorbances of these mixtures were measured using a spectrophotometer at 560 nm. The GE value (%) was calculated as 100-(A/B) × 100, where A is the test stomach absorbance (560 nm) and B is the control stomach absorbance (560 nm) immediately after phenol red administration.

**Drugs**

All drugs were purchased from Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, United States). In addition, an aqueous extract of the dried immature fruit of Poncirus trifoliate Raf. (PF) was prepared as previously described[17,18] and its prokinetic activities were compared with the Lizhong Tang extract. PF is one of the most popular traditional folk medicines used in South Korea and is obtained from Rutaceae fruits. PF has been shown to possess unique, potent prokinetic activities in normal rodents and rodents with GI motility dysfunction (GMD)[13,17].

**Statistical analysis**

The results are expressed as the means ± SE. Statistical analysis was performed using Student’s t test or analysis of variance followed by Tukey’s multiple comparison test, as appropriate. Statistical significance was accepted for P values < 0.05.

**RESULTS**

**Identification of standard compounds in the Lizhong Tang extract**

The following components of the Lizhong Tang extract were detected by HPLC using commercial standards (retention time): liquiritin (25.1 min); ononin (35.9 min); isoliquiritin (36.2 min); ginsenoside Rg1 (36.7 min); glycyrrhizin (58.2 min); 6-gingerol (63.0 min); and atractylenolide III (65.8 min) (Figure 1).

**Effects of the Lizhong Tang extract on ITR in normal mice**

After 30 min, the mean ITR (%) for Evans blue in normal mice was 54.4% ± 1.9% (Figure 2). PF (1 g/kg), which has been shown to have prokinetic activity in the GI tract[17,18], significantly accelerated the ITR [79.4% ± 2.3% (P < 0.01)], similar to the Lizhong Tang extract, which dose-dependently increased the ITR (%) [ITR values at 0.1, 0.01, and 1 g/kg were 56.1% ± 2.1%, 65.2% ± 1.8% (P < 0.01) and
Figure 1  Chromatograms of liquiritin, 6-gingerol, ononin, glycyrrhizin, ginsenoside Rg1, isoliquiritin, and atractylenolide III in Lizhong Tang extract.
Loperamide decreased the ITR (%), which is consistent with previous reports \[19\], and the Lizhong Tang extract inhibited this loperamide-induced decrease in ITR \[ITR value for loperamide was 56.1% ± 2.1%; and ITR value for loperamide with the Lizhong Tang extract was 65.2% ± 1.8% \[P < 0.01\]; Figure 2].

Effects of the Lizhong Tang extract on ITR in mice with GMD

We used the AA and STZ-induced diabetic mouse models of experimental GMD to examine the effect of the Lizhong Tang extract on GI motility. As mentioned above, the AA mouse model showed a significant retardation of ITR (%) \[23.2% ± 1.5% \[P < 0.01 \] vs normal]; Figure 3]. However, a significant inhibition of this retardation was observed when the mice were intragastrically administered 0.01, 0.1, or 1 g/kg of the Lizhong Tang extract \[25.3% ± 2.4%, 34.5% ± 2.1% \[P < 0.01 \] and 51.8% ± 5.7% \[P < 0.01 \], respectively; Figure 3]. No abnormal clinical signs or changes were observed in the AA mice after administration of the Lizhong Tang extract. In addition, loperamide decreased the ITR in the AA mice \[13.5% ± 2.4% \[P < 0.01 \], and the Lizhong Tang extract increased this value \[26.7% ± 2.1% \[P < 0.01 \]; Figure 3].

Furthermore, the STZ-induced diabetic mice also showed a significant ITR (%) retardation \[44.1% ± 3.5% \; Figure 4], which was also significantly inhibited by treatment with the Lizhong Tang extract at 0.01, 0.1 or 1 g/kg \[53.8% ± 1.5% \[P < 0.01 \], 57.7% ± 1.4% \[P < 0.01 \] and 71.5% ± 3.0% \[P < 0.01 \], respectively; Figure 4]. No abnormal clinical signs or changes were observed in the STZ-induced diabetic mice after the administration of the Lizhong Tang extract. In addition, loperamide decreased the ITR in the STZ-induced diabetic mice \[20.6% ± 1.8% \[P < 0.01 \], and the Lizhong Tang extract increased this value \[40.6% ± 2.2% \[P < 0.01 \]; Figure 4]. These results indicate that the Lizhong Tang extract increased the ITR in mice with GMD.

Effect of the Lizhong Tang extract on accelerating GE

In normal mice, the groups treated with the
Lizhong Tang extract (0.01, 0.1 and 1 g/kg) showed significantly enhanced GE (%) values compared to that of the normal group [the GE values with 0.01, 0.1 and 1 g/kg of the Lizhong Tang extract were 61.7% ± 1.6%, 66.8% ± 2.1% (P < 0.05) and 72.5% ± 1.7% (P < 0.01), respectively; Figure 5]. Its effects were dose-dependent in the dosage range from 0.01 g/kg to 1 g/kg, and 1 g/kg of the Lizhong Tang extract displayed effects similar to those of 5 mg/kg mosapride [74.4% ± 3.3% (P < 0.01)] and 5 mg/kg domperidone [72.9% ± 1.9% (P < 0.01)] (Figure 5). Next, we examined loperamide-induced and cisplatin-induced models of GE delay to determine whether the Lizhong Tang extract could increase GE in abnormally depressed GE models. In the loperamide-induced model of GE delay, the GE value was lower than normal [40.9% ± 1.6% (P < 0.01); Figure 6], and this decrease was recovered by treatment with the Lizhong Tang extract at doses from 0.01 to 1 g/kg [the GE values for the Lizhong Tang extract at 0.01, 0.1 and 1 g/kg were 41.8% ± 2.2%, 47.8% ± 1.2% (P < 0.01) and 59.4% ± 1.5% (P < 0.01), respectively; Figure 6]. The maximal effect was obtained at 1 g/kg, and at this dose, the effect of the Lizhong Tang extract was comparable to that of 5 mg/kg mosapride [61.4% ± 2.3% (P < 0.01)] or 5 mg/kg domperidone [61.5% ± 1.7% (P < 0.01)] (Figure 6). In addition, in the cisplatin-induced model of GE delay, the decreased GE was recovered by treatment with the Lizhong Tang extract (0.01, 0.1 and 1 g/kg) [GE values of the Lizhong Tang extract at 0.01, 0.1 and 1 g/kg were 31.7% ± 1.3%, 43.1% ± 2.1% (P < 0.01) and 60.8% ± 1.7% (P < 0.01), respectively; Figure 7]. The maximal effect was obtained at 1 g/kg, and at this level, the effect of the Lizhong Tang extract was comparable to that of 5 mg/kg mosapride [65.6%...
motility disorders and are regarded as one of the most efficacious therapeutics for this disorder. Cholinergic agonists, the original promotility agents, stimulated muscarinic M2-type receptors on the smooth muscle cells, but their effectiveness in motility disorders is inconsistent. Metoclopramide and domperidone, dopamine antagonists, have been the most widely used as prokinetic agents, but their long-term use has been complicated by a trend toward tolerance and a significant incidence of central nervous system (CNS) side effects. Cisapride was shown to promote esophageal peristalsis, augment lower esophageal sphincter pressure, and accelerate gastric emptying. However, the use of this drug is now restricted due to serious cardiac arrhythmias related to a prolonged QT interval. Mosapride, a selective 5-HT4 agonist, is available as a prokinetic agent in a number of Asian countries, but the efficacy data are contradictory. Itopride is a dopamine D2 antagonist with prokinetic effects that is devoid of CNS or cardiovascular side effects and causes minimal elevations of prolactin levels. In this study, we did not directly compare the GE and intestine motility rates with these prokinetics agents. However, in a previous study, we showed that Lizhong Tang depolarized the pacemaker potentials through G-protein-, PLC- and Ca2+-dependent pathways. Moreover, the nonselective cationic channel was involved in these effects. Therefore, we believe that Lizhong Tang might mimic the major excitatory neurotransmitters of the GI tract and act as a gastroprokinetic agent. Additionally, herbal products may be an attractive alternative based on the perception of their “natural” approach and their low risk of side effects. Therefore, we believe that Lizhong Tang may be a good gastroprokinetic agent, and in the future, we should compare the experimental results with those of known prokinetics and analyze the side effects.

In summary, in normal ICR mice, both the ITR and GE values were significantly and dose-dependently increased by treatment with the Lizhong Tang extract. Furthermore, the ITRs of GMD mice were significantly reduced compared with those of the normal mice, and these reductions were significantly and dose-dependently reversed by treatment with the Lizhong Tang extract. In addition, in the loperamide-induced and cisplatin-induced model of GE delay, the Lizhong Tang extract prevented the observed GE delays. Taken together, our results suggest that Lizhong Tang is a good candidate for the development of a gastroprokinetic agent.
has been widely used in China, Japan and South Korea for many years to ameliorate the symptoms of gastrointestinal (GI) disorders. However, despite the considerable use of Lizhong Tang in traditional medicine to treat GI dysfunction, little was known of its regulatory effects on GI motility in vivo.

**Research frontiers**

Lizhong Tang is a good candidate for development as a gastroprokinetic agent.

**Innovations and breakthroughs**

In normal ICR mice, both the ITRs and GE values were significantly and dose-dependently increased by treatment with Lizhong Tang (0.1-1 g/kg). The ITRs of the GDM mice were significantly reduced compared with those of the normal mice, and the values were significantly and dose-dependently reversed by treatment with Lizhong Tang (0.1-1 g/kg). Moreover, in loperamide-induced and cisplatin-induced models of GE delay, Lizhong Tang prevented the observed GE delays.

**Applications**

Lizhong Tang may be a new target or a novel candidate prokinetic agent for the pharmacological treatment of GI motility disorders.

**Peer-review**

This study is relevant, interesting, is written in suitable English, and have a correct methodological design. It is important to emphasize the contribution that this study provides for integration between western and eastern medicine, correct methodological design. It is important to emphasize the contribution that this study provides for integration between western and eastern medicine, which is fundamental to the advancement of modern science.

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