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ORIGINAL ARTICLE

Effects of the Japanese Kampo Medicine, Rikkunshito, on Gastrointestinal Motility Functions

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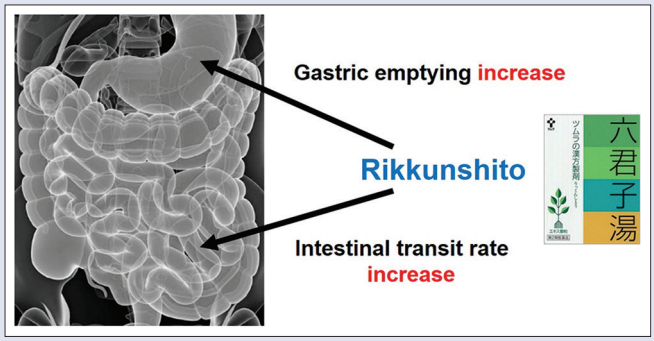
ABSTRACT

Background: Rikkunshito is known as a prokinetic agent for gastrointestinal (GI) diseases. **Objectives:** The objective was to find the effect of GI motility with Rikkunshito. **Materials and Methods:** The prokinetic effect of Rikkunshito was investigated by studying the gastric emptying (GE) and intestinal transit rate (ITR) or experimentally induced GI motility dysfunction (GMD). **Results:** The oral administration of Rikkunshito significantly increased GE and ITR and restored the delayed GE and ITR. Its effect was similar to that of conventional prokinetics, such as domperidone and mosapride. Moreover, we made the mouse GMD models, such as acetic acid or streptozotocin, and ITR had shown a great decrease. This decrease was recovered by Rikkunshito. **Conclusion:** Rikkunshito revealed its prokinetic effect through an increase of GE and ITR. We found a great possibility of Rikkunshito for the GI control drug.

Key words: Gastric emptying, gastrointestinal disease, intestinal transit rate, motility, rikkunshito

SUMMARY

- Rikkunshito is better gastric emptying (GE) (%) than standard [Figure 1a]. In case of loperamide or cisplatin, the GE was below normal [Figure 1b and c]
- Rikkunshito increased intestinal transit rate (ITR), and Rikkunshito recovered the loperamide responses in ITR [Figure 2]
- The acetic acid (AA) mouse model reduced the ITR. However, Rikkunshito increased the ITR. Loperamide decreased the ITR in case of AA and Rikkunshito reduced this decrease [Figure 3]
- Furthermore, loperamide reduced the ITR results in case of streptozotocin-induced ITR inhibition and Rikkunshito reduced this response [Figure 4].



Abbreviations used: GI: Gastrointestinal; GE: Gastric emptying; ITR: Intestinal transit rate; GMD: Gastrointestinal motility dysfunction; AA: Acetic acid; STZ: Streptozotocin.

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INTRODUCTION

Rikkunshito is a Japanese herbal medicine (Kampo medicine) and has been prescribed to treat various diseases or symptoms.[1] Rikkunshito is consisted of compounding eight herbal medicines.[2] Many studies have suggested the excellence of Rikkunshito in anorexia, gastric dysmotility, and gastrointestinal (GI) disorders.[3-5] Thus, Rikkunshito is widely known as a remedy for various GI disorders. Although Rikkunshito is known to alleviate GI diseases, its gastroprokinetic functions have rarely been investigated.

GI motility disorders can cause a tremendous impact on the patient and on the society as a whole.[6] Many people are suffering from discomfort in the stomach, intestines, or bowel movements. These disturbances impair the quality of life and result in a considerable increase in health-care costs.[7] In this study, we explored the effect of GI motility with Rikkunshito *in vivo* by studying gastric emptying (GE) and intestinal transit rate (ITR) in mice.

MATERIALS AND METHODS

Rikkunshito

Rikkunshito was purchased from Tsumura and Co. (Tokyo, Japan) and was prepared as described in a previous study.[8] Chromatographic preparation was in process on a high-performance liquid chromatography (HPLC) column.[8] Rikkunshito was dissolved in distilled water and mice were administered doses in the quantities of 0.01, 0.1, and 1 g/kg.

Evaluation of gastric emptying

Animal experiments have complied with the rules of the Animal Experiment Ethics Committee of Pusan National University (no. PNU-2018-1832). After 20-min phenol red solution administration, the stomachs cut the tissue into several pieces in sodium hydroxide NaOH. The pieces were centrifuged for 10 min at 1050 × g with NaOH. Absorbance and formula are the same as the existing method of research.[2]

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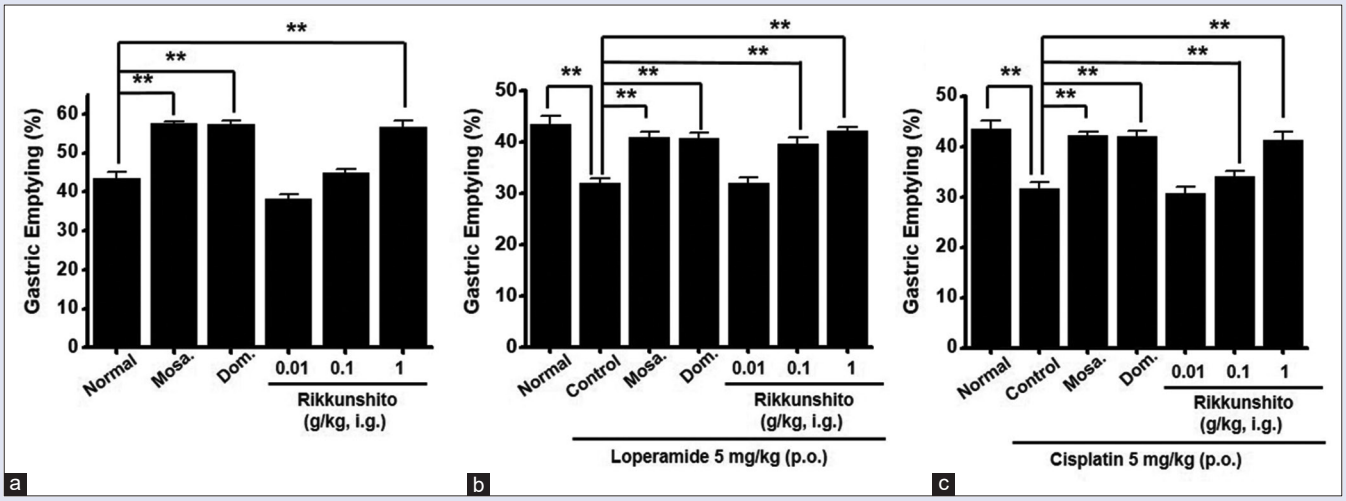

Figure 1: Effect of Rikkunshito on normal gastric emptying and on loperamide or cisplatin-induced gastric emptying (a) First, gastric emptying value was checked. To compare efficacy, we used a mosapride (5-HT4 receptor agonist) or a domperidone (dopamine receptor antagonist). (b and c) Loperamide or cisplatin-induced delay was suppressed by Rikkunshito. Bars represent mean ± standard error $^{**}P < 0.01$. CTRL: Control. Mosa.: Mosapride; Dom.: Domperidone. i.g.: Intragastric

Intestinal transit rate evaluation

After Rikkunshito administration, Evans blue was administered through the mouth. After 30 min, the animals were sacrificed and ITR was measured by Evans blue as the length past in the intestine. ITR has measured the length of the entire length as a percentage of the length that it had passed.

Gastrointestinal motility disease mice

With acetic acid (AA) and a streptozotocin (STZ), which shown peritoneal stimulation and diabetic, respectively, we made animal models. AA or STZ was injected intraperitoneally and the research process was carried out in the same way as the existing research method.[9,10] During this study, the animals did not die and the diabetic did not recover.

Drugs

All drugs were purchased in Sigma-Aldrich and *Poncirus trifoliata* Raf. (PF) with good GI motility was used to compare the efficacy of Rikkunshito.[10]

Statistical analysis

The results were represented as mean ± standard error of the mean. We analyzed the results with ANOVA and Prism 6.0 (La Jolla, CA, USA) programs. $P < 0.05$ was considered statistically important.

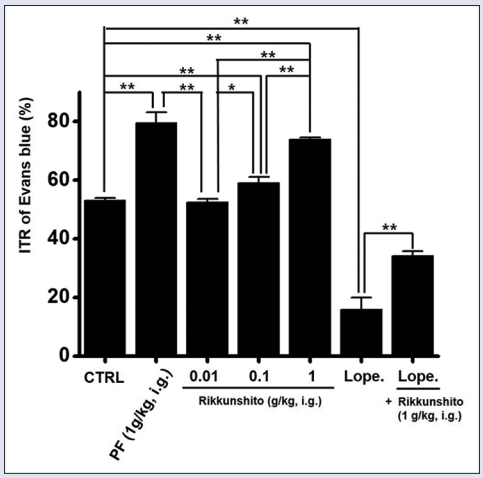

Figure 2: Effect of Rikkunshito on intestinal transit rates in normal mice. Rikkunshito increased intestinal transit rate (n = 8/bar). Bars represent mean ± standard error $^{*}P < 0.05$. $^{**}P < 0.01$. PF: *Poncirus trifoliate* Raf. Lope.: Loperamide

RESULTS

Rikkunshito components

The composition content in Rikkunshito was confirmed by HPLC and the degrees were also measured.[8]

Rikkunshito on gastric emptying in normal mice

Rikkunshito (0.01–1 g/kg) showed more GE values than the controls (43.5% ± 1.7%). The GE values of Rikkunshito at 0.01, 0.1, and 1 g/kg were 38.2% ± 1.2%, 44.8% ± 1.1%, and 56.6% ± 1.6% ($P < 0.01$), respectively [Figure 1a]. The effects of Rikkunshito 1 g/kg were similar to those of mosapride (57.5% ± 0.6%, $P < 0.01$) and domperidone (57.3% ± 0.9%, $P < 0.01$) [Figure 1a]. Moreover, we investigated the loperamide or cisplatin-induced GE delay. In case of loperamide, the mean GE delay was higher than normal (32.1% ± 0.9%, $P < 0.01$) [Figure 1b] and this delay was blocked by Rikkunshito (0.01, 0.1, and 1 g/kg). The GE values for Rikkunshito were 32.1% ± 1.1%, 39.7% ± 1.3% ($P < 0.01$), and 42.3% ± 0.6% ($P < 0.01$) [Figure 1b]. In case of 1 g/kg Rikkunshito, it worked best, which was similar to that of mosapride (40.9% ± 1.1%, $P < 0.01$) or domperidone (40.8% ± 1.0%, $P < 0.01$) [Figure 1b]. Furthermore, in case of cisplatin, the decrease in GE was blocked by Rikkunshito (0.01, 0.1, and 1 g/kg). The GE values of Rikkunshito were 30.8% ± 1.3%, 34.0% ± 1.1% ($P < 0.01$), and 41.2% ± 1.8% ($P < 0.01$) [Figure 1c]. In case of 1 g/kg Rikkunshito, it worked best, which was comparable to that of mosapride (42.3% ± 0.7%, $P < 0.01$) or domperidone (41.9% ± 1.3%, $P < 0.01$) [Figure 1b].

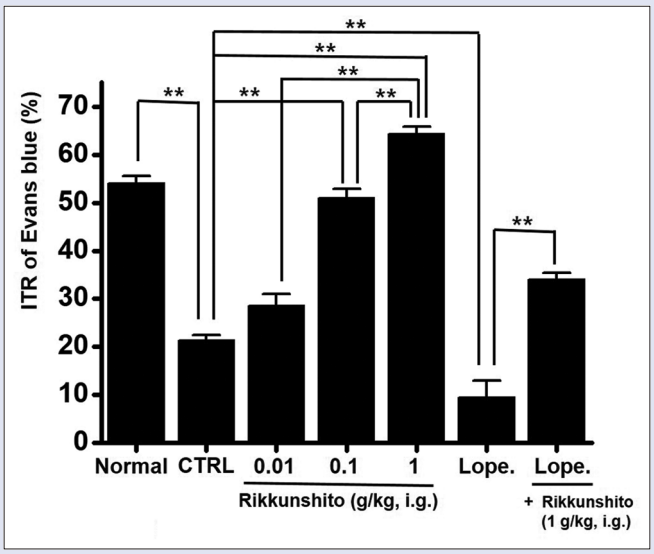

Figure 3: Effect of Rikkunshito on intestinal transit rate in acetic acid mice. In this acetic acid-induced case, the intestinal transit rate was recovered by Rikkunshito (n = 9/bar). Bars represent mean ± SE $^{**}P < 0.01$. CTRL: Control; Lope.: Loperamide

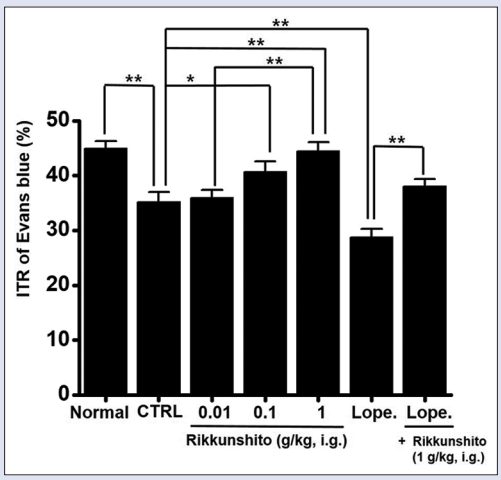

Figure 4: Effect of Rikkunshito on intestinal transit rate in streptozotocin-induced diabetic mice. In this streptozotocin-induced case, the intestinal transit rate was recovered by Rikkunshito (n = 6/bar). Bars represent mean ± standard error $^{*}P < 0.05$. $^{**}P < 0.01$. CTRL: Control; Lope.: Loperamide

Rikkunshito on intestinal transit rate in normal mice

The ITR was 53.3% ± 0.8% in normal mice [Figure 2]. PF (1 g/kg)[10] caused a substantial increase in the ITR (79.5% ± 3.7%, $P < 0.01$). The ITR values at Rikkunshito were 52.5% ± 1.1%, 59.2% ± 2.0% ($P < 0.01$), and 73.9% ± 0.7% ($P < 0.01$) [Figure 2]. Loperamide inhibited ITR,[11] but Rikkunshito restored the loperamide response in ITR %. The ITR of loperamide was 16.0% ± 4.1% and ITR for both loperamide and Rikkunshito was 34.3% ± 1.5%, respectively ($P < 0.01$) [Figure 2].

Effects of Rikkunshito on intestinal transit rate in mice with gastrointestinal motility dysfunction

We used GI motility dysfunction (GMD) models (AA and STZ models). The AA model decreased ITR (21.4% ± 1.1% vs. 54.1% ± 1.5% in normal controls; $P < 0.01$) [Figure 3]. However, Rikkunshito at 0.01, 0.1, and 1 g/kg restored this response to 28.6% ± 2.4%, 50.9% ± 1.9% ($P < 0.01$), and 64.3% ± 1.6% respectively ($P < 0.01$) [Figure 3]. Loperamide reduced the ITR in AA models to 9.5% ± 3.6% ($P < 0.05$) and Rikkunshito recovered this value to 34.1% ± 1.4% ($P < 0.05$) [Figure 3]. Moreover, STZ-induced models reduced ITR to 35.3% ± 1.7% [Figure 4], which was restored by Rikkunshito at 0.01, 0.1, and 1 g/kg with ITR values of 36.0% ± 1.3%, 40.7% ± 1.9% ($P < 0.05$), and 44.5% ± 1.6% ($P < 0.01$) [Figure 4]. Loperamide reduced the ITR in STZ-induced mice to 28.8% ± 1.5% ($P < 0.01$). Rikkunshito recovered this value to 38.1% ± 1.3% ($P < 0.01$) [Figure 4]. These results suggest that Rikkunshito brings to restorative the ITR in GMD mice.

DISCUSSION

GI motion is caused by electrical and contractile stimulations of the smooth muscles and is controlled by the enteric nervous system and the autonomic nervous system.[12] GI motility disorder works with many digestive disorders, such as functional dyspepsia (FD).[13-15] Several studies have published the action of Rikkunshito on the GI tract,[3-5] but the effect of Rikkunshito on GI motility is not yet studied.

There are various mechanisms for FD. There are many ways to treat FD.[16] Rikkunshito has many effects as it is made up of multiple constituents.[17] In the GI tract, it increases gastric accommodation and cures GI motion disorder through nitrergic and serotonergic pathways.[1,18,19] Rikkunshito also regulates esophageal motion[20,21] and inhibits clinically stressed GI hyperactivity.[19] Rikkunshito has beneficial effects in FD patients for simultaneous treatment of GI and psychological symptoms.

In this study, we studied the effect of Rikkunshito on GI function by GE and ITR in normal or experimentally-induced GMD mice. The oral administration of Rikkunshito raised GE and ITR and restored the GE and ITR delay. The cases of AA-induced and the STZ-induced indicated a significant decrease in ITR. This decrease was significantly blocked by Rikkunshito.

In a previous study, we suggested that Rikkunshito depolarized membrane potential of the interstitial cells of Cajal (ICCs) through several signaling-dependent and transient receptor potential melastatin-7 and Anoctamin-1-independent pathways.[8] Therefore, we could propose that Rikkunshito may control the GI motility through the ICCs.

In modern medicine, alternative medicine is not accepted as general medicine. However, an estimated 51% of patients with GI diseases receive treatment through alternative medicine. Indeed, 10% of all alternative medicine drugs are for digestive disorders. Furthermore, herbal substances are becoming the source of these alternative medicines and are known to have fewer side effects.[22] Gastroenterologists often find themselves facing tough questions regarding the efficacy and safety of herbal medicines in the GI tract. However, Rikkunshito is being used to treat GI diseases, and we think that especially it is a good choice to treat FD. This Rikkunshito has been shown to increase GI motility, but it is not yet clear which specific substance plays this role. Therefore, future research will need to determine what exactly substance is involved in this role.

CONCLUSION

The present study shows that Rikkunshito remarkably accelerates GE and ITR in normal and dysfunction models. The effect of this Rikkunshito seems to be significant in cases of FD patients. In the future, we need to study the exact mechanisms and composition of this Rikkunshito in detail.

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Conflicts of interest

There are no conflicts of interest.

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