

# The effectiveness of the herbal medicine, rikkunshito (TJ-43), on the absorption of levodopa and in the treatment of gastrointestinal symptoms in Parkinson's disease\*

Yasuhiro Suzuki<sup>1</sup>, Takashi Kimura<sup>1</sup>, Kohei Kano<sup>1</sup>, Hideaki Kishi<sup>1</sup>, Kenta Nomura<sup>1</sup>,  
Kosuke Yoshida<sup>1</sup>, Yoko Aburakawa<sup>1</sup>, Kenji Kuroda<sup>1</sup>, Chisato Murakami<sup>2</sup>,  
Sachiko Okuno<sup>3</sup> and Osamu Yahara<sup>1</sup>

<sup>1</sup>Department of Neurology, Asahikawa Medical Center, National Hospital Organization, Asahikawa, Japan

<sup>2</sup>Department of Clinical Research, Asahikawa Medical Center, National Hospital Organization, Asahikawa, Japan

<sup>3</sup>Department of Hospital Pharmacy, Asahikawa Medical Center, National Hospital Organization, Asahikawa, Japan

---

---

## Abstract

**Object** The aim of this prospective study was to assess the effectiveness of rikkunshito on the absorption of administrated levodopa and in the treatment of gastrointestinal symptoms in Parkinson's disease patients.

**Materials and Methods:** Eight participants with Parkinson's disease were enrolled. The serum levodopa concentration, maximum concentration, and area under the plasma concentration-time curve of levodopa before and after treatment were measured in all patients taking rikkunshito in conjunction with levodopa for 4 weeks. Gastrointestinal manifestations were evaluated by the Gastrointestinal Symptom Rating Scale (GSRS).

**Results:** After administration of rikkunshito, the maximum concentration of levodopa improved in 5 Parkinson's disease patients, while the area under the plasma concentration-time curve of levodopa increased in 4 Parkinson's disease patients. The GSRS showed amelioration of the symptoms in the upper gastrointestinal tract in 3 of the patients, one of whom exhibited a normalized levodopa absorption pattern. In contrast, the GSRS showed the symptoms improved in the lower gastrointestinal tract in 6 of the Parkinson's disease patients.

**Conclusion:** Rikkunshito treatments improved lower gastrointestinal symptoms such as constipation and defecatory dysfunction in Parkinson's disease patients.

**Key words:** Parkinson's disease, rikkunshito, levodopa, GSRS, ghrelin

## Introduction

Non-motor manifestations of Parkinson's disease (PD) are recognized as derangements of behavior, sleep, sensation, and autonomic function. The most common non-motor feature of PD is gastrointestinal dysfunction. Gastrointestinal motility is regulated by both the extrinsic inputs from the dorsal motor nucleus of the vagus (DMV) and the paravertebral sympathetic ganglia, and by the local reflexes mediated by the intrinsic neurons of the enteric nervous system (ENS), which consists of the myenteric plexus (of Auerbach) and the submucosal plexus (of Meissner).<sup>1,2)</sup> Well known characteristics of PD include an accumulation of alpha-synuclein, which is commonly seen as Lewy bodies and Lewy neuritis. Moreover, during the early stages of PD, both DMV and EMS have been shown to be affected by Lewy body pathology, resulting to provide the gastrointestinal dysmotility.<sup>3,4,5)</sup>

Impaired gastric emptying and accommodation in PD can potentially have profound pharmacokinetic implications. Delayed gastric emptying and delayed levodopa arrival at intestinal absorptive sites can result in erratic responses to these medications. Moreover, absorptive variations can also lead to activation of one of the mechanisms of motor fluctuation that are found in PD.<sup>6)</sup>

Several approaches to the treatment of gastrointestinal dysmotility in PD have been investigated. Domperidone, which blocks dopamine receptors but does not pass through the blood-brain barrier, can be used in PD and improves both the gastric emptying and gastrointestinal symptoms.<sup>7)</sup> The prevalence of gastrointestinal symptoms reported to occur before the onset of motor symptoms of PD include constipation (87%), and defecatory dysfunction (58.9%).<sup>8)</sup> It has also been proposed that the onset of the PD pathology is non-motor, with the non-motor symptoms beginning as early as 10 to 20 years before the actual onset of the motor symptoms.<sup>9)</sup> A previous report has confirmed that daikenchuto improves constipation in PD patients.<sup>10)</sup> The prokinetic effect of daikenchuto on colonic motility was shown to be mediated by an increase in the level of serum motilin, vasoactive intestinal polypeptide (VIP), and 5-HT. Recently Kusunoki et al. demonstrated that rikkunshito

may be beneficial in treating functional dyspepsia patients, who have impaired gastric motility by extracorporeal ultrasonography.<sup>11)</sup> Hiyama et al. further demonstrated that rikkunshito administered with levodopa improved erratic gastric emptying and stabilized the plasma levodopa levels, thereby resulting in an improvement in the motor fluctuations in Parkinsonian patients.<sup>12)</sup> However, there have been few reports on whether rikkunshito can improve the lower gastrointestinal dysmotility.

Therefore, this study was designed to investigate if rikkunshito could improve the pharmacological manifestations for levodopa absorption, and to examine whether rikkunshito could ameliorate the known pre-motor gastrointestinal dysfunctions associated with PD.

## Materials and Methods

### *Patients*

Eight patients (5 men and 3 women) with idiopathic PD were enrolled in this prospective study. Age, sex, clinical stage, evolution, and treatment course are listed in Table 1. Mean age of the patients was  $72 \pm 2$  years old and mean disease duration was  $8.75 \pm 3.46$  years. Patient AMC5 received anticholinergic medication, while patients AMC3, 5, 7, and 8 were given medications for constipation and defecatory dysfunction. None of the patients suffered from any gastrointestinal disease or had any history of gastrointestinal surgery. Diagnosis of PD was made according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria.<sup>13)</sup> This study was approved by the Ethics Committee of Asahikawa

**Table 1.**

Clinical characteristic of 8 Parkinson's disease patients treated with rikkunshito. mH & Y; modified Hoehn and Yahr staging scale, yr; year.

Patient no.	Age (yr)	Sex	Stage (mH & Y)	Evolution (yr)	Treatment (yr)
AMC1	72	M	2.5	2	1
AMC2	72	M	3.5	5	0
AMC3	76	M	3.5	9	5
AMC4	72	F	3.0	12	4
AMC5	70	M	2.5	11	6
AMC6	74	M	3.5	10	6
AMC7	70	F	3.5	10	1.5
AMC8	70	F	3.0	13	3.5

Medical Center. Informed consent was obtained from each participant prior to the study.

### Methods

Eight PD patients received 2.5 g of rikkunshito 30 minutes after each meal, (total 7.5 g per day), for 4 weeks in conjunction with levodopa/carbidopa (100 mg/10 mg). If patients were taking other medications, these were continued until the study was finished.

Blood samples for the single-time plasma levodopa concentration were collected immediately before and after the levodopa/carbidopa morning dose and at the end of the 4-week rikkunshito administration. Depending upon the protocol, patients took 1 tablet of levodopa/carbidopa (100 mg/10 mg) at 0.5 hour intervals for up to 1.0 hour, and then at 1.0 hour intervals for up to 4 hours. All patients fasted prior to the blood sampling.

To estimate the concentration of the plasma levodopa, blood samples were promptly centrifuged at 4°C, with the plasma samples then frozen at -80°C. SRL Inc., (Tokyo, Japan) performed all measurements of the levodopa concentration using HPLC-ECD. The maximum concentration (C<sub>max</sub>) and the area under the plasma concentration-time curve of levodopa (AUC) were calculated using the trapezoidal method in each patient.

Gastrointestinal functions were estimated using the GSRS.<sup>14)</sup> GSRS is a disease-specific methodology that includes 15 items that are then combined into five-symptom clusters that address different gastrointestinal symptoms. The five-symptom clusters depict reflux, abdominal pain, indigestion, diarrhea and constipation. The GSRS uses a seven-level Likert-type graded scale where 1 represents the absence of bothersome symptoms and 7 represents very bothersome symptoms.

### Statistical analysis

GSRS differences with or without rikkunshito at 4 weeks after administration were estimated using a two-way ANOVA. The C<sub>max</sub> and AUC were compared before and at 4 weeks after administration using a two-way ANOVA. All statistical calculations were two-side, and  $P < 0.05$  indicated statistical significance.

## Results

Serum levodopa concentration results for the 8 patients are shown in Figure 1. A single mean C<sub>max</sub> peak was observed for rikkunshito at 0.5 hours after taking the medication, after which the levels decreased during fasting conditions. Delayed and incomplete absorption of levodopa were seen in patients AMC2, 6, and 8 prior to taking the oral rikkunshito. Figure 2 shows the clinical estimations for the C<sub>max</sub>, AUC and GSRS. Mean C<sub>max</sub> increased in patients AMC2, 3, 5, 6, and 8 after the 4-week administration of rikkunshito. In addition, mean AUC increased in patients AMC2, 3, 6, and 8 under the same conditions. Although the pattern of absorption of the levodopa exhibited a single peak in patient AMC5 after taking rikkunshito for 4 weeks, there was no improvement observed in the AUC. The upper gastrointestinal tract GSRS improved in patients AMC6, 7, and 8. Although the lower gastrointestinal tract GSRS in patients AMC2, 3, 5, 6, 7, and 8 showed amelioration of the symptoms, with the exception of case AMC6, all of these patients required a prescription for constipation. The respective differences noted for the lower gastrointestinal tract GSRS in each patient were statistically significant ( $P < 0.05$ ). No adverse effects were observed while taking rikkunshito during this study.

## Discussion

The present study demonstrated that rikkunshito treatment in PD patients led to an improvement in lower gastrointestinal tract symptoms such as constipation and defecatory dysfunction. Gastrointestinal symptoms such as nausea, abdominal pain, and bloating are frequent complaints of PD patients. Disturbance of levodopa absorption due to delayed and erratic gastric emptying contributes to the development of “delayed on” and “no on” motor fluctuations in PD. At the present time, partial improvements in patients can sometimes be achieved by combining oral levodopa with prokinetic drugs such as domperidone, which accelerate gastric motility.<sup>7)</sup> Rikkunshito, an herbal medicine, contains 8 mixed raw herbs in the following ratios: *JP (Japanese Pharmacopoeia)*

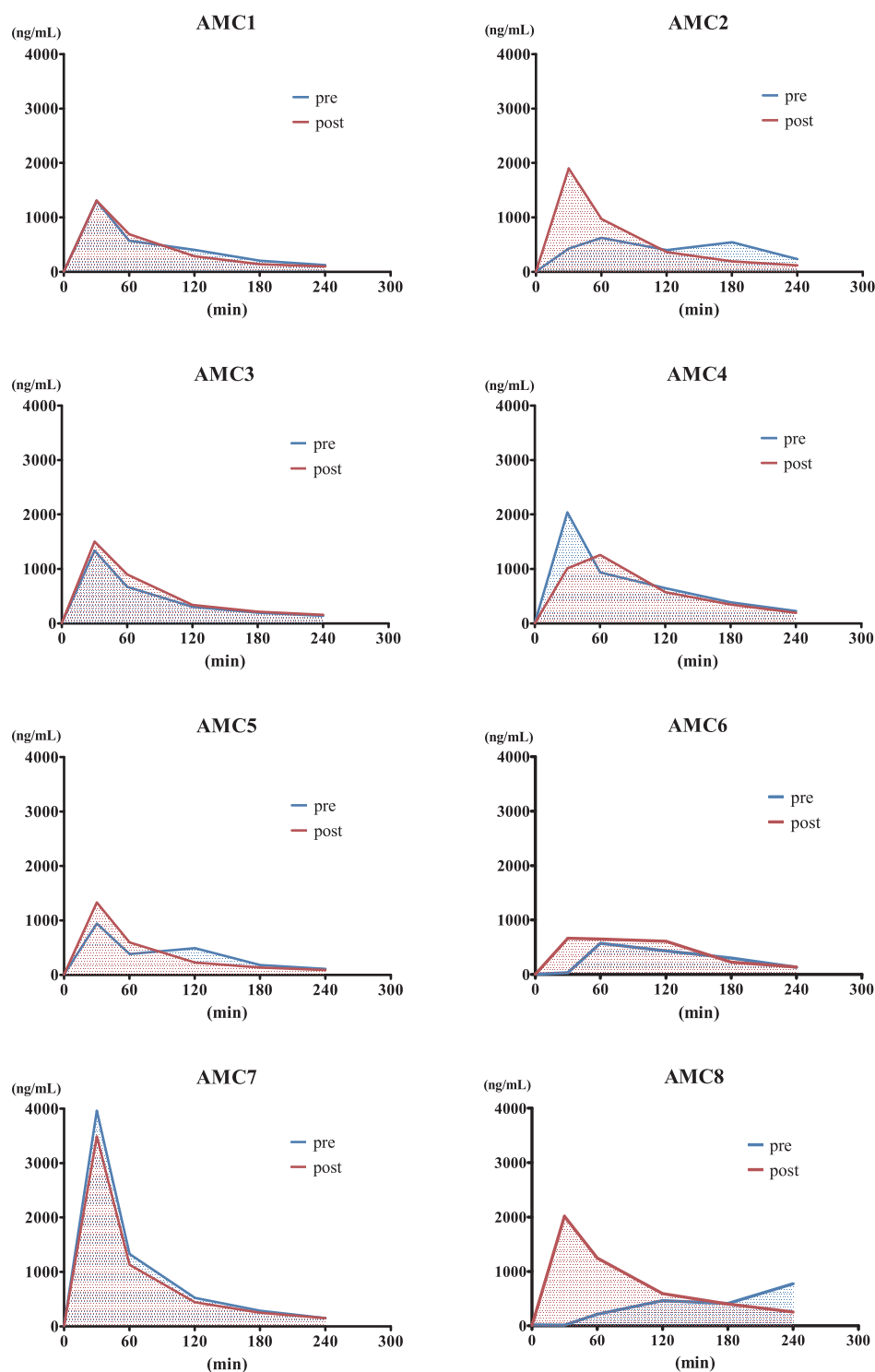


Figure 1.

Concentration of plasma levodopa before and at 4 weeks after oral administration of rikkunshito. The efficacy of levodopa absorption was improved in patients AMC2, 3, 5, 6, and 8, whose absorption of levodopa was unstable. Pre; before treatment with rikkunshito. Post; 4 weeks after rikkunshito.

*Atractylodes Lancea* Rhizome 4.0 g, *JP Ginseng* 4.0 g, *JP Pinellia Tuber* 4.0 g, *JP Poria Sclerotium* 4.0 g, *JP Jujube* 2.0 g, *JP Citrus Unshiu Peel* 2.0 g, *JP Glycyrrhiza* 1.0 g, and *JP Ginger* 0.5 g. Rikkunshito has been shown

to be effective for improving the symptoms of functional dyspepsia, gastroesophageal reflux disease, and cisplatin-induced anorexia.<sup>11,15)</sup> Thus, this herbal medicine has the potential to be successfully used in the treatment of

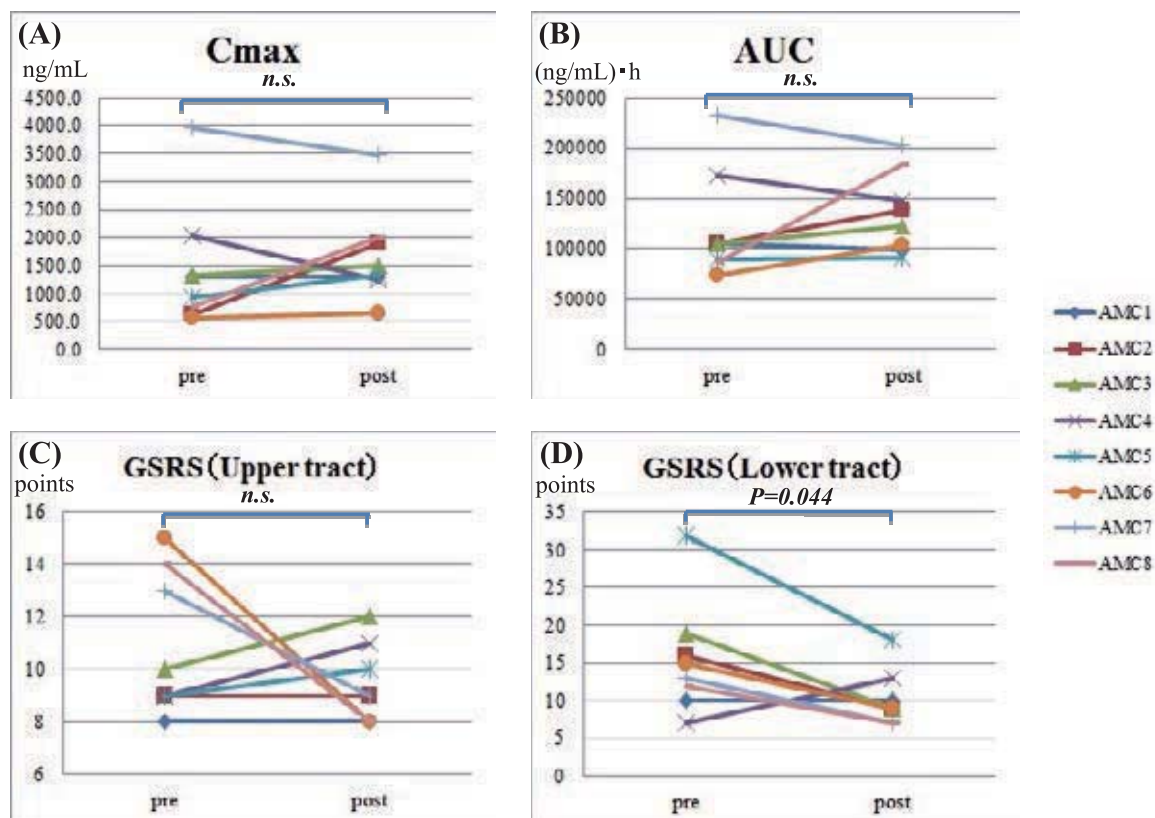


Figure 2.

Comparison of clinical and pharmacokinetic data from Parkinson's disease patients after 4 weeks of administration of rikkunshito.

No statistical differences were seen for the Cmax, AUC, and GSRS (upper tract). In contrast, statistically significant differences were seen for the GSRS (lower tract).  $P = 0.044$ .

Cmax; maximum concentration, AUC; area under the plasma concentration-time curve, GSRS; Gastrointestinal Symptom Rating Scale, n.s.; not significant. Pre; before treatment with rikkunshito. Post; 4 weeks after treatment with rikkunshito.

gastrointestinal disorders in Japan.

Several previous studies have examined the mechanism of rikkunshito when used to treat gastrointestinal dysfunctions in animal models. Hayakawa et al. demonstrated that rikkunshito in isolated guinea pig stomachs promoted adaptive relaxation, i.e., gastric accommodation.<sup>16)</sup> Kido et al. proposed that rikkunshito ameliorated the effects of nitric oxide (NO)-mediated gastric functions including delayed gastric emptying.<sup>17)</sup> Hesperidin and L-arginine have been identified as two of the active ingredients that contribute to the ability of rikkunshito to facilitate gastric emptying in rats. Furthermore, Tominaga et al. reported that rikkunshito appeared to improve the delay in gastric emptying via the antagonistic action of the 5-hydroxytryptamine (HT)<sub>3</sub> receptor pathway in rats.<sup>18)</sup> Based on this previous evidence, we speculate that improvement in the absorption of levodopa after rikkunshito administration in PD patients

with autonomic dysfunction may occur via the NO or 5-HT<sub>3</sub> receptor pathways.

Interestingly, we observed statistically significant improvements in the GSRS scores for the lower gastrointestinal tract in 6 of the participants after rikkunshito treatment. Using the Sitzmarks radiopaque marker (Konsyl Inc., USA), Doi et al. were the first to demonstrate that rikkunshito improved colonic transit time in 7 of 8 PD patients.<sup>19)</sup> However, it remained unclear as to how rikkunshito affected the lower gastrointestinal dysfunction in PD.

Ghrelin, which was identified as the natural secretagogue for growth hormone in 1999,<sup>20)</sup> was shown to be abundantly synthesized by specialized mucosal cells in the stomach. Matsumura et al. showed that rikkunshito increased the plasma acylated ghrelin level in healthy volunteers and normal mice.<sup>21)</sup> In addition, Hirayama et al. demonstrated

the ghrelin receptor existed in the lumbosacral defecation control center (L6-S1 region of the spinal cord) and that the acylated ghrelin peptide was essential for promoting propulsive contractions of the colorectum in rats.<sup>22)</sup>

Although we did not examine patient ghrelin levels in this study, we speculated that acylated ghrelin might have modified the gastrointestinal function in 7 cases. Even though there has been little previous evidence that rikkunshito can modify clinical symptoms, especially constipation, our current study clearly indicated that rikkunshito has a potent and special effect on lower intestinal dysfunction in PD. It is our belief that rikkunshito not only improves the function of the upper gastrointestinal tract, but also has an effect on the lower gastrointestinal tract. This effect occurs via different mechanism that found for daikenchuto, and leads to an improvement in the defecation dysfunction found in PD. In order to definitively elucidate how rikkunshito regulates the lower intestinal tract in PD patients, further studies will need to be undertaken.

In conclusion, we demonstrated that rikkunshito treatments improved the defecation dysfunction and constipation as well as the gastric dysmotility and thus, would be of benefit in PD patients. However, in order for this herbal medicine to gain wider acceptance in other countries, further studies on the specifics of the physiological and clinical effects will need to be performed.

\*An earlier version of this paper was read at the 54<sup>th</sup> Annual Meeting of the Japanese Society of Neurology, May 29 to June 1, 2013.

The authors state that they have no conflict of interest (COI).

## Acknowledgements

This study was supported in part by a grant-in-Aid for Clinical Research from the National Hospital Organization.

## References

1. Travagli RA, Hermann GE, Browning KN, Rogers RC. Brainstem circuits regulating gastric function. *Annu Rev Physiol.* 2006;68:279-305

2. Benarroch EE. Enteric nervous system: functional organization and neurologic implications. *Neurology.* 2007;69:1953-1957
3. Braak H, Del Tredici KD, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging.* 2003;24:197-211
4. Braak H, de Vos RA, Bohl J, Tredici K. Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett.* 2006;396:67-72
5. Cersosimo MG, Benarroch EE. Neural control of the gastrointestinal tract: implications for Parkinson disease. *Mov Disord.* 2008;23:1065-1075
6. Djaldetti R, Barron J, Ziv I, Melamed E. Gastric emptying in Parkinson's disease: patients with and without response fluctuations. *Neurology.* 1996;46:1051-1054
7. Soykan I, Sarosiek I, Shifflett J, et al. Effect of chronic oral domperidone therapy on gastrointestinal symptoms and gastric emptying in patients with Parkinson's disease. *Mov Disord.* 1997;12:952-957
8. Cersosimo MG, Raina GB, Pecci C, et al. Gastrointestinal manifestations in Parkinson's disease: prevalence and occurrence before motor symptoms. *J Neurol.* 2013;260:1332-1338
9. Gaig C, Tolosa E. When does Parkinson's disease begin? *Mov Disord.* 2009;24:S656-S664
10. Sakakibara R, Odaka T, Lui Z, et al. Dietary herb extract daikenchu-to ameliorates constipation in parkinsonian patients (Parkinson's disease and multiple system atrophy). *Mov Disord.* 2005;20:261-261
11. Kusunoki H, Haruma K, Hata J, et al. Efficacy of Rikkunshito, a traditional Japanese medicine (Kampo), in treating functional dyspepsia. *Intern Med.* 2010;49:2195-2202
12. Hiyama Y, Tosa H, Terasawa K, et al. The effects of Rikkunshito on parkinsonian patients with unstable effect of levodopa/carbidopa. *J Trad Med.* 1991;8:83-88
13. Fahn S, Elton RL, UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent developments in Parkinson's disease.* Vol. 2. Florham Park, N.J.: Macmillan Healthcare Information. 1987; p153-163, p293-304
14. Svedlund J, Sjodin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci.* 1988;33:129-134
15. Takeda H, Sadakane C, Hattori T, et al. Rikkunshito, an herbal medicine, suppresses cisplatin-induced anorexia in rats via 5-HT2 receptor antagonism. *Gastroenterology.* 2008;134:2004-2013
16. Hayakawa T, Arakawa T, Kase Y, et al. Liu-Jun-Zi-Tang, a kampo medicine, promotes adaptive relaxation in isolated guinea pig stomachs. *Drug Exp Clin Res.* 1999;25:211-218
17. Kido T, Nakai Y, Kase Y, et al. Effects of rikkunshi-to, a

- traditional Japanese medicine, on the delay of gastric emptying induced by NG-Nitro-L-arginine. *J Pharmacol Sci.* 2005;98:161-16
- 18.Tominaga K, Kido T, Ochi M, et al. The traditional Japanese medicine rikkunshito promotes gastric emptying via the antagonistic action of the 5-HT<sub>3</sub> receptor pathway in rats. *Evid Based Complement Alternat Med.* 2009;2011:1-8
- 19.Doi H, Sakakibara R, Kishi M, et al. Gastric emptying and colonic transit in patients with Parkinson's disease. Effects of Rikkunshi-to on gastrointestinal dysfunction. *The Autonomic Nervous System.* 2013;50: 300-305
- 20.Kojima M, Hosoda H, Date Y, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature.* 1999;402:656-660
- 21.Matsumura T, Arai M, Yonemitsu Y, et al. The traditional Japanese medicine Rikkunshito increases the plasma level of ghrelin in humans and mice. *J Gastroenterol.* 2010;45:300-307
- 22.Hirayama H, Shiina T, Shima T, et al. Contrasting effects of ghrelin and des-acyl ghrelin on the lumbo-sacral defecation center and regulation of colorectal motility in rats. *Neurogastroenterol Motil.* 2010;22:1124-113