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JAPANESE HERBAL MEDICINE IN FUNCTIONAL GASTROINTESTINAL DISORDERS

Hidekazu Suzuki, John M. Inadomi, and Toshifumi Hibi

Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160–8582, JAPAN; Department of Medicine, University of California, San Francisco, and the San Francisco General Hospital, San Francisco, CA, USA

Abstract

Background—Management of functional gastrointestinal disorders is hindered by both poor efficacy and adverse effects of traditional pharmacological therapy. Herbal medicine may be an attractive alternative based on the perception of its “natural” approach and low risk of side effects; however, the lack of standardization of drug components has limited the ability to perform rigorous clinical studies in Western countries. Japanese herbal medicine (JHM) is a standardized form of herbal medicine with regards to the quality and quantities of ingredients. While extensively studied and widely used in Asia, there is a paucity of data upon which physicians in other parts of the world may draw conclusions regarding the effectiveness of herbal medicine for gastrointestinal disorders.

Aim—To summarize the most recent developments in JHM for treatment of functional gastrointestinal disorders.

Methods—Animal and human studies were systematically reviewed to identify published data of JHM used for treatment of gastrointestinal disorders. The herbal components of JHM were examined. Results describing the physiological and clinical effects of JHM were abstracted, with an emphasis on functional gastrointestinal disorders.

Results—JHM are associated with a variety of beneficial physiological on the gastrointestinal system. Patient-based clinical outcomes are improved in several conditions. Rikkunshi-to reduces symptoms and reverses physiological abnormalities associated with functional dyspepsia, while Dai-Kenchu-to improves symptoms of post-operative ileus and constipation in children.

Conclusions—This updated summary of JHM in the field of gastrointestinal disorders illustrates the potential for herbal medication to serve a valuable role in the management of patients with functional disorders.

INTRODUCTION

Functional gastrointestinal disorders (FGIDs), including functional dyspepsia and irritable bowel syndrome, occurs in up to one quarter of people in Western countries [1]. Since functional disorders are not lethal, the threshold for safety of medication to treat these disorders has been set higher than for therapy to treat non-functional disease. Recent data, however, illustrate the substantial health impact of functional gastrointestinal disorders and the need for more effective therapy [2]. Management of patients with functional disorders has become more difficult because several drugs that reduced symptoms were associated

with significant adverse events leading to the withdrawal of medication such as cisapride [3] and tegaserod [4].

Herbal therapy, which has been used in Asia for thousands of years is currently manufactured in Japan in standardized form with regards to the quality and quantities of ingredients, and has been termed “Japanese herbal medicine” (JHM) or “Kampo medicine.” An emerging therapeutic target for this class of medicine is functional disorders. Since conventional pharmacology has been either poorly effective or associated with adverse events the use of complementary and alternative medicine (CAM) including herbal medicines is gaining appeal for use in clinical practice. The present article reviews the underlying physiology and clinical benefits associated with Japanese herbal medicine in treating gastrointestinal diseases, with a special focus on gastrointestinal functional disorders.

Methods

A literature search was performed in Pubmed using the keywords [gastrointestinal] and [Japanese herbal medicine], or [gastrointestinal] and [kampo]. After identification of the JHM used for gastrointestinal disorders, additional searches were performed using each of the specific JHM as search terms to ensure inclusion of all relevant publications. After accumulating the combined list of included studies, publications not examining the use of JHM for gastrointestinal functional disorders were excluded. Data abstraction was performed to characterize the physiological and clinical effects of each JHM. A formal meta-analysis was not possible based on the variation in study populations, disorders and study protocols retrieved; therefore, the data are presented descriptively with regards to the physiological and clinical effects of individual JHM.

Results

The initial search terms yielded 30 original manuscript of JHM. The most frequently cited JHM were Rikkunshi-to (RKT: 6 studies) and Daikenchu-to (DKT: 6 studies), followed by Hangeshasin-to (HST: 2 studies). By expanding the search algorithm to include keywords of these JHM, a total of 17 publications of RKT and 27 studies of DKT were retrieved. Expansion of other medicine-specific search terms did not yield additional results.

I. Rikkunshi-to (RKT, TJ-43)—Rikkunshi-to (RKT, TJ-43) is prepared from 8 crude herbs: Atractylodes, Lancea Rhizome, Ginseng, Pinellia Tuber, Poria Sclerotium, Jujube, Citrus Unshiu Peel, Glycyrrhiza and Ginger (Table 1). RKT is widely prescribed in Japan for patients with a variety of gastrointestinal symptoms including anorexia [5], nausea and vomiting [6, 7].

Among 17 manuscripts related to RKT, 8 articles were animal studies and 9 were human studies. Among 8 animal studies, 5 articles focused on upper gastrointestinal (GI) function [5,8,9,10,11]. Of the 9 human studies, only one was randomized controlled study [12] and 6 were related to upper GI function [6,7,12,13,14,15] (Figure 1, Table 2).

Effects on putative receptors or neurotransmitters: According to a recent report by Takeda et al. [5] components of RKT, 3,3',4',5,6,8-heptamethoxyflavone, hesperidin, and iso-liquiritigenin showed a 5-HT_{2B}-antagonistic effect in vitro. They also showed in vivo that RKT suppressed the cisplatin- or 5-HT-induced decrease in plasma acylated ghrelin levels as well as in food intake [5].

In another experiment, a single oral dose of RKT resulted in significant increases in plasma somatostatin and gastrin levels 60 to 240 minutes after administration compared with a

placebo group [13]. Conversely, RKT was observed to have no effect on motilin or VIP levels.

Effects on motor patterns

Gastric emptying: RKT has been shown to ameliorate the effects of nitric oxide (NO)-mediated gastric functions including delayed gastric emptying. Hesperidin and L-arginine have been identified as two of the active ingredients contributing to the ability of RKT to facilitate gastric emptying [8].

Adaptive relaxation: Some patients with dysmotility-like functional dyspepsia (equivalent to postprandial distress syndrome by Rome III classification [16,17]) have been shown to exhibit impaired reservoir function including gastric adaptive relaxation. In a guinea pig model using luminal distension to invoke gastric adaptive relaxation, RKT (100 mg/ml) induced gastric adaptive relaxation at lower intragastric pressures and increased both the proportion and absolute volume of the gastric adaptive relaxation. These effects were inhibited by N^G-nitro-L-arginine (0.1 mM). Conversely, metoclopramide, trimebutine and cisapride did not affect gastric adaptive relaxation. Thus, RKT (100 mg/ml), but not gastroprokinetic agents overcame the effect of N^G-nitro-L-arginine. These results suggested that RKT promotes gastric adaptive relaxation. This effect might, at least in part, contribute to the symptom relief in patients with functional dyspepsia [9].

In isolated guinea pig ileal longitudinal muscle, RKT inhibited the concentration-response curve for acetylcholine (ACh)-contraction in a non-competitive manner, similar to the effect seen with domperidone [10].

Gastroesophageal reflux disease (GERD): The effects of RKT on clinical symptoms and esophageal acid exposure in children with symptomatic gastroesophageal reflux (GER) have been examined. In one study, 8 children, aged from 2 months to 15 years, 6 of who had neurological impairment were studied. The clinical symptoms and esophageal pH were compared before and after RKT therapy for 1 week. The percentage time that distal esophageal pH < 4.0 and the mean duration of reflux decreased significantly ($P < 0.05$); however, the number of acid reflux events per hour did not change significantly, and none of the pH parameters measured at the proximal electrode differed significantly. In concert with these physiological changes, clinical symptoms of GER were significantly reduced, supporting the hypothesis that short-term administration of RKT reduces the distal esophageal acid exposure through improved esophageal acid clearance [14].

Functional dyspepsia (FD): In a randomized, placebo controlled trial of RKT, gastric emptying and gastrointestinal symptoms were evaluated in 42 patients with FD. Subjects were randomized to receive either oral treatment with 2.5 g RKT three times daily (22 subjects) or placebo (20 subjects). Gastric emptying was measured by the acetaminophen absorption method. After 7 days of treatment, gastric emptying was significantly accelerated and gastrointestinal symptoms were significantly reduced in patients treated with RKT, indicating that RKT has a prokinetic action on gastric emptying and may be useful in treating FD [12].

The effect of RKT on symptoms and gastric myoelectric activity has been evaluated in dyspeptic patients whose symptoms persisted for over 1 year after gastrointestinal surgery. All patients exhibited symptomatic relief with the administration of RKT, with a significant decrease in mean symptom scores that were sustained over a 1-month period ($p < 0.0001$). The variability index (VI) and the percentage of normal waves (PNW) were calculated as irregularity parameters of dominant peak frequency (DPF). There were no significant differences in the VI and PNW between the controls and patients during the postprandial

state after therapy, even though significant differences in those parameters were present between the controls and patients before the therapy. Postprandial dip was observed in all control subjects and two patients after administration of RKT. The coordinating and stimulating effect of RKT on the gastric myoelectric activity therefore seems to play an important role in the reduction of dyspeptic symptoms [15].

Other dyspeptic conditions: Diacylglycerol kinase (DGK) activity in diabetic gastric smooth muscle in the resting state is approximately 3.5-fold greater than that in non-diabetic controls. Oral administration of RKT for 2 weeks in streptozotocin-induced diabetic rats (DM) normalizes DGK abnormalities by influencing the hyperreactivity of DGK and diacylglycerol formation via phospholipase C activity [11].

Upper gastrointestinal (GI) symptoms such as nausea and vomiting are common adverse events associated with selective serotonin reuptake inhibitors (SSRIs), and may result in discontinuation of drug therapy in patients with depressive disorders. RKT was shown to reduce the fluvoxamine-associated adverse events, especially nausea, and improve QOL related to GI symptoms without affecting the antidepressant effect of fluvoxamine [6].

One case report illustrated that oral administration of RKT stopped the vomiting of infantile hypertrophic pyloric stenosis (IHPS) refractory to atropine, possibly by improving gastric motility and restoring normal gastric myoelectric activity [7].

Other effects: RKT significantly inhibits rat gastric mucosal damage caused by absolute ethanol dose-dependently. Pretreatment with indomethacin or with N-ethylmaleimide does not affect the gastroprotective effect of RKT; however, pretreatment with N^G-nitro-L-arginine significantly reverses the protective effect of this drug, suggesting that the gastroprotective effect of RKT occurs partly through NO but not through prostaglandin or sulfhydryl pathways [18]. Moreover, oral administration of RKT extract significantly prevented ethanol-induced rat gastric mucosal damage through the 140% increase in the surface mucin content [19].

Gastric mucosal blood flow is significantly decreased in a model of gastric mucosal hemorrhagic injury produced by repeated electrical stimulation of the rat gastric artery, with an increase in platelet-activating factor (PAF) and myeloperoxidase (MPO) activity in the gastric mucosa and in oxygen radical formation in the local venous blood [20]. In this model, oral RKT attenuates such increases in PAF, MPO and oxygen radicals, and reverses the mucosal blood flow reduction and mucosal injury [20].

II. Dai-Kenchu-to (DKT, TJ-100)—Dai-Kenchu-to (DKT, TJ-100), prepared from 3 crude herbs: Ginseng, Zanthoxylum Fruit and Dried Ginger (Table 1), is often used in Japan in the treatment of gastrointestinal hypomotility such as ileus following abdominal surgery .

Among 27 manuscripts related to DKT, 18 were animal studies and 9 were human studies. There was only one randomized controlled study has been performed to evaluate the clinical effects of DKT [21]. Among 18 animal studies, 16 articles were related to intestinal function [22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37]. All 9 human studies examined intestinal function [21,38,39,40,41,42,43,44,45] (Figure 1, Table 2).

Effects on putative receptors or neurotransmitters: A single oral administration of DKT caused significant increases in plasma levels of motilin [38], vasoactive intestinal peptide (VIP), 5-HT [39], CGRP and substance P [40], but not of gastrin and somatostatin [38]. DKT induces the release of motilin and VIP into plasma mainly through the activation of M(1) muscarinic receptors [41]. DKT and one of its active components, 6-shogaol, produced

an increase in intestinal blood flow that was mainly mediated by CGRP [46], suggesting that DKT may be useful in the treatment of intestinal ischemia-related organic as well as functional GI diseases. DKT also prevented bacterial translocation by reducing inflammatory reaction for maintaining intestinal integrity [47].

Effects on motor patterns

GI Motility: Intragastric DKT and a variety of agents including zanthoxylum fruit, ginseng root, and dried ginger rhizome stimulate upper gastrointestinal motility in dogs through cholinergic and 5-HT₃ receptors [22]. The prokinetic effects of DKT differ with the site (stomach, duodenum, jejunum, ileum, colon) or timing (the fasting and the fed) of administration [23].

DKT induced contractions accompanied by autonomous contraction at a concentration of more than 3×10^{-4} g/ml in a dose-related manner in the isolated guinea pig ileum [24]. DKT-induced ileal contraction was suppressed by atropine and tetrodotoxin, but not by hexamethonium, and was partially suppressed in the presence of 5-HT₄ receptor antagonist. In addition, DKT was associated with an acetylcholine (ACh)-releasing action in the ileal smooth muscle, suggesting that contractile response induced by DKT is partially mediated by ACh released from the cholinergic nerve endings and that 5-HT₄ receptors are involved in the effect of DKT [24]. Tachykinins may be also involved in the atropine-resistant contraction by DKT [25].

In an isolated rabbit jejunum, DKT acted on multiple points of the intestine to improve ileus [26]. While DKT evoked both contraction and relaxation by releasing ACh, NO and other excitatory neurotransmitters in mouse small intestine, it had no effects on pacemaker mechanisms and electrical coupling between ICC-MY and smooth muscle cells [27], suggesting that DKT may contract smooth muscles directly. Abatement of morphine-induced transit disorders by DKT in the guinea pig ileum was reported to be caused by both moderate contraction of morphine-treated longitudinal muscle and relaxation of morphine-induced tonic contraction of circular muscle [28]. In terms of colonic motility, DKT-extract powder caused a significant inhibition on carbachol-induced contraction of the rat distal colon in a concentration dependent manner [29].

Small intestinal motility: DKT improves accelerated small intestinal movement with mechanisms mainly through the direct inhibition of smooth muscle and partially through neural inhibition [30]. The components of DKT (Table 1) that provide this effect may be dried ginger root and ginseng, which also contribute to the action of DKT on small intestinal transit [31].

DKT also induces phasic contractions in the duodenum and proximal jejunum, possibly mediated through cholinergic receptors [32]. Such stimulatory effects on intestinal motility by DKT is selective on GI tract since DKT has no effect on the uterine motility [33].

Chlorpromazine-induced hypoperistalsis: DKT also improves chlorpromazine-induced hypoperistalsis via cholinergic systems. One of ingredients in DKT, zanthoxylum fruit is likely the main contributor to this action. In addition, endogenous CCK release, which has been demonstrated to occur in response to maltose syrup may also contribute to the reversal of hypoperistalsis [34].

Postoperative ileus (POI): POI is a transient bowel motor dysfunction that occurs after surgery. Delays in gastrointestinal transit may be prolonged after laparotomy plus intestinal manipulation. DKT accelerated the delayed GI transit induced by intestinal manipulation, with or without concomitant morphine administration [35].

The improvement in motor function is inhibited by pretreatment with atropine or ruthenium red. In addition, DKT-induced contractions are inhibited by tetrodotoxin, and capsazepine. Since the effect of hydroxyl sanshool, one of the active compounds of DKT, is mediated by sensory nerves, the effect of DKT may be due to a combination of sensory and cholinergic nerves [36]. Alternatively, the effect may be due to reversal of transient ischemia through the improvement of the intestinal mucosal blood flow [46]. In postoperative intestinal adhesion, repeated administrations of DKT significantly inhibited the formation of intestinal obstruction [37]. A single administration of DKT significantly reduce intestinal transit time in POI and chemically induced ileus [37].

DKT ameliorated postoperative hypoperistalsis is via cholinergic nerves and 5-HT₄ receptors [48].

DKT treatment may be useful for the patients with POI, which is a common adverse consequence of abdominal surgical procedures. According to a double-blind, randomized study examining the effects of DKT was performed in 24 patients with POI, DKT was significantly more effective than placebo in reducing both the need for further surgery and the recurrence of POI [21]. Among patients with total gastrectomy with jejunal pouch interposition, DKT increased intestinal motility and decreased postoperative symptoms [42]. Furthermore, administration of DKT in conjunction with Keish-bukuryo-gan was highly effective in improving postoperative bowel motility and in reducing hospital stay [43]. Also in children [44], DKT had incremental but significant effects for a variety of obstructive bowel diseases.

Constipation: In a study of children with chronic constipation, DKT reduced symptoms of constipation and improved rectal reservoir function demonstrated through anorectal manometry. DKT was shown to stimulate peristalsis of the intestine, which was associated with resumption of regular bowel habits [45].

III. Hangeshasin-to (HST, TJ-14)—Hangeshasin-to (HST, TJ-14) is prepared from 6 herbs: Pinellia Tuber, Scutellaria Root, Processed Ginger, Glycyrrhiza, Jujube, Ginseng and Coptis Rhizome, and is used in clinical practice to treat diarrhea.

Some of the anti-diarrheal effects of Hange-shashin-to (TJ-14) may be through the attenuation of the increase in the amount of prostaglandin E₂ (PGE₂) as well as promotion of the colonic water absorption [49].

HST and Sairei-to (TJ-114)-treated animals have less damage to the intestinal epithelium induced by irinotecan hydrochloride (CPT-11), suggesting a possible prophylactic use of HST and Sairei-to against CPT-11-induced intestinal toxicity [50].

Drug-associated diarrhea: HST contains baicalin, a beta-glucuronidase inhibitor that has been shown to alleviate diarrhea induced by CPT-11. Based on results of a randomized trial, HST treated subjects showed a significant improvement in diarrhea severity ($p < 0.05$) as well as a reduced frequency of diarrhea among grades 3 and 4 ($p = 0.018$), suggesting the effectiveness of HST on preventing and controlling CPT-11-induced diarrhea [51].

IV. Other herbal medications

Oren-gedoku-to (OGT, TJ15): Oral administration of Oren-gedoku-to extract (OGT, TJ-15) dose-dependently prevented the progression of acute gastric mucosal lesions in rats with water immersion restraint (WIR) stress. The preventive effect of OGT on the lesion progression was stronger than that of Saiko-keishi-to extract (TJ-10) or Shigyaku-san extract (TJ-35). OGT administration attenuated increases in gastric mucosal lipid peroxide

concentration and xanthine oxidase and myeloperoxidase activity that were associated with gastric mucosal lesion progression, and repleted gastric mucosal non-protein SH that was otherwise diminished. These results indicate that OGT exerts a therapeutic effect on WIR stress-induced acute gastric lesions in rats more strongly than Saiko-keishi-to extract or Shigyaku-san extract. The therapeutic effect of OGT may be due to its protective effects against lipid peroxidation and sulphydryl oxidation caused by oxygen free radicals generated by neutrophils in the gastric mucosa [52].

Hange-koboku-to (HKT, TJ-16): The gastric emptying rate in FD patients is significantly lower than in the healthy subjects. However, after 2 weeks of medication with HKT gastric emptying in FD patients and in healthy volunteers was significantly increased and gastrointestinal symptoms improved significantly in the FD patients [53].

Gorei-san (TJ-17): Gorei-san has been used to treat a variety of symptoms including nausea, dry mouth, edema, headache, and dizziness. In a prospective cohort study of 20 patients who experienced nausea or dyspepsia associated with SSRIs, 9 patients were completely resolved, 4 were decreased, 2 were decreased slightly, and 5 were not changed [54].

Summary: Japanese herbal medicines are associated with clinical benefit in the management of several functional gastrointestinal disorders. Physiological studies suggest that the effect of JHM is mediated by either direct or indirect alteration of gastrointestinal motility. RKT is associated with improved symptoms in gastroesophageal reflux disease, and functional and drug-associated dyspepsia. DKT is associated with improvement in post-operative ileus and reduced symptoms in children with constipation. Other herbal medicines are beneficial for diarrhea or dyspepsia associated with administration of other drugs.

There is a paucity of randomized, placebo-controlled trials examining standardized herbal medicine for FGIDs. Studies illustrating the superiority of peppermint and caraway oils, or Iberogast (peppermint, caraway, bitter candy tuft, licorice, lemon balm, angelica, celandine, milk thistle and chamomile) compared to placebo in patients with FD have been published [55]. However, there remains a distinct gap between the evidence supporting CAM in the U.S. and the prevalence of its use. Up to 85% of cancer patients in a California registry reported use of CAM in a recent survey [56]. However, the majority of published studies of CAM have methodological flaws that reduce the impact of results [57]. The disconnect between evidence supporting the effectiveness of CAM and the prevalence of CAM use must be addressed through rigorous clinical trials, which include the use of standardized herbal medicine.

A major limitation of our findings is the lack of availability of herbal medicines that are standardized in both the quantity and quality of ingredients outside of Japan. For this reason, the physiological and clinical effects of herbal medicine in other countries may not be consistent with these data. In addition, few studies have been designed to test the efficacy of JHM in a definitive manner. In order to confirm their efficacy, large-scale, randomized, placebo-controlled, and preferably international studies of JHM are warranted.

In summary, our review reveals that several FGIDs have the potential to be successfully treated with herbal medicine. The evidence is not currently based on multiple, randomized, placebo-controlled trials using common endpoints. However, there are several clinical and multiple physiological studies that support the rationale to examine these medicines in a rigorous manner. As these data are extrapolated to patients outside of Japan, it is important to ensure that herbal medicine is replicated in the quality and quantity of ingredients. It is recommended that future studies use standardized formulations of herbal medicine in

research protocols that evaluate clinically relevant endpoints. Based on the prevalence of CAM use by patients, it appears that there is a mandate to provide accurate data regarding the effectiveness of non-traditional therapy not only to our patients but also to healthcare providers who face the dilemma of recommending or opposing management strategies that incorporate herbal medicine.

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Figure 1.
Extractions of manuscripts

Table 1

Japanese herbal medicine for the treatment of gastrointestinal disorders

Generic Name	Bland Number	Component
Saiko-keishi-to	TJ-10	Bupleurum Root Pinellia Tuber Scutellaria Root Glycyrrhiza Cinnamon Bark Peony Root Jujube Ginseng Ginger
Hange-shasin-to (HST)	TJ-14	Pinellia Tuber Scutellaria Root Processed Ginger Glycyrrhiza Jujube Ginseng Coptis Rhizome
Oren-gedoku-to (OGT)	TJ-15	Scutellaria Root Coptis Rhizome Gardenia Fruit Phellodendron Bark
Hange-koboku-to (HKT)	TJ-16	Pinellia Tuber Poria Sclerotium Magnolia Bark Perilla Herb Ginger
Goreisan	TJ-17	Alisma Rhizome Atractylodes Lancea Rhizome Polyporus Sclerotium Poria Sclerotium Cinnamon Bark
Shigyakusan	TJ-35	Bupleurum Root Peony Root Immature Orange Glycyrrhiza
Rikkunshi-to (RKT)	TJ-43	Atractylodes Lancea Rhizome Ginseng Pinellia Tuber Poria Sclerotium Jujube

Generic Name	Bland Number	Component
		Citrus Unshiu Peel Glycyrrhiza Ginger
Saiboku-to	TJ-96	Bupleurum Root Pinellia Tuber Poria Sclerotium Scutellaria Root Magnolia Bark Jujube Ginseng Glycyrrhiza Perilla Herb Ginger
Dai-Kenchu-to (DKT)	TJ-100	Ginseng Zanthoxylum Fruit Dried Ginger
Sairei-to	TJ-114	Bupleurum Root Alisma Rhizome Pinellia Tuber Scutellaria Root Astractylodes Lancea Rhizome Jujube Polyporus Sclerotium Ginseng Poria Sclerotium Glycyrrhiza Cinnamon Bark Ginger

Table 2

Preclinical and clinical effects of Rikkunshi-to (RKT) and Dai-Kenchu-to (DKT).

	Preclinical	Clinical
Rikkunshi-to (RKT, TJ-43)	reversal of gastric mucosal blood flow reduction [20]	increase in plasma somatostatin and gastrin [13]
	decrease in platelet activating factor (PAF) level and myeloperoxidase activity [20]	improvement of esophageal acid clearance [14]
	increase in gastric surface mucin [19]	reduction of the distal esophageal acid exposure [14]
	gastroprotective effect through nitric oxide [18]	relief of gastrointestinal symptoms in dyspepsia [12]
	increase in plasma acylated ghrelin and food intake [5]	facilitation of gastric emptying [12]
	increase in acetylcholine-induced smooth muscle contraction [10]	restoration of SSRI-related or IHPS (infantile hypertrophic pyloric stenosis)-related nausea [7]
	facilitation of gastric emptying through nitric oxide [8]	coordinating and stimulating effect on gastric myoelectric activity [15]
	induction of gastric adaptive relaxation (accommodation) [9]	reduction of fluvoxamine-associated nausea [6]
	normalization of the hyperreactivity of diacylglycerol kinase and diacylglycerol formation in diabetes mellitus [11]	
Dai-Kenchu-to (DKT, TJ-100)	increase in intestinal blood flow [46]	increase in plasma motilin [38]
	prevention of bacterial translocation [47]	increase in plasma VIP [39,40,41]
	prokinetic effect [22,23,35]	improvement of postoperative bowel motility [42]
	smooth muscle contraction [24,25,27]	reduction of further surgery and recurrence of post-operative ileus [21]
	abatement of morphine-induced colonic transit disorders [28]	reduction of hospital stay of patients with post-operative ileus [43]
	inhibition on carbacol-induced muscular contraction [29]	improvement of obstructive bowel disease in children [44]
	acceleration of small intestinal movement [26,30,31,32,33]	improvement of chronic constipation in children [45]
	improvement of chlorpromazine-induced hypoperistalsis [34]	
	prevention of post-operative intestinal obstruction [36,37]	
	reduction of intestinal transit time in ileus [37]	