Mini-Review

Evidence-based research on traditional Japanese medicine, Kampo, in treatment of gastrointestinal cancer in Japan

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ABSTRACT: Gastrointestinal cancer is a great threat to human health in Japan. Conventional anti-cancer therapies including surgery, radiation, and chemotherapy are the main strategies and play important roles in curing this disease or extending the life of patients with these cancers. On the other hand, patients undergo great suffering induced by these treatments. Kampo, the Japanese traditional medicine, has been used in clinics to reduce side effects and to improve the quality of life of gastrointestinal cancer patients in Japan. In order to testify to the efficacy and safety of these Kampo medicines and to clarify the underlying mechanisms, a number of clinical and basic studies were implemented in the past several decades. These studies suggested the benefits of Kampo medicine as an adjuvant to conventional anti-cancer therapies in treating gastrointestinal cancer. Since the safety and efficacy as well as quality control of traditional medicine have long been focused worldwide, the development course of Kampo medicine may provide reference to other countries in the world.

Keywords: Kampo, traditional medicine, gastro-intestinal cancer, side effects, quality of life

1. Introduction

Traditional medicine, defined in contrast to Western medicine, is the sum total of knowledge, skills and practices based on theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses (*1*). In the world, traditional medicine is generally available, affordable, and commonly used in large parts of Asia, Africa, and Latin America (*2*). In some of the African countries such as Uganda, Tanzania and Ethiopia, 60-90% of the population depends on traditional medicine for primary health care at the present time (*3*). Moreover, the use of traditional medicine as complementary/alternative medicine (CAM) has been reported in 70-90% of populations in developed countries such as Canada, France, Germany and Italy (*3*). In Asia, the use of traditional medicine in Japan (Kampo) has a history of thousands of years and plays an important role to insure human health. Indeed, it is reality that traditional medicine can treat various chronic conditions (*4*). However, evidence of safety and efficacy as well as quality control of traditional medicine have long been focused and highlighted by policy-makers, medical professionals and/or the public in many countries in the world (*5-9*).

Cancer has been the leading cause of death in Japan since 1981 (*10*). In 2010, a total of 353,000 people died of this disease, accounting for one in every three deaths, according to the statistics published by the Japan Ministry of Health, Labor and Welfare. Among causes of cancer deaths in 2009, stomach, colon, rectum, liver, gallbladder and bile ducts, and pancreas cancers lead to 169,932 deaths which make up 49.4% of all deaths induced by malignant tumors (*11*). Thus gastrointestinal tumors are extremely serious cancer types and the most common causes of cancer-related death in Japan at the present stage. Due to early detection by mass screening and application of modern cancer treatment strategies including surgery, radiation, and chemotherapy, the 5-year survival rates of patients with gastrointestinal cancers have shown steady improvement since 1962 according to the hospital-based cancer registry of Japan National Cancer Center Hospital (*12*). On the other hand, those conventional therapies inflict great suffering and require stoic endurance on the part of the patients. In this context, Kampo was introduced into gastrointestinal tumortherapy, aiming to deal with problems such as the side effects of radiotherapy and chemotherapy and various types of general malaise (*13-15*).

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2. Research on Kampo medicine in treatment of gastrointestinal cancer

Kampo medicine plays an important role in cancer prevention in high-risk groups, enhancement of tumor immunity, improvement of general condition after operations, and attenuation of adverse reactions to chemotherapy and radiation. Although several herbs were supposed to have direct antitumor activity, Kampo medicine mainly acts as a kind of adjuvant to conventional antitumor treatments in clinical practice, contributing to the maintenance of a good quality of life for cancer patients (*16*). In this regard, Kampo formulas such as Juzentaihoto, Ninjin'yoeito, Hochuekkito, Shosaikoto, Daikenchuto, and Hangeshashinto are often prescribed to patients with gastrointestinal cancers in Japan (Table 1) (*17-21*).

2.1. *Clinical studies on Kampo medicine used for care of gastrointestinal cancer*

The approval of the currently used Kampo for application in clinics is without rigorous clinical trials from phases I to III but simply based on that Kampo medicine had passed the test of a thousand years of historical experience in Japan (*22*). Although the efficacy of Kampo is believed by many prescribers and patients, objective evaluation of those Kampo medicines to attain scientific evidence is trend-driven. In this regard, a number of clinical trials were carried out to testify to the efficacy and safety of Kampo in Japan. In order to disseminate evidence-based medicine in Kampo products, the Japan Society for Oriental Medicine established the Special Committee for Evidence-based Medicine (EBM) in 2001, aiming to present evidence from "good" studies of Kampo products such as randomized controlled trials (RCTs) published from 1986 when the quality of Kampo formulations reached the present levels. According to their studies, based on the criteria that *i*) studies that employed Kampo formulations are approved by Japan government as a research object, *ii*) studies that used rational methods for experimental design including randomized controlled trials (RCTs), quasi-randomized controlled trials (quasi-RCTs), crossover trials, and meta-analyses, it was demonstrated that there are a total of 359 randomized controlled clinical trials and 1 meta-analysis on Kampo products from the year 1986 (including 1986) to June 2010 (*23*). Based on that evidence, fifty nine Kampo medicines were recommended and included in Japanese Clinical Practice Guidelines by March 31, 2011 (*24*).

The efficacy of Kampo medicine in preventing cancer occurrence, enhancing the immune system, and/or reducing the side effects of conventional therapies has been testified through EBM based clinical trials (Table 2). The combination of operations with chemotherapy is the most common treatment strategy

Table 1. Kampo medicines that are currently used for treatment of gastrointestinal cancers in Japan

Kampo	Formulation*	Composition of crude drugs**	Approved indications
Juzentaihoto	Granules	Astragalus Root, Cinnamon Bark, Rehmannia Root, Peony Root, Cnidium Rhizome, Atractylodes Lancea Rhizome, Japanese Angelica Root, Ginseng, Poria Sclerotium, Glycyrrhiza	Relief of declined constitution after recovery from disease, fatigue and malaise, anorexia, perspiration during sleep, cold limbs, and anemia.
Ninjin'yoeito	Granules	Rehmannia Root, Japanese Angelica Root, Atractylodes Rhizome, Poria Sclerotium, Ginseng, Cinnamon Bark, Polygala Root, Peony Root, Citrus Unshiu Peel, Astragalus Root, Glycyrrhiza, Schisandra Fruit	Relief of declined constitution after recovery from disease, fatigue and malaise, anorexia, perspiration during sleep, cold limbs, and anemia.
Hochuekkito	Granules	Astragalus Root, Atractylodes Lancea Rhizome, Ginseng, Japanese Angelica Root, Bupleurum Root, Jujube, Citrus Unshiu Peel, Glycyrrhiza, Cimicifuga Rhizome, Ginger	Indicated for the symptoms/conditions of patients having delicate constitution, reduced digestive functions, and severe fatigability of limbs.
Shosaikoto	Granules	Bupleurum Root, Pinellia Tuber, Scutellaria Root, Jujube, Ginseng, Glycyrrhiza, Ginger	Relief of the following symptoms of those patients with moderately strong constitution, right upper abdominal tenderness accompanied by fullness and discomfort, coated tongue, oral cavity discomfort, anorexia, and/or those with slight fever and nausea; Improvement of liver dysfunction due to chronic hepatitis.
Daikenchuto	Granules	Processed Ginger, Ginseng, Zanthoxylum Fruit	Relief of abdominal cold feeling and pain accompanied by abdominal flatulence.
Hangeshashinto	Granules	Pinellia Tuber, Scutellaria Root, Processed Ginger, Glycyrrhiza, Jujube, Ginseng, Coptis Rhizome	Relief of the symptoms of those patients with blocked feeling in the stomach pit and occasional nausea, vomiting, anorexia, borborygmus, and a tendency to loose stools or diarrhea.

* Granules are a mixture of extract of crude drugs indicated and certain medicinal accessory materials.
** All the crude drugs comply with the Japanese Pharmacopoeia.

Table 2. Clinical trials of Kampo in treatment of gastrointestinal cancer in Japan

Kampo Formula	Tumor	Study Design	Study Purpose	Conclusion	*Ref.*
Juzentaihoto	Gastric cancer	RCT-envelope 33 patients	Improvement effect on host-immunity in patients undergoing postoperative adjuvant chemotherapy (tegafur/uracil (UFT) 300 mg/day).	Juzentaihoto is useful in gastric cancer patients undergoing postoperative adjuvant UFT.	*27*
Juzentaihoto	Gastric cancer	RCT 94 patients	Efficacy of Juzentaihoto combined with oral 5-fluorouracil (5-FU) as postoperative adjuvant chemotherapy in patients with surgically treated gastric cancer.	Combination of Juzentaihoto with oral 5-FU is effective for patients with surgically treated stage III or IV gastric cancer.	*28*
Juzentaihoto	Colorectal cancer	RCT-envelope 44 patients	To elucidate the mechanism by which Juzentaihoto reduces the adverse reaction to treatment with 5-FU (hepatopathy) by determining the distribution of 5-FU in tissues of patients with colorectal cancer receiving slow-release tegafur preoperatively.	Administration of Juzentaihoto in patients receiving slow-release tegafur capsules increases 5-FU concentration in tumor tissues but decreases 5-FU concentration in normal tissues, enhancing the tumor selectivity of tegafur. This effect may be partly due to the modulation by Juzentaihoto of thymidine phosphorylase activity in tissues and of cytochrome P-450.	*36*
Juzentaihoto	Colorectal cancer	RCT 168 patients	To evaluate the clinical efficacy of Juzentaihoto for the prevention of postoperative recurrence of colorectal cancer.	Juzentaihoto may have a metastasis-suppressive effect, but since these are interim reports, the follow-up is still ongoing.	*37* *38*
Juzentaihoto	Hepatocellular carcinoma	RCT 20 patients	To evaluate the effect of Juzentaihoto for reducing adverse effects of spongel + lipiodol + phosphatidyl choline + cisplatin treatment in transarterial embolization (TAE) for hepatocellular carcinoma.	Juzentaihoto significantly suppresses nausea/vomiting after TAE with spongel + lipiodol + phosphatidyl choline + cisplatin for hepatocellular carcinoma.	*34*
Juzentaihoto	Esophageal, gastric, or colorectal cancer	RCT-envelope 174 patients	Effect on the cell-mediated immunity of postoperative patients with esophageal, gastric, or colorectal cancer.	Juzentaihoto postoperatively administered for treatment of esophageal, gastric, or colorectal cancer may act as a biological response modifier (BRM).	*39*
Juzentaihoto	Gastric and colorectal cancer	RCT-envelope 284 patients	To evaluate the efficacy of Juzentaihoto for reducing adverse effects and improving quality of life (QOL) in postoperative patients undergoing chemotherapy (UFT 4 capsules/day) for gastric, colorectal, or breast cancer (curative resection/non-curative resection).	Juzentaihoto reduces the number of adverse drug reactions and improves QOL in postoperative patients on chemotherapy (UFT 4 capsules/day) for gastric, colorectal, or breast cancer.	*29* *30*
Ninjin'yoeito	Gastric cancer	RCT-envelope 46 patients	Efficacy for reducing adverse effects and improving performance status in patients undergoing postoperative adjuvant chemotherapy (fluoropyrimidine anticancer drug).	Ninjin'yoeito tends to suppress the decreases in RBC count and platelet count but not the decrease in WBC count and does not improve performance status in patients undergoing postoperative adjuvant fluoropyrimidine-based chemotherapy for gastric cancer.	*31*
Ninjin'yoeito	Colorectal cancer	RCT-envelope 23 patients	Immunostimulation and improvement of nutritional status in postoperative patients with colorectal cancer.	Ninjin'yoeito significantly promotes improvement of lymphocyte count and PHA-stimulated lymphocyte proliferation in postoperative patients with colorectal cancer, suggesting its role as a possible biological response modifier.	*40*
Shosaikoto	Colorectal cancer	RCT 20 patients	Immunostimulation and suppression of liver metastasis in postoperative patients with colorectal cancer.	Saiko agents increased PHA-stimulated lymphocyte proliferation and NK cell activity, evaluated by CD57 and CD16, suggesting its immunostimulating effect.	*41*
Shosaikoto	Liver cancer	quasi-RCT 95 patients	Preventive effect on the progression of cirrhosis to liver cancer.	While not significant, the Shosaikoto treatment tends to lower the incidence of liver cancer and AFP.	*33*
Hochuekkito	Large intestine carcinoma	RCT-envelope 20 patients	To evaluate the efficacy of 1-week preoperative treatment with Hochuekkito for improving pre- and post-operative nutritional status and immune function in patients scheduled to undergo laparotomy for large intestine carcinoma.	Preoperative treatment with Hochuekkito may be useful for early recovery from surgery for large intestine carcinoma.	*42*

Continued

Hochuekkito	Gastric/colon cancer	RCT 51 patients	To evaluate the efficacy of pre-operative administration of Hochuekkito for postoperative systemic inflammatory response syndrome (SIRS) in gastric/colon cancer.	Preoperative administration of Hochuekkito significantly suppresses the postoperative inflammatory response to surgical wounding.	25
Hochuekkito	Gastric or colorectal cancer	RCT 48 patients	To evaluate whether preoperative administration of Hochuekkito relieves surgical stress in patients with gastric or colorectal cancer.	Preoperative administration of Hochuekkito extract granules reduces the response to surgical stress and may be helpful for accelerating postoperative recovery.	26
Daikenchuto	Large intestine carcinoma	RCT 30 patients	To evaluate the reduction in the number of days to post-operative flatulence and the anti-inflammatory efficacy of Daikenchuto in patients who underwent laparotomy for large intestine carcinoma.	Daikenchuto is useful in promoting flatulence and inhibiting inflammation after surgery for large intestine carcinoma.	35
Daikenchuto	Colorectal cancer	RCT 175 patients	To evaluate the effects of Daikenchuto on intestinal obstruction following colorectal cancer surgery.	Daikenchuto extract fine granules do not prevent ileus following colorectal cancer surgery, but do result in the reduction of postoperative abdominal pain and irregular bowel movements.	43
Daikenchuto	Liver carcinoma	RCT 20 patients	To evaluate the anti-inflammatory efficacy of Daikenchuto in postoperative patients with liver carcinoma.	Daikenchuto may be useful in inhibiting early postoperative inflammation after surgery for liver carcinoma.	35
Daikenchuto	Gastric and colorectal cancer	RCT-envelope 20 patients	To evaluate the efficacy of Hangeshashinto for delayed diarrhea induced by irinotecan in patients with metastatic gastric and colorectal cancer.	Hangeshashinto is a useful supportive therapy from the viewpoint of QOL in patients treated for advanced gastric and colorectal cancer with S-1/irinotecan combination therapy.	32

Abbreviations: RCT-envelope, randomized controlled trial using sealed envelopes for allocation; RCT, randomized controlled trial; quasi-RCT, quasi-randomized controlled trial.

for gastric cancer. It was demonstrated that preoperative administration of the Kampo medicine Hochuekkito could be helpful in suppressing the postoperative inflammatory response to surgical wounding and accelerating postoperative recovery (*25,26*). In addition, Juzentaihoto, Ninjin'yoeito, and Hangeshashinto were exhibited to have abilities in improving host-immunity and reducing side effects in gastric cancer patients undergoing postoperative adjuvant chemotherapy including tegafur-uracil (UFT), 5-FU, fluoropyrimidine, and irinotecan treatments (*27-32*). The application of Kampo medicine in treatment of liver cancer were also studied (*33-35*). For example, Juzentaihoto was found to suppresses nausea/vomiting after transarterial embolization (TAE) with spongel + lipiodol + phosphatidyl choline + cisplatin for hepatocellular carcinoma (*34*). In addition, Daikenchuto may be useful in inhibiting early postoperative inflammation after surgery for liver carcinoma (*35*). The efficacy of Kampo medicine in treating large intestine cancer and colorectal cancer were extensively investigated. A series of Kampo products including Juzentaihoto, Ninjin'yoeito, Shosaikoto, Hochuekkito, Daikenchuto, and Hangeshashinto were proved to be effective in stimulating immune system, improving nutritional status, acting as biological response modifier, enhancing the tumor selectivity of chemotherapy drugs, or improving the quality of life of cancer patients (Table 2).

These clinical studies suggested the benefits of Kampo medicine in combination with conventional anti-cancer strategies in treatment of gastrointestinal cancers.

2.2. *Basic studies on the mechanisms underlying the effects of Kampo medicine*

Mechanisms underlying the effects of those Kampo medicines have been extensively investigated. Studies indicated that the immunity regulation effects of **Juzentaihoto** and **Hochuekkito** were related with enhancement of humoral immunity, cell-mediated immunity, natural killer (NK) activity, macrophage activity, and production of immunity related cytokines. It was found that oral administration of Juzentaihoto inhibited liver metastasis of colon cancer cells implanted in mice. However, this inhibitory effect was not observed in mice pretreated with 2-chloroadenosine which had an effect to inactivate macrophages. Hochuekkito enhanced the *in vitro* cytotoxic activity of activated T lymphocytes from healthy volunteers and cancer patients (*44*). In a mouse cancer metastasis model prepared by implanting mouse colon cancer cells (Colon 26-L5), removal of NK cells led to the disappearance of the inhibitory effects of Hochuekkito on cancer metastasis (*45*). In addition, oral administration of Hochuekkito to mice enhanced the anti-tumor cytotoxic activity of peritoneal exudate

cells (*46*) and inhibited restraint of a stress-induced decrease of serum interleukin (IL)-12 in tumor bearing mice (*47*). These studies indicated that Juzentaihoto and Hochuekkito may exhibit indirect antitumor activity through enhancing the organism's antineoplastic immune response.

Shosaikoto was shown to lower the incidence of liver cancer in clinical studies (*33*). Basic studies indicated that Shosaikoto has ability to prevent hepatopathy. In hepatocytes isolated from rats, Shosaikoto inhibited antibody-dependent cellular cytotoxicity (ADCC) responses and cell impairment induced by the culture supernatant of activated macrophages (*48*). In addition, Shosaikoto could inhibit liver fibrosis, which may decrease the risk of liver cancer. In rat liver stellate cells, Shosaikoto inhibited proliferation and transformation to myofibroblast-like cells, and suppressed type I/III procollagen mRNA expression (*49*). In another study, a diet containing Shosaikoto was given to a rat fibrosis model induced by dimethylnitrosamine or porcine serum. It inhibited an increase in the malondialdehyde level *in vivo*. Furthermore, it inhibited oxidative stress in rat liver stellate cells and hepatocytes *in vitro* (*50*). These studies illustrated the direct protective effects of Shosaikoto on liver cells. Also, Shosaikoto was found to exhibit an immune stimulatory effect. Oral administration of Shosaikoto to mice and rats activated macrophages (*48*). Other studies demonstrated that Shosaikoto showed a regulatory effect on production of cytokines. For example, oral administration of Shosaikoto increased the production of IL-1, IL-2, IL-1β, IL-6, IL-10, GM-CSF, TNF-α, and IFN-γ and decreased the excessive production of IL-4 and IL-5 in peripheral blood mononuclear cells derived from healthy individuals or chronic hepatitis patients (*48,51-53*). The activities of lymphokine-activated killer (LAK) cells and NK cells in human peripheral blood mononuclear cells were also enhanced after oral administration of Shosaikoto (*48*). All these experimental studies elucidated the mechanisms underlying the anti-tumor effects of Shosaikoto.

Daikenchuto showed benefits to patients with ileus following colorectal cancer surgery in clinical studies. The pharmacological effects of Daikenchuto are displayed in two aspects (*54*). First, oral administration of Daikenchuto promoted gastrointestinal motility through enhancing the contraction of stomach/duodenum in the resting phase in healthy subjects. Second, oral administration of Daikenchuto increased the plasma motilin, gastrin, plasma vasoactive intestinal polypeptide (VIP), calcitonin gene related peptide (CGRP), substance P, and serotonin levels in healthy subjects or patients with paralytic ileus after extensive hysterectomy with pelvic lymphadenectomy (*55-57*). Mechanisms behind the pharmacological actions of Daikenchuto were illustrated in animal studies.

Daikenchuto improved chlorpromazine-induced decrease of small intestinal and distal colonic transit in mice. It was found that atropine and a cholecystokinin receptor antagonist, lorglumide, could antagonize the activities of Daikenchuto (*58*). In isolated rabbit jejunum, Daikenchuto also enhanced spontaneous contractions and reversed the decrease of spontaneous contractions inhibited by atropine. In the longitudinal muscle of isolated guinea pig ileum, Daikenchuto induced contractions and acetylcholine (ACh) release. The contraction induction effect could be inhibited by pretreatment or concurrent use of atropine, tetrodotoxin, noradrenaline, substance P receptor antagonist, or one 5-HT$_4$ receptor inhibitor ICS205930, but not by pre-exposure to hexamethonium (*59,60*). These experimental studies on laboratory animals suggested that the contractile response induced by Daikenchuto is partially mediated by ACh released from cholinergic nerve endings and that 5-HT$_4$, substance P, and cholecystokinin receptors would be involved in this effect of Daikenchuto.

Hangeshashinto was found to be useful in relieving delayed diarrhea induced by irinotecan which is usually employed to treat metastatic gastric and colorectal cancer (*32*). Studies indicated that Hangeshashinto exhibits pharmacological effects *via* actions including protection of the gastric mucosa, anti-inflammatory actions, and enhancement of large intestinal water absorption. Oral administration of Hangeshashinto to rats inhibited taurocholic acid-induced decreases in the gastric mucosa levels of phospholipids, a reduction of gastric mucosal potential differences, and gastric mucosa back diffusion of H$^+$ (*61*). In addition, Hangeshashinto inhibited an ethanol-induced decrease in the volume of mucus in the superficial gastric mucosa and the deep mucosa of the gastric body (*61*). These results demonstrated the protective effects of Hangeshashinto on gastric mucosa. In regard to its anti-inflammatory actions, oral pretreatment with Hangeshashinto in rats inhibited irinotecan induced production of prostaglandin E$_2$ in the large intestinal mucosa (*62*). In terms of enhancement of large intestinal water absorption, oral administration of Hangeshashinto to rats enhanced water absorption in the large intestine (*63*). In another study, oral pre-treatment of this drug to rats inhibited the irinotecan induced reduction of water absorption in the large intestine (*62*). Thus, these studies suggested the efficacy of Hangeshashinto in reducing side effects induced by the chemotherapy drug irinotecan.

3. Quality control of Kampo medicine

Japan is currently the only developed country where traditional medicine, *i.e.* Kampo, is widely believed by the public, officially recognized by the Government, and mostly (148 of all 210 formulae) covered by the

national health insurance system. Thus far, much progress has been made in scientifically evaluating Kampo medicine. These achievements may be ascribed to, if not all, the standardization of Kampo products. In order to improve quality control of Kampo medicine, an Advisory Committee for Kampo Drugs which is in close association with the Ministry of Health, Labor and Welfare was established in 1982. Since the implementation of Good Manufacturing Practice Law in 1986, equal standards were applied to all pharmaceutical drugs including Western drugs and Kampo drugs. Moreover, guidelines for ethical extract products in oriental medicine formulations were developed in 1985 (*64*). One characteristic of Kampo is that every formulation has consisted of fixed combinations of herbs in standardized proportions, which is different from traditional Chinese medicine with modifying formulas. Although each Kampo product may be produced by various manufacturers, it is composed of exactly the same ingredients under the Ministry's standardization methodology. Moreover, the herbs used in the formulas must have the required levels of at least two marker components in order for the formula to be approved as a medicament (*65*). Because of that, the quality of crude drugs receives a high degree of attention. Since the majority of crude drugs are imported from different countries, they were subjected to rigorous checks such as quantification of the possible active ingredients to guarantee consistency in quality. The herbs also undergo tests for any possible contaminants of agricultural pesticides or environmental pollutants, especially heavy metals. Microbial tests for bacteria, yeast and mold are also carried out. These measures ensure the quality of Kampo products from the very beginning. It is the high and consistent quality of Kampo products that have prepared the groundwork for clinical and basic studies on the therapeutic value of Kampo medicine.

4. Prospects and conclusions

The evaluation of the efficacy and safety of traditional medicine including Kampo is not without challenges. The clinical application of Kampo medicine has long been based on its own diagnosis theory called 'Sho' in Japanese which refers to a particular pathological status of a patient and is patterned according to the patient's constitution and symptoms. The term 'Sho' is different from the disease entities understood in terms of modern Western medicine. However, the currently used evaluation model employed in clinical studies are nearly based on the disease terms defined by Western medicine. Considering the characteristics of Kampo medicine, *i.e.* the uncertainty of active ingredients, the combination of diagnosis theories of Kampo medicine and Western medicine would be more rational in patients selected and grouped in clinical trials in the future. Despite all of this, in terms of scientific evaluation and quality control of traditional medicine, some meaningful conclusions on Kampo medicine are put forward as an exploration for reducing the side effects and improving the quality of gastrointestinal cancer patients subjected to conventional anti-cancer therapies. These achievements may provide reference for the development and dissemination of other traditional medicines in the world.

Acknowledgements

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