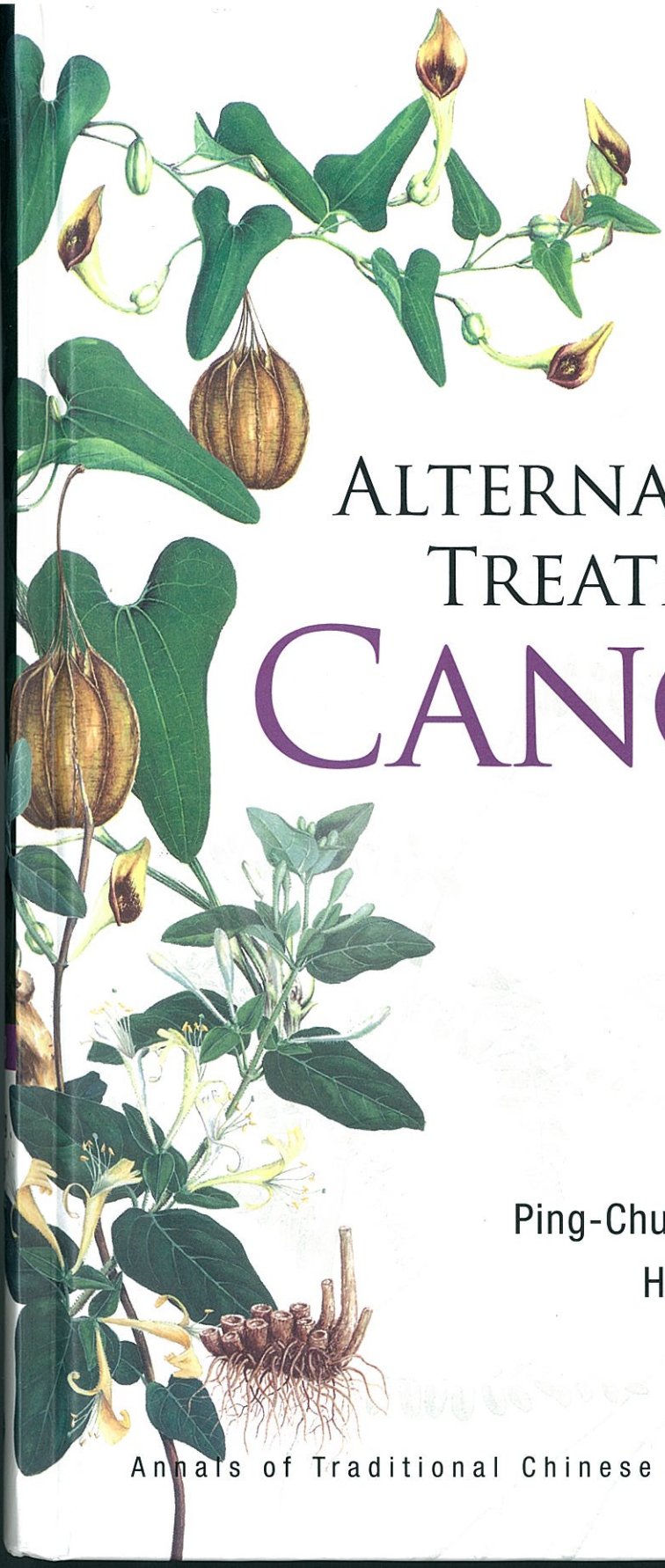

ALTERNATIVE TREATMENT *for* CANCER

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Chapter 6

Kampo Treatment for Cancer

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Abstract

Kampo medicine originated in ancient China and developed uniquely in Japan. More than 70% of Japanese physicians use Kampo medicine in daily practice. As for cancer treatment, Kampo medicine is widely used by surgeons and oncologists. It is used in the regular practice for the treatment of cancer and cancer-related symptoms from the early stage to the terminal care. This paper describes Kampo treatment for cancer, making references to publications in clinical and basic research.

Keywords: Kampo Medicine; Cancer.

6.1 Introduction

Kampo medicine originated in ancient China and developed uniquely in Japan. It has been both taught to, and used by, conventional Western physicians for the last 30 years.

Currently, more than 70% of Japanese physicians (including nearly 100% of Japanese obstetrics and gynaecology (Ob/Gyn) doctors) use Kampo medicine in daily practice including the university hospital, together with high-tech medical treatments like organ transplantation or robotic surgery (Watanabe *et al.*, 2001). Kampo medicine is considered a government-regulated prescription drug and currently 148 formulas are listed on the Japanese national insurance program.

As for cancer treatment, Kampo medicine is widely used by surgeons and oncologists. It is widely used in the regular practice for the treatment

of cancer and cancer-related symptoms from the early stage to the terminal care. Because Kampo medicine has been totally integrated into Western medicine in Japan, motivation to promote clinical trials is lacking. On the contrary, basic research concerning cancer treatment have piled over the last 30 years by the physicians and pharmaceutical researchers. Prevention of recurrence or metastasis of cancer cells have been well studied in basic research, however there is little data in the clinical study because it takes time to accomplish.

In this review article, Kampo treatment for cancer will be described based on the clinical and basic research articles.

6.2 Prevention of Cancer

Chemoprevention is one of the topics in cancer treatment since it has been reported that non-steroidal anti-inflammatory drugs (NSAIDs) reduce the prevalence of colon cancer (Thun *et al.*, 1991).

6.2.1 *Shosaikoto* (小柴胡湯) *for the prevention of the hepatocellular carcinoma*

Since *Shosaikoto* was reported to decrease the serum levels of AST and ALT (Fujiwara *et al.*, 1988), it has been widely used for the treatment of chronic hepatitis. Because chronic hepatitis is very common in Japan as well as other Asian countries and no established treatment is available, *Shosaikoto* is widely used for the purpose of liver protection. Oka *et al.* (2002) reported on a five-year follow-up study of liver cirrhosis patients. The subjects were 260 patients and randomly divided into two groups, one treated with *Shosaikoto* and the other without. Onset of the hepatocellular carcinoma and survival rate were evaluated. The results revealed that the onset of hepatocellular carcinoma decreased and longevity improved in the group with *Shosaikoto* especially in the group of liver cirrhosis by non-B viruses. In the US, the effectiveness of *Shosaikoto*, *Hochuekkito* and *Ninjinyoueito* as well as glycirrhizine are listed as the effective treatment for chronic hepatitis (Shiota *et al.*, 2002). However

the mechanism is not obvious, it is assumed that oxidative stress plays an important role in hepatocarcinogenesis. Shiota *et al.* (2002) investigated the anti-oxidative actions of *Shosaikoto*, and found that, *Shosaikoto* inhibited the 8-hydroxy-2′- deoxyguanosine (8-OHDG) formation, which is a DNA adduct by reactive oxygen species and known to be a genetic risk for hepatocarcinogenesis (Seeff *et al.*, 2001).

6.2.2 *Shoseiryuto* (小青竜湯) *for the prevention of lung cancer*

In the basic research, there are several reports. One is the *Shoseiryuto* (小青竜湯) for the prevention of lung cancer (Konoshima *et al.*, 1994). Lung cancer was induced in the mouse model by 4-nitroquinolone-N-oxide (4NQO) s.c. followed by the glycerol intake. This treatment induced the lung tumor in 93.3% of mice without *Shoseiryuto*, and 33.3% with *Shoseiryuto*. This data showed the reduction of the onset of lung cancer with *Shoseiryuto*.

6.2.3 *Shosaikoto* (小柴胡湯) *for the prevention of melanoma*

Another study was done by Kato *et al.* (1998). He established a *RET*-transgenic mouse line (304/B6) in which stepwise development of a skin melanocytic benign tumor and malignant melanoma can be observed. In this mouse model, he demonstrated that the herbal medicine *Shosaikoto* has anti-tumor and anti-metastatic effects on malignant melanoma through regulation of protein expression levels of matrix metalloproteinase (MMP) and its inhibitor. This study was followed by additional evidence showing that Ret protein expression levels of tumors in *Shosaikoto*-treated mice were higher than those of tumors in untreated mice at benign, malignant, and terminal stages of the tumors. The reduced Ret expression at the terminal stage was partially restored. From this experiment, it was concluded that the anti-tumor effect of *Shosaikoto* involves the promoted preparation of Ret protein as a tumor transplantation antigen, which probably overcomes its potentially increased oncogenic activity (Kato *et al.*, 2005).

6.3 Treatment with Surgical Operation

6.3.1 *Daikenchuto* (大建中湯) *for the prevention of post-surgical ileus*

Daikenchuto has been shown to be effective in preventing the post-surgical ileus and widely used to prevent ileus after abdominal surgeries in the field of not only gastrointestinal but also gynecology (Itoh *et al.*, 2002). *Daikenchuto* also prevents post-surgical intestinal adhesion by gastroprokinetic and anti-inflammatory effects. Motilin, one of the neuropeptides which is a powerful inducer of motor activity in the gastrointestine, was elevated in the blood after the administration of *Daikenchuto* in humans (Nagano *et al.*, 1999). In addition, *Daikenchuto* has been shown to induce production of vasoactive intestinal peptide (VIP) and 5-hydroxytryptamine (serotonin) in human plasma (Nakamura *et al.*, 2002). These neuropeptides may play a role to induce the motility of the gastrointestine. Also, Sanshol in *Zanthoxylum piperitum* binds to the vaniloid receptor and stimulates the peristalsis (Satoh *et al.*, 2001). [6]-shogaol is an important component in dried ginger and produces an increase in the gastrointestinal blood flow, which is medicated by calcitonine gene-related peptide (CGRP), and explains why *Daikenchuto* is useful in the treatment of intestinal ischemia-related diseases (Murata *et al.*, 2001; Hashimoto *et al.*, 2001). This action is observed only when steamed ginger is used and not the dry ginger. Steam manipulation is observed in converting the Gingerol to Shogaol in the ginger and this Shogaol is important in secreting CGRP leading to the increase of blood flow of the gut as a result.

Prolonged paralytic ileus occurring in the hepatectomized patients may induce hyperammonemia. *Daikenchuto* is used to suppress the elevation of serum ammonia in hepatectomized patients (Kaiho *et al.*, 2005). Presumably, *Daikenchuto* stimulates the peristalsis and does not allow the growth of the intestinal bacteria producing ammonia. Imazu *et al.* (2006) showed this hypothesis with a different Kampo formula, *Juzentaihoto*. He showed that the change of the intestinal flora is the main resource of the serum ammonia elevation and this is suppressed by *Juzentaihoto*, because with *Juzentaihoto*, the change of the intestinal flora was suppressed.

6.4 Treatment with Chemotherapy

There are many reports that Kampo treatment reduces the side-effects of chemotherapy. *Juzentaihoto* alleviates the side-effect of UFT (Uracil-Tegafur, anti-cancer drug). Six months follow-up study of gastric cancer patients with UFT after curative operation revealed that suppressor T cell function was lower and cytotoxic/killer cell function higher in the group with *Juzentaihoto* (Yamada *et al.*, 1993). This study also showed that subjective and objective adverse symptoms caused by UFT were less with *Juzentaihoto*.

6.4.1 *Saireito* (柴苓湯) *alleviates the side-effects of CDDP*

Another study examined 26 cases of lung cancer, which was divided into 2 groups, one with *Saireito* (n = 10) and the other without (n = 16) (Okimoto *et al.*, 1991). Nephrotoxicity with cis-diamminedichloroplatinum (CDDP) was evaluated. Serum levels of BUN increased in the group without *Saireito*, while serum BUN levels were not elevated in the group with *Saireito*. Also, creatinin clearance became lower and N-acetyl-D-glucosaminidase increased, while those markers stayed as normal in the group with *Saireito*. This study showed that *Saireito* is effective in alleviating the nephrotoxicity of CDDP.

6.4.2 *Juzentaihoto* (十全大補湯) *alleviates the side-effects of CDDP*

Sugiyama *et al.* screened 11 Kampo formulae to evaluate the protection of nephrotoxicity induced by CDDP (Sugiyama *et al.*, 1993a and 1994). Among the 11 Kampo formulae, nine formulae showed significant reduction of nephrotoxicity. Although Flosemide also reduced the nephrotoxicity, it also diminished the effectiveness of CDDP. Among nine Kampo formulae that reduced the nephrotoxicity, *Juzentaihoto* was the most effective. *Juzentaihoto* also protected the liver and suppressed the liver injury. Among the herbs in *Juzentaihoto*, *Angelicae radix* showed the most effectiveness in liver and kidney protection (Sugiyama *et al.*, 1993b). Sodium malate in *Angelicae radix* was responsible for protecting the liver and kidney functions. The mechanism of action of sodium malate

was that this compound binds to CDDP and forms the diammino-platinum(II) malate, which has a similar chemical structure to the CDDP-derived chemical, Carboplatin (CBDCA). This CBDCA is used clinically and it has less toxicity against the kidney, however, the effect is weaker. Also, this sodium malate did not increase bone toxicity; *Juzentaihoto* protected the bone marrow and blood cell count was not decreased with *Juzentaihoto*.

6.4.3 *Hangeshashinto* (半夏瀉心湯) *alleviates the side-effects of CPT-11*

Another good example that showed the reduction of the side-effects of chemotherapy is *Hangeshashinto*. Irinotecan hydrochloride (CPT-11), a semi-synthetic derivative of camptothecin, is an anti-cancer drug which inhibits nucleic acid synthesis by topoisomerase I inhibition. CPT-11 possesses a wide anti-tumor spectrum and is widely used for the treatment of lung cancer, colon cancer and malignant lymphoma. Diarrhea is the main side-effect that occurs in the early stage and causes the discontinuation of the drug administration. *Hangeshashinto* is used to stop the irinotecan-induced diarrhea. Mori *et al.* (2003) reported the result of RCT of *Hangeshashinto* and CPT-11. Of the 41 patients with advanced lung cancer, 18 took *Hangeshashinto* and 23 did not. Among 41 patients, 39 experienced diarrhea. Although there were no differences of diarrhea frequency and duration, severe diarrhea (grades 3 and 4) was reduced in the group with *Hangeshashinto* (one among 18 patients) as compared to the group without *Hangeshashinto* (nine among 23 patients). This study showed that *Hangeshashinto* is recommended for use with CPT-11. The mechanism of action is also well studied (Takasuna *et al.*, 1995). CPT-11 is changed to 7-ethyl-10 hydroxy-camptotecin (SN-38) in the liver and SN-38 undergoes glucronate conjugation changing into inactive SN-38 glucronide. Later, it is excreted into the bile, and is then deconjugated by β-glucronidase, which was contained in the intestinal bacteria to become SN-38 again. This SN-38 induces delayed diarrhea. *Hangeshashinto* contains baicalin, which serve as another resource of β-glucronidase. This competitive action of baicalin against SN-38 glucronide inhibited the formation of active form of SN-38 without glucronide. As a result, the delayed diarrhea caused by deconjugated SN-38 was alleviated by *Hangeshashinto*.

6.5 Treatment with Irradiation

There is a report that the irradiation with Kampo improved the survival rate in the progressive uterus cervical cancer. Treatment was the combination of low dose *in situ* irradiation and external irradiation. Kampo formulae were *Juzentaihoto* (十全大補湯), *Ninjinyoueito* (人參養栄湯) and *Hochuekkito* (補中益気湯). Irradiation only survival rate is higher in the group treated with Kampo formulae. Five- and ten-year survival rates were 65.6% and 49.1% in the irradiation only group (total number was 119; stage IIb, 64 cases and stage IIIb, 55 cases). On the other hand, these were 75.6% and 65.9% in the irradiation with Kampo group (total number was 82; stage IIb, 43 cases and stage IIIb, 39 cases). This study showed that the combination of Kampo formula and irradiation improved the survival rate of progressive uterus cancer patients (Takekawa *et al.*, 2000).

6.5.1 *Juzentaihoto for the hematopoiesis after irradiation*

Effects of *Juzentaihoto* on the recovery of hemopoietic systems from radiation injury are analyzed (Ohnishi *et al.*, 1990). Colony-forming unit-spleen (CFU-S) are hematopoietic colonies formed in the spleen of recipient mice that have been lethally irradiated and injected with donor bone marrow cells. Day-14 CFU-S represents primitive hematopoietic stem cells (HSCs) and day-9 CFU-S represents more mature HSCs. The mice injected with *Juzentaihoto*-treated bone marrow cells showed better general condition, heavier spleens with larger and more numerous colonies than the control mice on day 14. On the other hand, there was no difference in the number of CFU-S between *Juzentaihoto*-treated and control groups on day 9. Since the day-14 CFU-S assay is thought to reflect the most primitive progenitor cells in the hematopoietic system, these results strongly suggested that *Juzentaihoto* acts on stem cells in the G0 phase to manifest recovery-enhancing effects from radiation injury. After this study, the same group fractionated *Juzentaihoto* to obtain oleic acid and found that

linolenic acid in *Juzentaihoto* was the responsible compound (Hisha *et al.*, 1997).

6.6 Prevention of Recurrence and/or Metastasis

This is one of the very interesting points with Kampo treatment. There are a lot of basic research studies and several clinical studies currently ongoing. The mechanism is also being studied.

6.6.1 *Juzentaihoto for the prevention of colon cancer metastasis*

Oral administration of *Juzentaihoto* before tumor inoculation resulted in the dose-dependent inhibition of liver metastasis of colon 26-L5 carcinoma cells and significant enhancement of survival rate compared to the untreated control (Ohnishi *et al.*, 1998). This effect was lost when macrophages and T-cells were eliminated. These data support the fact that immunological function plays a central role in the mechanism of *Juzentaihoto*.

6.7 Palliative Care

Kampo medicine is also used in palliative care. *Ninjinto* (人参湯), *Shikunshito* (四君子湯), *Rikkunshito* (六君子湯) and *Bukuryoshigyakuto* (茯苓四逆湯) were often used to improve patients' appetite and help them recover from the cachexia.

6.7.1 *Daikenchuto for the constipation by morphine*

Morphine is the most effective anti-nociceptive agent and is used to manage pain experienced by terminal cancer patients. However, it induces severe constipation, causing an obvious reduction in quality of life. *Daikenchuto* is evaluated in the mouse model and has been shown to improve the gastrointestinal movement. The mechanism is assumed to enhance the contraction of longitudinal muscle and relax the tonic contraction of circular muscle (Fukuda *et al.*, 2006). This mechanism explains the mechanism of action of *Daikenchuto* for the constipation induced by morphine.

6.8 Conclusion

I introduced a part of the evidences of Kampo medicine for the treatment of cancer. As a matter of fact, Kampo medicine is broadly used for the treatment of cancer from the early stage to the end of life care. *Juzentaihoto* and *Hochuekkito* are the most commonly used; *Juzentaihoto* is investigated to a greater extent than *Hochuekkito*. However, we need to further investigate the indications and mechanism of action and clarify the usefulness of Kampo treatment for cancer.

References

Fujiwara, K., Ohta, H. and Oka, H. (2002) Suppression of the liver function with Shosaikoto and its components. *J. Tradit. Med.* **5**, 238–241.

Fukuda, H., Chen, C., Mantyh, C., Ludwig, K., Pappas, T.N. and Takahashi, T. (2006) The herbal medicine, Dai-kenchu-to, accelerates delayed gastrointestinal transit after the operation in rats. *J. Surg. Res.* **131**, 290–295.

Hashimoto, K., Satoh, K., Kase, Y., Ishige, A., Kubo, M., Sasaki, H., Nishikawa, S., Kurosawa, S., Yakabi, K. and Nakamura, T. (2001) Modulatory effect of aliphatic acid amides from *Zanthoxylum piperitum* on isolated gastrointestinal tract. *Planta Med.* **67**, 179–181.

Hisha, H., Yamada, H., Sakurai, H., *et al.* (1997) Isolation and identification of hematopoietic stem cell-stimulating substances from Japanese herbal medicine, *Juzen-Taiho-to* (TJ-48). *Blood* **90**, 1022–1030.

Imazu, Y., Tsuiji, K., Toda, T., *et al.* (2006) Juzentaihoto reduces post-partial hepatectomy hyperammonemia by stabilizing intestinal microbiota. *J. Tradit. Med.* **23**, 208–215.

Itoh, T., Yamakawa, J., Mai, M., Yamaguchi, N. and Kanda, T. (2002) The effect of the herbal medicine *Dai-kenchu-to* on post-operative ileus. *J. Int. Med. Res.* **30**, 428–432.

Kaiho, T., Tanaka, T., Tsuchiya, S., *et al.* (2005) Effect of the herbal medicine Dai-kenchu-to for serum ammonia in hepatectomized patients. *Hepatogastroenterology* **52**(61), 161–165.

Kato, M., Liu, W., Yi, H., Asai, N., Hayakawa, A., Kozaki, K., Takahashi, M. and Nakashima, I. (1998) The herbal medicine *Sho-saiko-to* inhibits growth

and metastasis of malignant melanoma primarily developed in ret-transgenic mice. *J. Invest. Dermatol.* **111**(4), 640–644.

Kato, M., Isobe, K., Dai, Y., Liu, W., Takahashi, M. and Nakashima, I. (2005) Further characterization of the *Sho-saiko-to*-mediated anti-tumor effect on melanoma developed in RET-transgenic mice. *J. Invest. Dermatol.* **114**, 599–601.

Konoshima,, T., Takasaki, M., Kozuka, M. and Tokuda, H. (1994) Anti-tumor promoting activities of *kampo* prescriptions. II. Inhibitory effects of *souseiryu-to* on two-stage carcinogenesis of mouse skin tumors and mouse pulmonary tumors. *Yakugaku Zasshi* **114**(4), 248–256.

Mori, K., Kondo, T., Kamiyama, Y., Kano, Y. and Tominaga, K. (2003) Preventive effect of *Kampo* medicine (*Hangeshashin-to*) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer. *Cancer Chemother. Pharmacol.* **51**(5), 403–406.

Murata, P., Hayakawa, T., Sato, K., Kase, Y., Ishige, A. and Sasaki, H. (2001) The herbal medicine *Dai-kenchu-to* and one of its active components [6]-shogaol increase intestinal blood flow in rats. Effects of *Dai-kenchu-to*, a herbal medicine, on uterine and intestinal motility. *Phytother. Res.* **15**(4), 302–306.

Nagano, T., Itoh, H. and Takeyama, M. (1999) Effects of Dai-kenchu-to on levels of 3 brain-gut peptides (motilin, gastrin and somatostatin) in human plasma. *Biol. Pharm. Bull.* **22**(10), 1131–1133.

Nakamura, T., Sakai, A., Isogami, I., Noda, K., Ueno, K. and Yano, S. (2002) Abatement of morphine-induced slowing in gastrointestinal transit by *Daikenchuto*, a traditional Japanese herbal medicine. *Jpn. J. Pharmacol.* **88**, 217–221.

Ohnishi, Y., Yasumizu, R., Fan, H., Liu, J., *et al.* (1990) Effect of *Juzen-taiho-to* (TJ-48), a traditional Oriental medicine, on hematopoietic recovery from radiation injury in mice. *Exp. Hematol.* **18**, 18–22.

Ohnishi, Y., Fujii, H., Hayakawa, Y., *et al.* (1998) Oral administration of a *Kampo* (*Juzen-Taiho-to*) inhibits liver metastasis of colon 26-L5 carcinoma cells. *Jpn. J. Cancer Res.* **89**, 206–213.

Oka, H., Yamamoto, S., Kuroki, T., Harihara, S., Marumo, T., Kim, S.R., Monna, T., Kobayashi, K. and Thango, T. (2002) Prospective study of chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). *Cancer* **76**, 743–749.

Okimoto, J., Kimura, M., Hashiguchi, K., *et al.* (1991) The effect of Saireito on nephrotoxicity incuced by Cisplatin (CDDP). *Diagnos. Ther.* **79**, 1497–1501.

Satoh, K., Hashimoto, K., Hayakawa, T., Ishige, A., Kaneko, M., Ogihara, S., Kurosawa, S., Yakabi, K. and Nakamura, T. (2001) Mechanism of atropine-resistant contraction induced by *Dai-kenchu-to* in guinea pig ileum. *Jpn. J. Pharmacol.* **86**, 32–37.

Seeff, L.B., Lindsay, K.L., Bacon, B.R., Kresina, T.F. and Hoofnagle, J.H. (2001) Complemantary and alternative medicine in chronic liver disease. *Hepatology* **34**, 595–603.

Shiota, G., Maeta, Y., Mukoyami, T., *et al.* (2002) Effects of *Sho-saiko-to* on hepatocarcinogenesis and 8-hydroxy-2′-deoxyguanosine formation. *Hepatology* **35**(5), 1125–1133.

Sugiyama, K., Ueda, H., Suhara, Y., Kajima, Y., Ichio, Y. and Yokota, M. (1993a) Protective effects of *Kampo* medicines against cis-diamminedichloroplatinum (II)-induced nephrotoxicity and bone marrow toxicity in mice. *J. Med. Pharm. Soc.* **10**, 76–85.

Sugiyama, K., Ueda, H., Ichio, Y. and Yokota, M. (1993b) Improvement of cisplatin toxicity and lethality by Juzentaihoto in mice. *Biol. Pharm. Bull.* **18**, 53–58.

Sugiyama, K., Ueda, H., Suhara, Y., Kajima, Y., Ichio, Y. and Yokota, M. (1994) Protective effect of sodium L-malate, an active constituent isolated from *Angelicae Radix*, on cis-diamminedichloroplatinum (II)-induced toxic side effect. *Chem. Pharm. Bull.* **42**, 2565–2568.

Takasuna, K., Kasai, Y., Kitano, Y., Mori, K., Kobayashi, R., Hagiwara, T., Kakihata, K., Hirohashi, M., Nomura, M., Nagai, E. and Kamataki, T. (1995) Protective effects of *Kampo* medicines and baicalin against intestinal toxicity of a new anticancer camptothecin derivative, irinotecan hydrochloride (CPT-11), in rats. *Jpn. J. Cancer Res.* **86**(10), 978–984.

Takekawa, Y., Ikushima, J. and Matsumoto, H. (2000) Irradiation and Kampo. *Gan no Rinsho* **46**, 313–317 (in Japanese).

Thun, M.J., Namboodiri, M.M. and Heath, C.W. Jr. (2002) Aspirin use and reduced risk of fatal colon cancer. *N. Engl. J. Med.* **325**, 1593–1596.

Watanabe, S., Imanishi, J., Satoh, M. and Ozasa, K. (2001) Unique place of kampo (Japanese traditional medicine) in complementary and alternative medicine: A survey of doctors belonging to the regional medical association in Japan. *Tohoku J. Exp. Med.* **194**, 55–63.

Yamada, T., Nabeya, K. and Li, S. (1993) Postoperative combination therapy of chemotherapy and *Juzen-taiho-to* patients with digestive organ (especially gastric) cancer. *Igakuno Ayumi* **167**, 760–764 (in Japanese).