[4] E. Ernst and B. R. Cassileth, "The prevalence of complementary/alternative medicine in cancer: a systematic review," *Cancer*, vol. 83, no. 4, pp. 777–782, 1998.

[5] H. Boon, J. B. Brown, A. Gavin, M. A. Kennard, and M. Stewart, "Breast cancer survivors' perceptions of complementary/alternative medicine (CAM): making the decision to use or not to use," *Qualitative Health Research*, vol. 9, no. 5, pp. 639–653, 1999.

[6] T. G. Liu, S. Q. Xiong, Y. Yan, H. Zhu, and C. Yi, "Use of Chinese herb medicine in cancer patients: a survey in Southwestern China," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 769042, 7 pages, 2012.

[7] Y.-C. Lam, C.-W. Cheng, H. Peng, C.-K. Law, X. Huang, and Z. Bian, "Cancer patients' attitudes towards Chinese medicine: a Hong Kong survey," *Chinese Medicine*, vol. 4, article 25, 2009.

[8] C. Yang, L.-Y. Chien, and C.-J. Tai, "Use of complementary and alternative medicine among patients with cancer receiving outpatient chemotherapy in Taiwan," *Journal of Alternative and Complementary Medicine*, vol. 14, no. 4, pp. 413–416, 2008.

[9] M. J. Kim, S. D. Lee, D. R. Kim et al., "Use of complementary and alternative medicine among Korean cancer patients," *Korean Journal of Internal Medicine*, vol. 19, no. 4, pp. 250–255, 2004.

[10] I. Hyodo, N. Amano, K. Eguchi et al., "Nationwide survey on complementary and alternative medicine in cancer patients in Japan," *Journal of Clinical Oncology*, vol. 23, no. 12, pp. 2645–2654, 2005.

[11] K. M. Field, M. A. Jenkins, M. L. Friedlander et al., "Predictors of the use of complementary and alternative medicine (CAM) by women at high risk for breast cancer," *European Journal of Cancer*, vol. 45, no. 4, pp. 551–560, 2009.

[12] A. Molassiotis, P. Fernandez-Ortega, D. Pud et al., "Use of complementary and alternative medicine in cancer patients: a European survey," *Annals of Oncology*, vol. 16, no. 4, pp. 655–663, 2005.

[13] B. R. Cassileth and A. J. Vickers, "High prevalence of complementary and alternative medicine use among cancer patients: implications for research and clinical care," *Journal of Clinical Oncology*, vol. 23, no. 12, pp. 2590–2592, 2005.

[14] K. M. Kelly, "Complementary and alternative medical therapies for children with cancer," *European Journal of Cancer*, vol. 40, no. 14, pp. 2014–2016, 2004.

[15] P. M. Barnes, B. Bloom, and R. L. Nahin, "Complementary and alternative medicine use among adults and children: United States, 2007," *National health statistics reports*, no. 12, pp. 1–23, 2009.

[16] L. Downey, P. T. Tyree, and W. E. Lafferty, "Preventive screening of women who use complementary and alternative medicine providers," *Journal of Women's Health*, vol. 18, no. 8, pp. 1133–1143, 2009.

[17] C. M. Gray, A. W. H. Tan, N. P. Pronk, and P. J. O'Connor, "Complementary and alternative medicine use among health plan members. A cross-sectional survey," *Effective Clinical Practice*, vol. 5, no. 1, pp. 17–22, 2002.

[18] R. L. Nahin, J. M. Dahlhamer, B. L. Taylor et al., "Health behaviors and risk factors in those who use complementary and alternative medicine," *BMC Public Health*, vol. 7, article 217, 2007.

[19] D. M. Upchurch, L. Chyu, G. A. Greendale et al., "Complementary and alternative medicine use among American women: findings from the National Health Interview Survey, 2002," *Journal of Women's Health*, vol. 16, no. 1, pp. 102–113, 2007.

[20] C. Lawsin, K. DuHamel, S. H. Itzkowitz et al., "Demographic, medical, and psychosocial correlates to CAM use among survivors of colorectal cancer," *Supportive Care in Cancer*, vol. 15, no. 5, pp. 557–564, 2007.

[21] V. B. Konkimalla and T. Efferth, "Evidence-based Chinese medicine for cancer therapy," *Journal of Ethnopharmacology*, vol. 116, no. 2, pp. 207–210, 2008.

[22] T. Efferth and B. Kaina, "Toxicities by herbal medicines with emphasis to traditional Chinese medicine," *Current Drug Metabolism*, vol. 12, no. 10, pp. 989–996, 2011.

[23] A. Molassiotis, M. Browall, L. Milovics, V. Panteli, E. Patiraki, and P. Fernandez-Ortega, "Complementary and alternative medicine use in patients with gynecological cancers in Europe," *International Journal of Gynecological Cancer*, vol. 16, supplement 1, pp. 219–224, 2006.

[24] G. A. Saxe, L. Madlensky, S. Kealey, D. P. H. Wu, K. L. Freeman, and J. P. Pierce, "Disclosure to physicians of CAM use by breast cancer patients: findings from the women's healthy eating and living study," *Integrative Cancer Therapies*, vol. 7, no. 3, pp. 122–129, 2008.

[25] G. Deng, B. R. Cassileth, and K. S. Yeung, "Complementary therapies for cancer-related symptoms," *Journal of Supportive Oncology*, vol. 2, no. 5, pp. 419–426, 2004.

[26] D. Alimi, C. Rubino, E. Pichard-Léandri, S. Fermand-Brulé, M.-L. Dubreuil-Lemaire, and C. Hill, "Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial," *Journal of Clinical Oncology*, vol. 21, no. 22, pp. 4120–4126, 2003.

[27] G. Yang, X. Li, X. L. Li et al., "Traditional Chinese medicine in cancer care: a review of case series published in the Chinese literature," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 751046, 8 pages, 2012.

[28] J. M. Ezzo, M. A. Richardson, A. Vickers et al., "Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting," *Cochrane Database of Systematic Reviews*, vol. 22, no. 2, pp. 138–141, 2006.

[29] S. L. Dibble, J. Luce, B. A. Cooper et al., "Acupressure for chemotherapy-induced nausea and vomiting: a randomized clinical trial," *Oncology Nursing Forum*, vol. 34, no. 4, pp. 813–820, 2007.

[30] T. S. K. Mok, W. Yeo, P. J. Johnson et al., "A double-blind placebo-controlled randomized study of Chinese herbal medicine as complementary therapy for reduction of chemotherapy-induced toxicity," *Annals of Oncology*, vol. 18, no. 4, pp. 768–774, 2007.

[31] P. A. S. Johnstone, Y. P. Peng, B. C. May, W. S. Inouye, and R. C. Niemtzow, "Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies," *International Journal of Radiation Oncology Biology Physics*, vol. 50, no. 2, pp. 353–357, 2001.

[32] P. A. S. Johnstone, R. C. Niemtzow, and R. H. Riffenburgh, "Acupuncture for xerostomia: clinical update," *Cancer*, vol. 94, no. 4, pp. 1151–1156, 2002.

[33] S. Schroeder, G. Meyer-Hamme, and S. Epplée, "Acupuncture for chemotherapy-induced peripheral neuropathy (CIPN)—a pilot study using neurography," *Acupuncture in Medicine*, vol. 30, no. 1, pp. 4–7, 2012.

[34] W. T. Y. Loo, L. Jin, L. W. C. Chow, M. N. B. Cheung, and M. Wang, "Rhodiola algida improves chemotherapy-induced oral mucositis in breast cancer patients," *Expert Opinion on Investigational Drugs*, vol. 19, supplement 1, pp. S91–S100, 2010.

[35] A. J. Vickers, D. J. Straus, B. Fearon, and B. R. Cassileth, "Acupuncture for postchemotherapy fatigue: a phase II study," *Journal of Clinical Oncology*, vol. 22, no. 9, pp. 1731–1735, 2004.

[36] C. P. Escalante, T. Grover, B. A. Johnson et al., "A fatigue clinic in a comprehensive cancer center design and experiences," *Cancer*, vol. 92, supplement 6, pp. 1708–1713, 2001.

[37] J. Filshie, K. Penn, S. Ashley, and C. L. Davis, "Acupuncture for the relief of cancer-related breathlessness," *Palliative Medicine*, vol. 10, no. 2, pp. 145–150, 1996.

[38] L. Y. Wong, C. K. Wong, P. C. Leung, and W. K. Lam, "The efficacy of herbal therapy on quality of life in patients with breast cancer: self-control clinical trial.," *Journal of Patient Preference and Adherence*, vol. 4, pp. 223–229, 2010.

[39] K. K. L. Chan, T. J. Yao, B. Jones et al., "The use of Chinese herbal medicine to improve quality of life in women undergoing chemotherapy for ovarian cancer: a double-blind placebo-controlled randomized trial with immunological monitoring," *Annals of Oncology*, vol. 22, no. 10, pp. 2241–2249, 2011.

[40] A. Molassiotis, J. Bardy, J. Finnegan-John et al., "Acupuncture for cancer-related fatigue in patients with breast cancer: a pragmatic randomized controlled trial," *Journal of Clinical Oncology*, vol. 30, no. 36, pp. 4470–4476, 2012.

[41] A. Enblom, A. Johnsson, M. Hammar, E. Onelöv, G. Steineck, and S. Börjeson, "Acupuncture compared with placebo acupuncture in radiotherapy-induced nausea—a randomized controlled study," *Annals of Oncology*, vol. 23, no. 5, pp. 1353–1361, 2012.

[42] J. P. Liu, M. Zhang, W. Y. Wang, and S. Grimsgaard, "Chinese herbal medicines for type 2 diabetes mellitus," *Cochrane Database of Systematic Reviews*, no. 3, Article ID CD003642, 2004.

[43] W. C. S. Cho, "Scientific evidence on the supportive cancer care with chinese medicine," *Chinese Journal of Lung Cancer*, vol. 13, no. 3, pp. 190–194, 2010.

[44] S. G. Li, H. Y. Chen, C. S. Ou-Yang et al., "The efficacy of Chinese herbal medicine as an adjunctive therapy for advanced non-small cell lung cancer: a systematic review and meta-analysis," *PLoS One*, vol. 8, no. 2, Article ID e57604, 2013.

[45] B. R. Cassileth, G. E. Deng, J. E. Gomez, P. A. S. Johnstone, N. Kumar, and A. J. Vickers, "Complementary therapies and integrative oncology in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition)," *Chest*, vol. 132, no. 3, pp. 340–354, 2007.

[46] Y. J. Lee, Y. R. Jin, W. C. Lim et al., "Ginsenoside-Rb1 acts as a weak phytoestrogen in MCF-7 human breast cancer cells," *Archives of pharmacal research*, vol. 26, no. 1, pp. 58–63, 2003.

[47] J.-H. Kang, K.-H. Song, J.-K. Woo et al., "Ginsenoside Rp1 from panax ginseng exhibits anti-cancer activity by down-regulation of the IGF-1R/Akt pathway in Breast Cancer Cells," *Plant Foods for Human Nutrition*, vol. 66, no. 3, pp. 298–305, 2011.

[48] Y. Motoo, I. Arai, I. Hyodo, and K. Tsutani, "Current status of Kampo (Japanese herbal) medicines in Japanese clinical practice guidelines," *Complementary Therapies in Medicine*, vol. 17, no. 3, pp. 147–154, 2009.

[49] H. A. Tindle, R. B. Davis, R. S. Phillips, and D. M. Eisenberg, "Trends in use of complementary and alternative medicine by us adults: 1997–2002," *Alternative Therapies in Health and Medicine*, vol. 11, no. 1, pp. 42–49, 2005.

[50] Y. Maimon, V. Karaush, N. Yaal-Hahoshen et al., "Effect of Chinese herbal therapy on breast cancer adenocarcinoma cell lines," *Journal of International Medical Research*, vol. 38, no. 6, pp. 2033–2039, 2010.

[51] S. Guan, W. Su, N. Wang, P. Li, and Y. Wang, "A potent tyrosinase activator from radix polygoni multiflori and its melanogenesis stimulatory effect in B16 melanoma cells," *Phytotherapy Research*, vol. 22, no. 5, pp. 660–663, 2008.

[52] C.-C. Lin, C.-L. Kuo, M.-H. Lee et al., "Extract of Hedyotis diffusa Willd influences murine leukemia WEHI-3 cells *in vivo* as well as promoting T- and B-cell proliferation in leukemic mice," *In Vivo*, vol. 25, no. 4, pp. 633–640, 2011.

[53] R. Min, J. Tong, Y. Wenjun et al., "Growth inhibition and induction of apoptosis in human oral squamous cell carcinoma Tca-8113 cell lines by Shikonin was partly through the inactivation of NF-κB pathway," *Phytotherapy Research*, vol. 22, no. 3, pp. 407–415, 2008.

[54] D. M. Eisenberg, E. S. J. Harris, B. A. Littlefield et al., "Developing a library of authenticated Traditional Chinese Medicinal (TCM) plants for systematic biological evaluation—rationale, methods and preliminary results from a Sino-American collaboration," *Fitoterapia*, vol. 82, no. 1, pp. 17–33, 2011.

[55] Q. Luo, Y. Cai, J. Yan, M. Sun, and H. Corke, "Hypoglycemic and hypolipidemic effects and antioxidant activity of fruit extracts from Lycium barbarum," *Life Sciences*, vol. 76, no. 2, pp. 137–149, 2004.

[56] D. Normile, "The new face of traditional Chinese medicine," *Science*, vol. 299, no. 5604, pp. 188–190, 2003.

[57] X. Y. Tian and L. Liu, "Drug discovery enters a new era with multi-target intervention strategy," *Chinese Journal of Integrative Medicine*, vol. 18, no. 7, pp. 539–542, 2012.

[58] J.-J. Lu, W. Pan, Y.-J. Hu, and Y.-T. Wang, "Multi-target drugs: the trend of drug research and development," *PLoS ONE*, vol. 7, no. 6, Article ID e40262, 2012.

[59] I. Raskin and C. Ripoll, "Can an apple a day keep the doctor away?" *Current Pharmaceutical Design*, vol. 10, no. 27, pp. 3419–3429, 2004.

[60] B. M. Schmidt, D. M. Ribnicky, P. E. Lipsky, and I. Raskin, "Revisiting the ancient concept of botanical therapeutics," *Nature Chemical Biology*, vol. 3, no. 7, pp. 360–366, 2007.

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Review Article

Role of Kampo Medicine in Integrative Cancer Therapy

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Clinical trials to date demonstrate that standard cancer treatments are currently the most efficient treatments for large numbers of cancer patients. Cancer treatments will increasingly require approaches that allow patients to live with cancer, by increasing their natural healing power and tumor immunity, as well as attenuating the progression of their cancers, instead of only attacking the cancer cells directly. Complementary and alternative medicine, including Kampo medicine, compensates for the drawbacks of western medicine by increasing patients' self-defense mechanisms. In Japan, clinicians who have studied both western medicine and Kampo treat cancer patients by fusing the two medical systems into a unitary one. The goal of the system is to assist the functional maintenance and recovery of the living body complex with the physical, mental, social, and spiritual balance, rather than addressing direct antitumor effects. In this review, we describe the usefulness of Kampo medicine, especially juzentaihoto, and outline the reports on evidence, in addition to the report on an attitudinal survey about the use of Kampo medicine in cancer treatment in Japan.

1. Limitations of Standard Cancer Treatment

Western medicine should be used in preference to Kampo medicine in the diagnosis and treatment of cancer. Medical diagnosis based on western medicine is essential to determine the exact degree of progression and malignancy of cancer [1–4]. Western medicine successfully treats many types of cancer, when the appropriate treatment is used. Clinical trials to date demonstrate that standard cancer treatments are currently the most efficient treatments for large numbers of cancer patients [5–8]. The current standard cancer treatments include surgery, chemotherapy, and radiation therapy. Reliable therapy has not been established yet for refractory cancer, including advanced or recurrent cancer.

Advanced experimental therapies using special anticancer agents, radiation, immunotherapy, and gene therapy have been attempted. Radiation therapy, chemotherapy, and surgery are called "invasive treatments" [9–12]. The term "invasive" means "harmful to the body" as well as "attacking the cancer." Aggressive treatment has the disadvantage of damaging normal tissue and reducing tumor immunity and physical strength. This is especially true in bone marrow cells or intestinal mucosal epithelia, in which the cell cycle is vigorous [13–18]. The tissues and organs of the whole body maintain order in their structure and function by incorporating nutrients and oxygen from the blood into cells, excreting waste, and repairing old and scar tissues. This is called "natural healing power" or "self-healing power." Abnormal cells such as cancer cells are constantly produced in our body, but as long as the immune system is maintained properly, they are eliminated prior to growth or progression. This means that as long as the immune system is working

properly, cancer is constantly being "cured," without any treatment.

Cancer treatments will increasingly require approaches that allow patients to live with cancer, by increasing their natural healing power and tumor immunity, as well as attenuating the progression of their cancers, instead of attacking the cancer cells [19–21]. Complementary and alternative medicine, including Kampo medicine [22–25], compensates for the drawbacks of western medicine by increasing the body's healing power and resistance [26–29]. The term "multidisciplinary treatment of cancer" refers to treatment that appropriately utilizes a combination of treatments such as standard treatment, advanced experimental treatments, medical care to enhance the anticancer and healing power of the body, and palliative care, depending on the state of the cancer patient. The goal of holistic treatment, or integrated care, is not only to kill cancer cells but also to address the healing power and resistance of the body. Kampo treatment can provide very useful therapeutic options to achieve holistic therapy and multidisciplinary treatment for cancer [30–36].

2. Surveys of the Use of Kampo in Cancer Treatment in Japan

Three papers investigating the use of Kampo in cancer treatment in Japan were published in 2012. Takeda et al. [37] conducted a self-reported questionnaire on Kampo medicine involving a total of 476 patients with gynecologic cancers. Anxiety was assessed using the State-Trait Anxiety Inventory. It was confirmed that 22.9% of the women had used Kampo medicine. Kampo users were more likely to have had chemotherapy and were more likely to have experienced uncomfortable adverse effects of cancer treatment. Kampo users were more likely to believe that Kampo offers relief of symptoms with less adverse effects and that Kampo is more effective than western medicine. Kampo users expressed stronger attitudes in regard to taking Kampo medicine. Multiple regression analysis revealed that chemotherapy (RR, 1.82; 95% CI, 1.14–2.91), lower state anxiety (RR, 0.76; 95% CI, 0.58–1.00), and higher trait anxiety (RR, 1.46; 95% CI, 1.11–1.92) were independently associated with Kampo use. The study showed that approximately one-fourth of Japanese gynecologic cancer patients take Kampo medicine. Kampo users made more favorable comments on Kampo medicine than nonusers. The authors concluded that the psychological characteristics of individual patients are one of the factors that can influence the usage of Kampo.

Iwase et al. [38] conducted a cross-sectional self-administered anonymous questionnaire among 549 physicians working in palliative care teams at 388 core cancer treatment hospitals and 161 certified medical institutions that have palliative care units (PCUs). Valid responses were obtained from 311 physicians (56.7%) who were evenly distributed throughout the country without significant geographical biases. Kampo medicines were prescribed for controlling cancer-related symptoms by 64.3% of the physicians. The symptoms treated with Kampo medicines were numbness/hypoesthesia (n = 99, 49.5%), constipation (n = 76, 38.0%), anorexia/weight loss (n = 72, 36%), muscle cramps (n = 71, 35.5%), and languor/fatigue (n = 64, 32.0%). Regarding open issues about prescription, 60.7% (n = 173) of the physicians raised the issue that the dosage forms need to be better devised. The authors concluded that more evidence from clinical studies is needed to increase the clinical use of Kampo medicines and that the action mechanisms of Kampo should be clarified through laboratory research.

Ito et al. [39] conducted a nationwide survey to investigate the use of Kampo medicine by Japanese physicians in the core cancer treatment hospitals designated by the national Ministry of Health, Labour and Welfare. Among the 900 physicians surveyed, 92.4% reported having prescribed Kampo medications, and 73.5% of those physicians reported having prescribed Kampo medications for cancer patients. Despite this high percentage of usage and the finding that 9.7% of the physicians considered Kampo medications to be harmful, only 23.1% of the physicians expressed high expectations of the efficacy of Kampo medicine in tumor suppression and exertion of an immunostimulatory action. In contrast, many of cancer patients expressed the belief that Kampo can suppress tumor growth. The authors concluded that further research on the efficacy and safety of Kampo medicine in cancer treatment is warranted to resolve this discrepancy between patients' and physicians' expectations.

3. The Role of Kampo Medicine in Multidisciplinary Treatment of Cancer

The Kampo medicine approach is to prevent cancer by emphasizing the body's defense mechanism and natural healing power [22–25]. The existence of even early stage cancer indicates that the healing system is already in functional decline. The fundamental approach of Kampo treatment is to remove obstacles to healing, compensate for deficiencies, and consider the required combination of crude drugs. In western medicine, ideas aimed at activation and nourishing of tissue function are scant, whereas Kampo medicine considers these ideas as the most important treatment strategy. Kampo medicine recognizes that diseases are processes of struggling between individual-specific resistance power and external force of robing those power (e.g., virus). And the former directly determines the occurrence, progression, and outcome of disease. Sanity is a Kampo concept including all of the antidisease substances in the living body, which in modern medicine equates to natural healing power, comprising the mechanisms of self-defense, homeostasis, immune surveillance, and tissue repair. The immune system, antioxidant actions to prevent harm by active oxygen, and the tissue repair system also basically correspond to the concept of sanity in Kampo medicine. In Kampo cancer treatment, we try to treat dysfunction of the body that leads to cancer progression and also try to enhance body function to regain sanity. This is a core characteristic of Kampo treatment of cancer.

The present position of Kampo medicine in the medical treatment of cancer in Japan allows patients to access western and Kampo medical treatments simultaneously. Kampo

medicine [22–25] is a unique medical system that originated from ancient China, was gradually imported to Japan, and has been improved and refined by many excellent physicians since the Edo period. Most Kampo preparations (Japanese traditional herbal medicines) are available as extract formulations, which are greatly different from the herbal medicine practiced in China, Taiwan, and Korea. Four ethical Kampo extract formulations were approved in 1967 in Japan. Since then, the number of ethical Kampo extract formulations covered by health insurance has grown to 148. Japan's universal health insurance system [40, 41] does allow for simultaneous access to traditional Kampo preparations and western medicines. However, physicians in Japan cannot be licensed without passing a board examination on western medicine, which means that patients in this country receive health care with a high degree of safety. This is another factor that distinguishes the health care system in Japan from other countries. In Japan, physicians who have studied western medicine and Kampo medicine practice these approaches in their medical treatment of cancer with the aim of fusing eastern and western medicine into a unitary medical system (unlike the dual medical systems in China or Republic of Korea).

The goal of the system is to assist the functional maintenance and recovery of the living body complex, a host incorporating a nutrient state, mental balance, and so forth, rather than addressing direct anticancer efficacy. The present condition and stance of Kampo medicine in the medical treatment of cancer in Japan clearly diverges from development of an anticancer herbal medicine and formulation of an antitumor herbal tablet.

4. Juzentaihoto: A Typical Kampo Formula for Cancer Treatment

Juzentaihoto is an effective Kampo medicine for promoting restoration of physical strength after surgery and alleviating adverse effects of anticancer drugs or radiation therapy. While there are many other useful Kampo medicines, this discussion focuses on juzentaihoto. Table 1 and Figure 1 show juzentaihoto's composition and constituent analysis. Juzentaihoto is indicated for the relief of declined constitution after recovery from disease, fatigue and malaise, anorexia, perspiration during sleep, cold limbs, and anemia. Important precautions, (1) when this product is used, patient's "*sho*" (constitution and symptoms) should be taken into account. Patient's progress should be carefully monitored, and if no improvement in symptoms or findings is observed, continuous treatment should be avoided. (2) Since this product contains Glycyrrhiza, careful attention should be paid to the serum potassium level, blood pressure, and so forth, and if any abnormality is observed, administration should be discontinued. (3) When this product is coadministered with other Kampo preparations (Japanese traditional herbal medicines), attention should be paid to the duplication of the contained crude drugs.

Juzentaihoto itself has also been reported to prevent cancer occurrence and recurrence, as well as to suppress metastasis. A major report found that juzentaihoto stimulated activation of pluripotent hematopoietic stem cells in irradiated mice [42]. It has also been reported to have an antiangiogenic action in malignant glioma. There have been studies of its actions in suppressing carcinogenesis and metastasis [43–48].

Table 1: Composition of juzentaihoto.

Description	Juzentaihoto extract granules for ethical use	
Composition	7.5 g of juzentaihoto extract granules contains 5.0 g of a dried extract of the following mixed crude drugs	
	JP Astragalus Root	3.0 g
	JP Cinnamon Bark	3.0 g
	JP Rehmannia Root	3.0 g
	JP Peony Root	3.0 g
	JP Cnidium Rhizome	3.0 g
	JP Atractylodes Lancea Rhizome	3.0 g
	JP Japanese Angelica Root	3.0 g
	JP Ginseng	3.0 g
	JP Poria Sclerotium	3.0 g
	JP Glycyrrhiza	1.5 g
	Inactive ingredients	
	JP Magnesium Stearate	
	JP Lactose Hydrate	

Juzentaihoto's biological activity has also been widely reported. Among these reports are studies that found that it activates macrophages, enhances antibody production, induces cytokine production, and has other immunoenhancement actions, in addition to protection against disturbance of myelopoiesis and against immune suppression in anticancer drug and radiation therapy [49].

Muraishi et al. [50] examined the effect of juzentaihoto on immunological functions and antitumor activity in old mice. Juzentaihoto increased the number of T cells remarkably and NK cells slightly in the aged mice, while a significant increase was not observed in young mice.

Treatment with juzentaihoto increased NK activity in both young and old mice. Therefore, the combination of IFNs with juzentaihoto may provide a means to increase the therapeutic potential of IFNs and to decrease their toxicity for the treatment of metastatic renal cell carcinoma. Juzentaihoto increased regulatory activities in T cells by decreasing Foxp3 (+) Treg populations in advanced pancreatic cancer patients [51]. This effect can lead to immunoaugmentation for various combination therapies. Genetic analysis using microarrays has recently been used to indicate its effects in germ-free mice [52]. Ogawa et al. also report that myelosuppression due to TS-1 in mice may be improved with coadministration of juzentaihoto [53]. It is often used for adjunct therapy to cancer therapy as well as the main clinical goals of improving patients' quality of life and alleviating the side effects of anticancer agents and radiation therapy, anorexia, fatigue, and malaise and reduced physical strength following illness. Tokushima University Hospital introduced Kampo

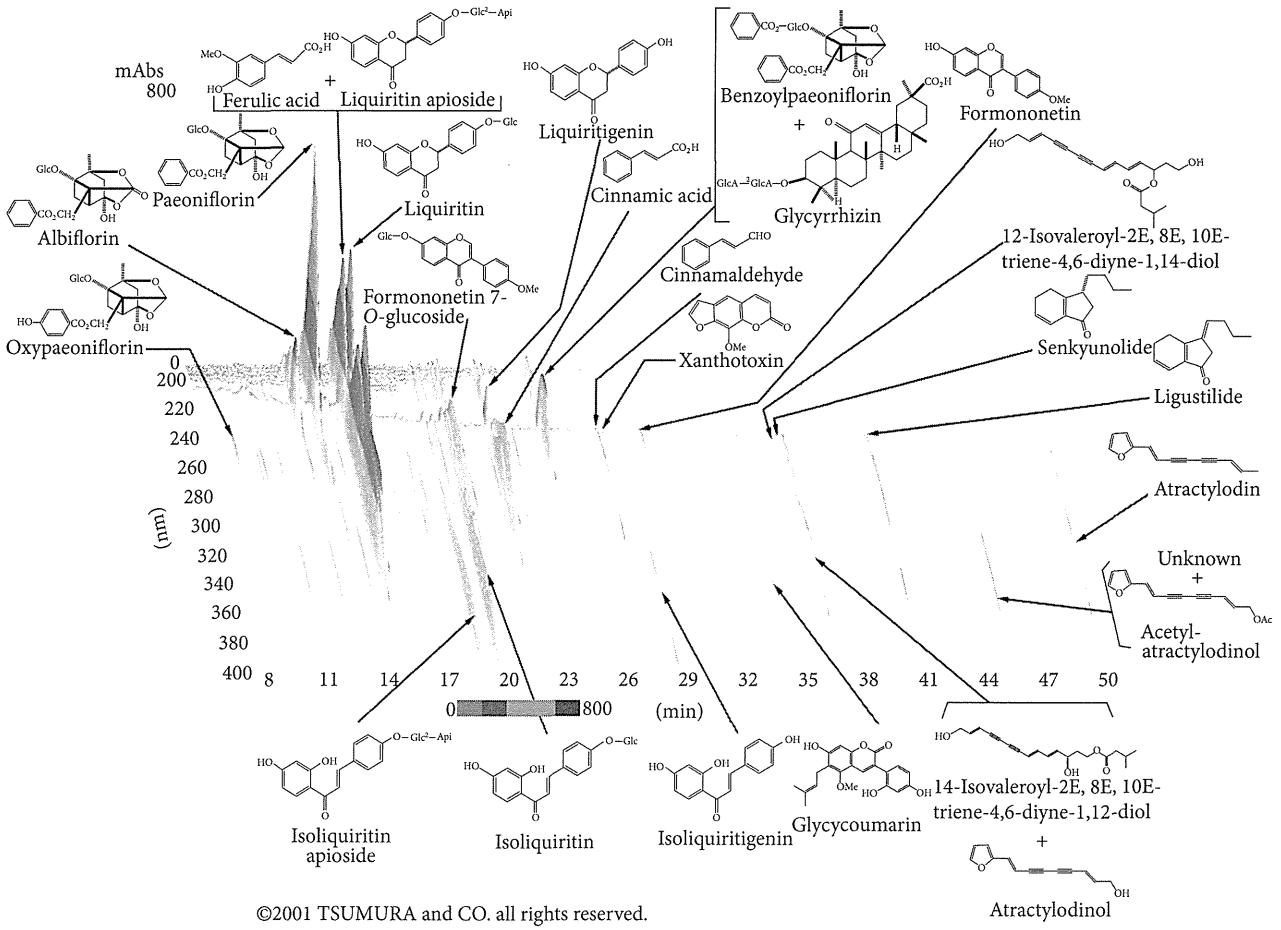

FIGURE 1: 3D-HPLC pattern of TJ-48 juzentaihoto.

medicine therapy to improve general malaise and the various side effects caused by chemotherapy and radiation therapy, which is used at the hospital for planocellular carcinoma of the uterine cervix [54]. The hospital reported that Kampo medicines are allowed for prolongation of the lives of cervical cancer patients. Satou and Arakawa investigated whether Kampo therapy based on traditional approaches is useful or not for inhibition of hepatic cell carcinogenesis (HCC) and reported that therapies based on traditional approaches are useful for HCC in chronic type C liver disease [55].

5. Summary

Several aspects of Kampo treatment in Japan have been introduced here with respect to holistic care, integrative therapy, and multidisciplinary treatment of cancer patients. The Kampo medicine approach is to control cancer by bringing out the natural healing power inherent to living bodies and emphasizing body's defense mechanism. In western medicine, ideas aimed at activation of organ functions and nourishment are scant, whereas Kampo medicine regards enhancement of self-defense mechanisms as the most important strategy. Integrative cancer therapy using Kampo medicine is expected to develop further in Japan.

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References

[1] T. C. Chua and A. Saxena, "Preoperative chemoradiation followed by surgical resection for resectable pancreatic cancer: a review of current results," *Surgical Oncology*, vol. 20, no. 4, pp. e161–e168, 2011.

[2] T. Waddell and D. Cunningham, "Impact of targeted neoadjuvant therapies in the treatment of solid organ tumours," *British Journal of Surgery*, vol. 100, pp. 5–14, 2013.

[3] F. Ferrara and C. A. Schiffer, "Acute myeloid leukaemia in adults," *The Lancet*, vol. 381, pp. 484–495, 2013.

[4] A. Pennathur, M. K. Gibson, B. A. Jobe et al., "Oesophageal carcinoma," *The Lancet*, vol. 381, pp. 400–412, 2013.

[5] J. J. Liu, J. Lu, and M. J. McKeage, "Membrane transporters as determinants of the pharmacology of platinum anticancer drugs," *Current Cancer Drug Targets*, vol. 12, pp. 962–986, 2012.

[6] L. T. MacEdo, J. Ribeiro, G. Curigliano et al., "Multidisciplinary approach in the treatment of patients with small cell bladder

carcinoma," *European Journal of Surgical Oncology*, vol. 37, no. 7, pp. 558–562, 2011.

[7] X. Song, S. R. Long, B. Barber et al., "Systematic review on infusion reactions associated with chemotherapies and monoclonal antibodies for metastatic colorectal cancer," *Current Clinical Pharmacology*, vol. 7, no. 1, pp. 56–65, 2012.

[8] M. J. Deenen, A. Cats, J. H. Beijnen, and J. H. M. Schellens, "Part 2: pharmacogenetic variability in drug transport and phase I anticancer drug metabolism," *Oncologist*, vol. 16, no. 6, pp. 820–834, 2011.

[9] E. S. Hsu, "A review of granisetron, 5-hydroxytryptamine3 receptor antagonists, and other antiemetics," *American Journal of Therapeutics*, vol. 17, no. 5, pp. 476–486, 2010.

[10] C. Lee, M. Gianos, and W. B. Klaustermeyer, "Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents," *Annals of Allergy, Asthma and Immunology*, vol. 102, no. 3, pp. 179–187, 2009.

[11] J. Bardy, N. J. Slevin, K. L. Mais, and A. Molassiotis, "A systematic review of honey uses and its potential value within oncology care," *Journal of Clinical Nursing*, vol. 17, no. 19, pp. 2604–2623, 2008.

[12] C. Grande, M. J. Villanueva, G. Huidobro, and J. Casal, "Docetaxel-induced interstitial pneumonitis following non-small-cell lung cancer treatment," *Clinical and Translational Oncology*, vol. 9, no. 9, pp. 578–581, 2007.

[13] E. A. Rodriguez-Frias and W. M. Lee, "Cancer chemotherapy II: atypical hepatic injuries," *Clinics in Liver Disease*, vol. 11, no. 3, pp. 663–676, 2007.

[14] E. A. Rodriguez-Frias and W. M. Lee, "Cancer chemotherapy I: hepatocellular injury," *Clinics in Liver Disease*, vol. 11, no. 3, pp. 641–662, 2007.

[15] T. M. Bosch, I. Meijerman, J. H. Beijnen, and J. H. M. Schellens, "Genetic polymorphisms of drug-metabolising enzymes and drug transporters in the chemotherapeutic treatment of cancer," *Clinical Pharmacokinetics*, vol. 45, no. 3, pp. 253–285, 2006.

[16] M. Ando, Y. Hasegawa, and Y. Ando, "Pharmacogenetics of irinotecan: a promoter polymorphism of UGT1A1 gene and severe adverse reactions to irinotecan," *Investigational New Drugs*, vol. 23, no. 6, pp. 539–545, 2005.

[17] Y. Ando and Y. Hasegawa, "Clinical pharmacogenetics of irinotecan (CPT-11)," *Drug Metabolism Reviews*, vol. 37, no. 3, pp. 565–574, 2005.

[18] R.-J. Bensadoun, N. Magné, P.-Y. Marcy, and F. Demard, "Chemotherapy- and radiotherapy-induced mucositis in head and neck cancer patients: new trends in pathophysiology, prevention and treatment," *European Archives of Oto-Rhino-Laryngology*, vol. 258, no. 9, pp. 481–487, 2001.

[19] R. L. Nahin, "Use of the best case series to evaluate complementary and alternative therapies for cancer: a systematic review," *Seminars in Oncology*, vol. 29, no. 6, pp. 552–562, 2002.

[20] J. D. White, "Complementary and alternative medicine research: a National Cancer Institute perspective," *Seminars in Oncology*, vol. 29, no. 6, pp. 546–551, 2002.

[21] M. A. Richardson and S. E. Straus, "Complementary and alternative medicine: opportunities and challenges for cancer management and research," *Seminars in Oncology*, vol. 29, no. 6, pp. 531–545, 2002.

[22] K. Terasawa, "Evidence-based reconstruction of Kampo medicine: part I-is Kampo CAM?" *Evidence-Based Complementary and Alternative Medicine*, vol. 1, pp. 11–16, 2004.

[23] K. Terasawa, "Evidence-based reconstruction of Kampo medicine: part II-the Concept of Sho," *Evidence-Based Complementary and Alternative Medicine*, vol. 1, pp. 119–123, 2004.

[24] K. Terasawa, "Evidence-based reconstruction of Kampo medicine: part-III-How Should Kampo be Evaluated?" *Evidence-Based Complementary and Alternative Medicine*, vol. 1, pp. 219–222, 2004.

[25] Y. Motoo, T. Seki, and K. Tsutani, "Traditional Japanese medicine, Kampo: its history and current status," *Chinese Journal of Integrative Medicine*, vol. 17, no. 2, pp. 85–87, 2011.

[26] J. D. White, "The National Cancer Institute's perspective and agenda for promoting awareness and research on alternative therapies for cancer," *Journal of Alternative and Complementary Medicine*, vol. 8, no. 5, pp. 545–550, 2002.

[27] L. A. Walker and S. Budd, "UK: the current state of regulation of complementary and alternative medicine," *Complementary Therapies in Medicine*, vol. 10, no. 1, pp. 8–13, 2002.

[28] J. D. White, "Cancer: current research in alternative therapies," *Primary Care*, vol. 29, pp. 379–392, 2002.

[29] M. Markman, "Safety issues in using complementary and alternative medicine," *Journal of Clinical Oncology*, vol. 20, no. 18, supplement, pp. 39S–41S, 2002.

[30] J.-I. Yamakawa, Y. Ishigaki, F. Takano et al., "The Kampo medicines orengedokuto, bofutsushosan and boiogito have different activities to regulate gene expressions in differentiated rat white adipocytes: comprehensive analysis of genetic profiles," *Biological and Pharmaceutical Bulletin*, vol. 31, no. 11, pp. 2083–2089, 2008.

[31] J.-I. Yamakawa, J. Moriya, T. Takahashi et al., "A Kampo medicine, boiogito, inhibits obesity in ovariectomized rats," *Evidence-Based Complementary and Alternative Medicine*, vol. 7, no. 1, pp. 87–95, 2010.

[32] J. J. Gao, P. P. Song, F. H. Qi et al., "Evidence-based research on traditional Japanese medicine, Kampo, in treatment of gastrointestinal cancer in Japan," *Drug Discoveries & Therapeutics*, vol. 6, pp. 1–8, 2012.

[33] H. Yoshiro, N. Sekiya, A. Chino et al., "Three cases of chemotherapy-induced peripheral neuropathy successfully treated with therapy based on kampo diagnosis," *Alternative Therapies in Health & Medicine*, vol. 17, pp. 26–30, 2011.

[34] H. Yasunaga, H. Miyata, H. Horiguchi, K. Kuwabara, H. Hashimoto, and S. Matsuda, "Effect of the Japanese herbal kampo medicine Dai-kenchu-to on postoperative adhesive small bowel obstruction requiring long-tube decompression: a propensity score analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 264289, 7 pages, 2011.

[35] R. Sharma, P. Tobin, and S. J. Clarke, "Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea," *The Lancet Oncology*, vol. 6, no. 2, pp. 93–102, 2005.

[36] K. Mori, T. Kondo, Y. Kamiyama, Y. Kano, and K. Tominaga, "Preventive effect of Kampo medicine (Hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer," *Cancer Chemotherapy and Pharmacology*, vol. 51, no. 5, pp. 403–406, 2003.

[37] T. Takeda, T. Yamaguchi, and N. Yaegashi, "Perceptions and attitudes of Japanese gynecologic cancer patients to Kampo (Japanese herbal) medicines," *International Journal of Clinical Oncology*, vol. 17, no. 2, pp. 143–149, 2012.

[38] S. Iwase, T. Yamaguchi, T. Miyaji et al., "The clinical use of Kampo medicines (traditional Japanese herbal treatments) for

controlling cancer patients' symptoms in Japan: a national cross-sectional survey," *BMC Complementary and Alternative Medicine*, vol. 20, p. 222, 2012.

[39] A. Ito, K. Munakata, Y. Imazu et al., "First nationwide attitude survey of Japanese physicians on the use of traditional Japanese medicine (Kampo) in cancer treatment," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 957082, 8 pages, 2012.

[40] T. Tsutsui and N. Muramatsu, "Japan's universal long-term care system reform of 2005: containing costs and realizing a vision," *Journal of the American Geriatrics Society*, vol. 55, no. 9, pp. 1458–1463, 2007.

[41] N. Ikegami, "The economics of health care in Japan," *Science*, vol. 258, pp. 614–618, 1992.

[42] H. Kamiyama, S. Takano, E. Ishikawa, K. Tsuboi, and A. Matsumura, "Anti-angiogenic and immunomodulatory effect of the herbal medicine "Juzen-taiho-to" on malignant glioma," *Biological and Pharmaceutical Bulletin*, vol. 28, no. 11, pp. 2111–2116, 2005.

[43] K. Tagami, K. Niwa, Z. Lian, J. Gao, H. Mori, and T. Tamaya, "Preventive effect of Juzen-taiho-to on endometrial carcinogenesis in mice is based on Shimotsu-to constituent," *Biological and Pharmaceutical Bulletin*, vol. 27, no. 2, pp. 156–161, 2004.

[44] H. Mori, K. Niwa, Q. Zheng, Y. Yamada, K. Sakata, and N. Yoshimi, "Cell proliferation in cancer prevention; effects of preventive agents on estrogen-related endometrial carcinogenesis model and on an in vitro model in human colorectal cells," *Mutation Research*, vol. 480-481, pp. 201–207, 2001.

[45] M. Matsuo, T. Tani, and I. Saiki, "Organ selectivity of Juzen-taiho-to and Ninjin-yoei-to in the expression of anti-metastatic efficacy," *Journal of Traditional Medicines*, vol. 19, pp. 93–97, 2002.

[46] Y. Onishi, T. Yamaura, K. Tauchi et al., "Expression of the anti-metastatic effect induced by Juzen-taiho-to is based on the content of Shimotsu-to constituents," *Biological and Pharmaceutical Bulletin*, vol. 21, no. 7, pp. 761–765, 1998.

[47] I. Saiki, "A Kampo medicine "Juzen-taiho-to"—prevention of malignant progression and metastasis of tumor cells and the mechanism of action," *Biological and Pharmaceutical Bulletin*, vol. 23, no. 6, pp. 677–688, 2000.

[48] S. Ishikawa, T. Ishikawa, K. Asano et al., "Suppressive effect of Juzentaihoto on vascularization induced by B16 melanoma cells in vitro and in vivo," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 945714, 9 pages, 2012.

[49] M. Utsuyama, H. Seidlar, M. Kitagawa, and K. Hirokawa, "Immunological restoration and anti-tumor effect by Japanese herbal medicine in aged mice," *Mechanisms of Ageing and Development*, vol. 122, no. 3, pp. 341–352, 2001.

[50] Y. Muraishi, N. Mitani, T. Yamaura, H. Fuse, and I. Saiki, "Effect of interferon-α A/D in combination with the Japanese and Chinese traditional herbal medicine Juzen-taiho-to on lung metastasis of murine renal cell carcinoma," *Anticancer Research*, vol. 20, no. 5, pp. 2931–2937, 2000.

[51] T. Ikemoto, M. Shimada, S. Iwahashi et al., "Changes of immunological parameters with administration of Japanese Kampo medicine (Juzen-Taihoto/TJ-48) in patients with advanced pancreatic cancer," 2013.

[52] K. Munakata, K. Takashima, M. Nishiyama et al., "Microarray analysis on germfree mice elucidates the primary target of a traditional Japanese medicine juzentaihoto: acceleration of IFN-α response via affecting the ISGF3-IRF7 signaling cascade," *BMC Genomics*, vol. 13, no. 1, article 30, 2012.

[53] K. Ogawa, T. Omatsu, C. Matsumoto et al., "Protective effect of the Japanese traditional medicine juzentaihoto on myelosuppression induced by the anticancer drug TS-1 and identification of a potential biomarker of this effect," *BMC Complementary and Alternative Medicine*, vol. 9, article 118, 2012.

[54] Y. Takegawa, H. Ikushima, K. Ozaki et al., "Can Kampo therapy prolong the life of cancer patients?" *Journal of Medical Investigation*, vol. 55, no. 1-2, pp. 99–105, 2008.

[55] H. Satou and S. Arakawa, "Inhibitory effect of Kampo (japanese traditional herbal medicine) therapy on the development of hepatocellular carcinoma in patients with HCV-related chronic hepatic disease: usefulness of Kampo therapy based on traditional theory," *Kampo Medicine*, vol. 55, pp. 455–461, 2004.

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Review Article

Significance of Kampo, Japanese Traditional Medicine, in the Treatment of Obesity: Basic and Clinical Evidence

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The cause of obesity includes genetic and environmental factors, including cytokines derived from adipocytes (adipo-cytokines). Although drug therapy is available for obesity, it is highly risky. Our main focus in this review is on the traditional form of Japanese medicine, Kampo, in the treated of obesity. Two Kampo formulas, that is, bofutsushosan (防通散) and boiogito (防己黄耆), are covered by the national health insurance in Japan for the treatment of obesity. Various issues related to their action mechanisms remain unsolved. Considering these, we described the results of basic experiments and presented clinical evidence and case reports on osteoarthritis as examples of clinical application of their two Kampo medicine. Traditional medicine is used not only for treatment but also for prevention. In clinical practice, it is of great importance to prove the efficacy of combinations of traditional medicine and Western medicine and the utility of traditional medicine in the attenuation of adverse effects of Western medicine.

1. Background

1.1. Historical Background. Until the 20th century, Japanese herbal medicine (Kampo medicine) had not been recognized as a useful tool for the treatment of obesity. Since the latter half of the 20th century, great attention has been paid to upper-body obesity or visceral obesity as a risk factor for several lifestyle-related diseases. In the 1980s and 1990s, several investigators proposed that dyslipidemia, high blood glucose, and high blood pressure were important risks for cardiovascular diseases due to metabolic disorders [1–3].

These days, this combination of disorders (i.e., dyslipidemia, hypertension, and hyperglycemia) is indicative of "metabolic syndrome." The initial cause of the metabolic syndrome or abdominal obesity is likely to be visceral fat accumulation (which is regulated by both genetic and environmental factors). It is generally recognized that the accumulation of visceral fat causes the secretion of adiponectin to decrease and the so-called bad adipocytokines (plasminogen activator inhibitor-1 [PAI-1] [4–6], tumour necrosis factor-α [TNF-α] [7–9], angiotensinogen, etc.) to increase. Proper diet and exercise are the basic therapeutic approaches to reduce abdominal obesity. Medications are considered afterwards.

1.2. Antiobesity Medication. Only one antiobesity medication orlistat (Xenical) is currently approved by the Food and Drug Administration (FDA) for long-term use [10–15]. It reduces intestinal fat absorption by inhibiting pancreatic lipase. Rimonabant (Acomplia), a second drug, works via specific blockade of the endocannabinoid system. Its development is originated from the knowledge that cannabis smoking often increases hunger, which is often referred to as "the munchies". Its use in the treatment of obesity had been approved in Europe but not in the USA or Canada due to safety concerns [16–20]. In October 2008, the European Medicines Agency recommended the suspension of the sale of rimonabant as the risks seemed to be greater than the benefits [21]. In October

2010, sibutramine (Meridia), which acts in the brain to inhibit neurotransmitters deactivation and thereby appetite, was withdrawn from the USA and Canadian markets due to cardiovascular concerns [11, 22]. Because of their potential side effects, anti-obesity drugs should only be prescribed for obesity when the benefits outweigh the risks of treatment [23, 24].

Hasani-Ranjbar et al. [25] have reported a systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity. This review focuses on the efficacy and safety of effective herbal medicines in the management of obesity in humans and animals. Of the publications identified in the initial database, 915 results were identified and reviewed, and a total of 77 studies were included (19 human and 58 animal studies). Studies with *Cissus quadrangularis, Sambucus nigra, Asparagus officinalis, Garcinia atroviridis*, and ephedra and caffeine, Slimax (extract of several plants including *Zingiber officinale* and bofutsushosan) showed a significant decrease in body weight. In 41 animal studies, significant weight loss or inhibition of weight gain was found. No significant adverse effects or mortality were observed except in studies with supplements containing ephedra, caffeine, and bofutsushosan.

Given this background, our focus will be on Kampo as the treatment for obesity [26, 27].

2. The Status of Kampo Medicine in the Treatment of Obesity

2.1. The Definition of Obesity. In 1997, the World Health Organization (WHO), in cooperation with the International Obesity Task Force (IOTF), defined normal weight as body mass index (BMI) from 18.5 to <25 kg/m^2 and obesity as BMI ≥25 kg/m^2. According to the Japan Society for the Study of Obesity criteria, obesity disease is diagnosed when individuals have obesity-associated disease or visceral fat area on abdominal CT scan equal to or greater than 100 cm^2 [28].

2.2. Kampo Medicine Provided under Health Insurance in Japan. The Kampo medicine of "traditional medical treatment" in Japan is in special environment. In a covered-medical-services system of Japan, getting a medical license for per the Forney Western medicine is mandate to prescribe Kampo medicine. Medical treatment is performed with the same stance as Western medicine. However, it is very difficult to understand Kampo medicine. Terasawa has indicated the outline of Kampo medicine to the first issue of this journal [29–31]. The universal healthcare system was established in Japan in 1961, and 4 Kampo extracts were approved as prescribable medications in 1967. That number is now 148. The application increased, and according to a survey by the Journal Nikkei Medical, more than 70% of physicians prescribe Kampo drugs today [32]. Physicians in Japan are entitled to prescribe both Western and Kampo medicines. Among the 148 Kampo formulas, only 2 are for the treatment of obesity. The concept of obesity is not described in classical Kampo. However, eating too much sweet food has been described as the cause of diabetes. On the other hand, how to manage and treat lifestyle-related disease is well described in classical Kampo medicine. In this paper, we focus on the two Kampo formulations used in the treatment of obesity, bofutsushosan (防風通聖散) and boiogito (防己黄耆湯).

2.3. Bofutsushosan. Chemical composition and HPLC fingerprint are shown in Figures 1 and 2. Bofutsushosan is indicated for the relief of the following symptoms in patients with thick subcutaneous abdominal fat and a tendency toward constipation: hypertension (palpitation, shoulder stiffness, and hot flushes), obesity, swelling, and constipation. The usual adult dose is 7.5 g/day orally in 2 or 3 divided doses before or between meals. The dosage may be adjusted according to the patient's age, body weight, and symptoms. Bofutsushosan should be administered with care in patients with the following conditions: (1) diarrhea or soft feces (these symptoms may be aggravated), (2) a weak gastrointestinal tract (anorexia, epigastric distress, nausea, vomiting, abdominal pain, soft feces, and diarrhea may occur), (3) anorexia, nausea, or vomiting (these symptoms may be aggravated), (4) a period of weakness after disease or with a greatly weakened constitution (adverse reactions are likely to occur, and the symptoms may be aggravated by treatment), (5) a marked tendency to sweat (excess sweating and/or generalized weakness may occur), (6) cardiovascular disorders including angina pectoris and myocardial infarction or those with a history of such disorders, (7) severe hypertension, (8) severe renal dysfunction, (9) dysuria, and (10) hyperthyroidism. The diseases and symptoms mentioned in (6)–(10) may be aggravated by treatment. The source is *Manbyo-kaishun-Chufumon* (万病回春, 中風門). The prescription was used in Ikkando (一貫堂) medicine, which was systematized by Dohaku Mori (1867–1931). Bofutsushosan is standard for apoplectic patients, whose appearance suggests they are at risk of future cerebral hemorrhage, and are slightly obese, have a paunch, and have a sturdy build with pale yellow skin color. Bofutsushosan is used for people with solid build, slight obesity, thick abdominal subcutaneous fat, strong intestines, and good appetite. They are more prone to constipation who suffer inflammation in the nose and throat because the whole body is susceptible to heating up, and they tend to have high blood pressure with sensitivity to heat.

2.4. Boiogito. Chemical composition and HPLC fingerprint are shown in Figures 3 and 4. Boiogito is indicated for the relief of the following symptoms in white-complexioned, soft-muscled, flabby patients who are easily fatigued, perspire profusely, do not excrete enough urine, and develop edema in the lower limbs, knee joint swelling, and pain: nephritis, nephrosis, nephropathy of pregnancy, hydrocele testis, obesity, arthritis, carbuncles, furuncles, myositis, edema, dermatosis, hyperhidrosis, and menstrual irregularity. The usual adult dose is 7.5 g/day orally in 2 or 3 divided doses before or between meals. The dosage may be adjusted according to the patient's age and body weight and symptoms. (1) When this product is used, the patient's "*Sho*" (証, patterns) should be

Description	Bofutsushosan extract granules for ethical use	
Composition	7.5 g of TSUMURA bofutsushosan extract granules contains 4.5 g of a dried extract of the following mixed crude drugs	
	JP scutellaria root	2.0 g
	JP glycyrrhiza	2.0 g
	JP platycodon root	2.0 g
	JP gypsum	2.0 g
	JP atractylodes rhizome	2.0 g
	JP rhubarb	1.5 g
	JP schizonepeta spike	1.2 g
	JP gardenia fruit	1.2 g
	JP peony root	1.2 g
	JP cnidium rhizome	1.2 g
	JP Japanese angelica root	1.2 g
	JP mentha herb	1.2 g
	JP saposhnikovia root	1.2 g
	JP *Ephedra* herb	1.2 g
	JP forsythia fruit	1.2 g
	JP ginger	0.3 g
	Talc	3.0 g
	Anhydrous mirabilitum	0.7 g
	(JP: the Japanese pharmacopoeia)	
Inactive ingredients	JP light anhydrous silicic acid JP magnesium stearate JP lactose hydrate	

FIGURE 1

taken into account. The patient's progress should be carefully monitored, and if symptoms/findings do not improve, continuous treatment should be avoided. (2) Since this product contains glycyrrhiza (甘草, kanzo), careful attention should be paid to the serum potassium level, blood pressure, and so forth, and if any abnormality is observed, administration should be discontinued. (3) When this product is coadministered with other Kampo preparations (Japanese traditional herbal medicines) and so forth, attention should be paid to duplication of crude drug contents. Sho: the term "Sho" refers to a particular pathological status (pattern of symptoms) determined by Kampo diagnosis. The pattern is based on the patient's constitution, symptoms, and so forth. Kampo preparations (Japanese traditional herbal medicines) should be used after their suitability for "Sho" has been confirmed. The source is the *Kinkiyoryaku* (金匱要略): convulsion, dampness, and heatstroke diseases—water qi diseases (痙湿暍病篇·水氣病編). It says "boiogito is chiefly used for people suffering neuralgia, floating pulse, heavy body, and sweating with aversion to wind. The external signs for boiogito include wind edema and floating pulse. The patient may appear to have a sweaty head, but no other external signs, except the lower body, feels heavy with edema extending to the groin, making bending and extending difficult, and yet suffer no ill effects above the low back." In other words, it is used for patients with the so-called flabby constitution, pale complexion, proneness to fatigue, sweatiness, and decreased urine output. Boiogito is effective for patients who often suffer arthralgia or low back pain, who are susceptible to edema and sensitive to cold, who demonstrate the so-called "frog belly" when lying down, and who have abdominal skin that shows dimpling, softness (deficiency *Nankyo*) when pinched, and flabbiness. Boiogito is more often used in women than men. Patients are pale, plump, flabby, and heavy; their demeanor is listless; they shy away from cleaning and cooking, move infrequently, and eat little. Patients generally pass stools daily, have low menstrual flow, and may complain of irregular menses. They readily perspire, and in summer, their perspiration is profuse. Edema develops in the legs to the degree that shoes and socks are tight by the end of the day.

2.5. Other Prescriptions. Daisaikoto (大柴胡湯) is used for obese patients with muscular build and robust appetite owing to their active lifestyle. When faced with stress or unpleasantness, patients readily develop liver qi depression, irritability, irascibility, a bitter taste in the mouth, and blood congestion in the eye. Transverse invasion of liver qi into the stomach upsets splenogastric function and abnormally promotes appetite, which in turn adds to the obesity [30]. Tokakujokito (桃核承氣湯) and keishibukuryogan (桂枝茯苓丸) are commonly used for women with sudden weight gain in menopause. In patients with blood stasis (Oketsu), the blood rises to the face turning the face and mucous membranes of the tongue and lips red. Venous engorgement and telangiectasia of the skin and mucous membranes is associated with dry, rough skin, lower abdominal bloating, resistance, and tenderness and autonomic symptoms such as upper heat and lower cold (*Hienobose*). Patients also often complain of numbness and pain in various parts of the body.

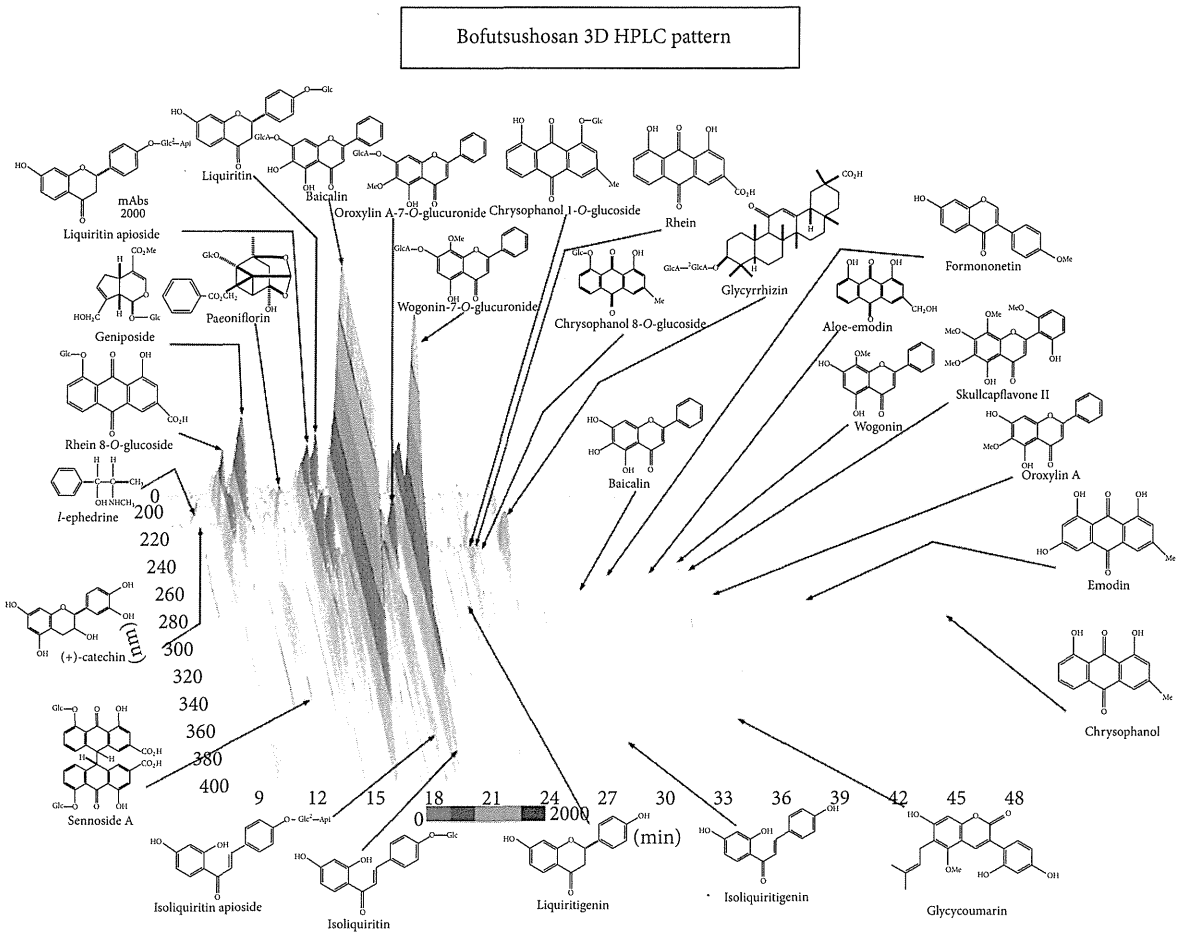

FIGURE 2

Description	Boiogito extract granules for ethical use	
Composition	7.5 g of TSUMURA boiogito extract granules contains 3.75 g of a dried extract of the following mixed crude drugs	
	JP astragalus root	5.0 g
	JP sinomenium stem	5.0 g
	JP atractylodes lancea rhizome	3.0 g
	JP jujube	3.0 g
	JP glycyrrhiza	1.5 g
	JP ginger	1.0 g
	(JP: the Japanese pharmacopoeia)	
Inactive ingredients	JP light anhydrous silicic acid JP magnesium stearate JP lactose hydrate	

FIGURE 3

3. Basic Research of Kampo

3.1. Introduction of Basic Research. Numerous investigators are attempting to clarify how Kampo exerts its effects. However, many issues need to be resolved before the mechanisms are clearly understood. First, as shown by the data on HPLC, many of the components of Kampo have effects. Also, HPLC analysis does not indicate volatile-element composition. Components may chemically react when mixed. Thus, it is hard to show which of the components in Kampo the active

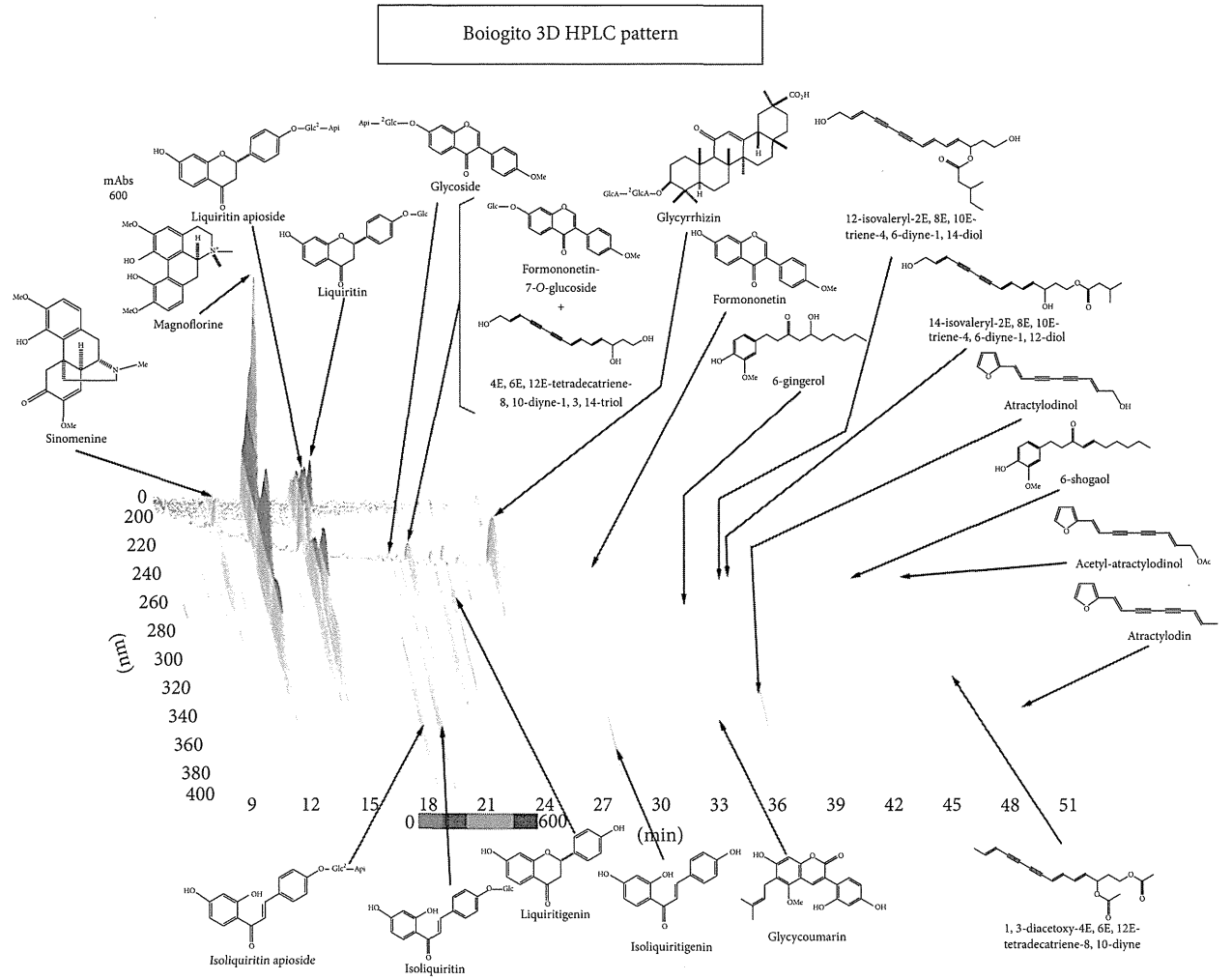

FIGURE 4

components are. Second, Kampo are components considered to be prodrugs, which exert their effects after being metabolized by the human body. On the other hand, some exert their effects immediately after oral administration.

3.2. Bofutsushosan. *Ephedra* herb (麻黄, mao) is one of the most important natural remedies in Kampo. Ephedrine, a main component of *Ephedra* herb, activates adrenalin receptors in sympathetic nerves, leading to increased production of cAMP and in turn to increased heat production from brown adipose tissue [33–35]. Nakayama et al. have reported bofutsushosan that seems effective in the activities of antiobesity, antihyperlipidemia, and antihyperlipids in liver cytoplasm [33]. In France, ephedrine combined with caffeine has been used for the treatment of obesity, and the action mechanism is considered to be phosphodiesterase inhibition [36]. Yoshida et al. have reported the antiobesity action of bofutsushosan in monosodium glutamate (MSG) obese mice [34]. The aim was to investigate whether the antiobesity action of bofutsushosan is due to the stimulation of brown adipose tissue thermogenesis and inhibition of phosphodiesterase activity. Bofutsushosan works by stimulating BAT thermogenesis and inhibiting phosphodiesterase activity in mice. Akagiri et al. have reported that bofutsushosan, an oriental herbal medicine, attenuates the weight gain of white adipose tissue and the increased size of adipocytes associated with the increase in their expression of uncoupling protein 1 in high-fat diet-fed male KK/Ta mice. Bofutsushosan decreases the weight and size gains of WAT along with upregulating UCP1 mRNA in WAT in high-fat diet-fed mice [37]. Shimada et al. have reported preventive effects of bofutsushosan on obesity and various metabolic disorders. In the TSOD mice treated with bofutsushosan, body weight gain and visceral/subcutaneous fat accumulation were significantly suppressed. Biochemical parameters in plasma (glucose, TC, insulin, and tumor necrosis factor-alpha level) were significantly suppressed, and abnormal glucose tolerance, elevation of blood pressure, and peripheral neuropathy accompanying progression of metabolic disorders were also significantly suppressed [27].

3.3. Boiogito. There are few basic experimental studies on boiogito. Shimada et al. have reported preventive effect of boiogito on metabolic disorders in the TSOD mouse,

a model of spontaneous obese type II diabetes mellitus. boiogito is effective as an antiobesity drug for the "asthenic constitution" type in which subcutaneous fat accumulates but cannot be expected to exert a preventive effect against various symptoms of metabolic syndrome that are based on visceral fat accumulation [26]. We previously reported that boiogito had antiobesity action in ovariectomized rats [38]. In this experiment, the antiobesity properties of boiogito were evaluated in ovariectomized rats by measuring changes in levels of serum cytokines and fat cell adipocytokines. After treatment with boiogito for 6 weeks (20-week-old rats), there was a significant weight decrease compared to the control group, a significant dose-dependent increase in serum tumor-necrosis-factor- (TNF-)α level, and a significant increase in adipose-tissue TNF-α level, suggesting that boiogito contributes to weight gain inhibition via the secretion of TNF-α by fat cells. On the other hand, peroxisome proliferator-activated receptor-γ and adiponectin protein levels did not differ significantly between experimental and control groups; the levels of their corresponding mRNAs tended to increase dose dependently, and the level of resistin did not change significantly.

Our previous study using rat preadipocytes suggests that bofutsushosan and boiogito inhibit differentiation and proliferation of white adipocytes through distinct mechanisms [39]. Three Kampo medicines, boiogito, bofutsushosan, and orengedokuto used for treatment of obesity were investigated to determine their effects on adipogenesis in cultured rat white adipocytes. Administration of the three extracts (1–100 mg/mL) suppressed adipogenesis in a concentration-dependent manner without any cytotoxicity. The three herbal extracts were found to have the potential to prevent adipogenesis in rat white adipocytes. Different mechanisms modulating gene expression levels were involved.

4. Clinical Application of Kampo

4.1. Introduction of Evidence-Based Medicine (EBM). Two randomized controlled trials (RCTs) of bofutsushosan show its potential as an antioxidant. Ogawa et al. conducted a double-blind (DB) RCT on the effect of bofutsushosan on the lag time of low-density lipoprotein (LDL) oxidation in healthy individuals [40]. Antioxidants are present in herbs or crude herbal formulations. The effect of bofutsushosan on *ex vivo* LDL oxidation lag time was studied in healthy human subjects. Although bofutsushosan had no detectable systemic antioxidative effects, *ex vivo* results suggested its antioxidative effect on LDL oxidation. The RCT by Hioki et al. demonstrated the effect and safety of bofutsushosan in Japanese obese subjects [41]. The aim was to determine whether bofutsushosan could decrease visceral adiposity and insulin resistance. They concluded that bofutsuhosan could be a useful herbal medicine in treating obesity with impaired glucose tolerance.

4.2. Case of Knee Osteoarthritis. After receiving sufficient medical treatment from an orthopedist, and also in order to raise a patient's quality of life (QOL), they introduce to a Kampo medicine medical specialist. Knee osteoarthritis is a degenerative disease of the knee joint that is more common in people older than 40 years and in women. The most important characteristic of knee osteoarthritis is the degeneration of the knee joint articular cartilage, causing decreased QOL in affected people. Obesity is one of the most important causes of osteoarthritis. We report the two cases of obese patients who showed marked improvement in osteoarthritis-related clinical symptoms as a result of Kampo treatment.

Case 1 (a 64-year-old female). Chief complaints: bilateral articular pain in the knee. Past history: hypertension, hyperlipidemia, obesity, and osteoarthritis. Present illness: from the age of 42 year, she underwent dietary therapy for obesity, which was not remarkably effective. She was referred to our department for Kampo therapy on May 12, 2004. Physical findings: body height 143 cm, body weight 76.4 kg, and BMI 37.4 kg/m^2. Oriental medical diagnosis: interior heat excess pattern (eight principles classification), sunken excessive pulse (pulse diagnosis), yellow slimy tongue fur (tongue diagnosis), and excessive abdominal strength, slight gastric stuffiness, and paunch (abdominal examination); therefore, bofutsushosan (TJ-62) 7.5 g t.i.d. was prescribed (pattern-based diagnosis). Clinical course: body weight was decreased by 4 kg (from 76 kg to 72 kg) in 14 days after the start of bofutsushosan (TJ-62) 7.5 g t.i.d. There was a remarkable improvement in leg edema and bowel movement. On day 28, her body weight was 70 kg, and she no longer needed a painkiller prescribed by her orthopedist for knee osteoarthritis.

Case 2 (a 76-year-old female). Chief complaints: poor condition of the knee. Past history: hyperlipidemia and osteoarthritis. Present illness: she had been treated for hyperlipidemia by her family doctor for a long time. four years ago, she received a diagnosis of knee osteoarthritis and was treated accordingly. She visited our department to receive Kampo treatment on April 20, 2007. Physical findings: body height 151 cm, body weight 60.3 kg, and BMI 26.4 kg/m^2. Oriental medical diagnosis: eight network classification: imaginary cold proof back. Pulse diagnosis: slightly floating. Tongue diagnosis: wet, frank color, and thin white moss. Abdominal examination: belly force: imaginary frog belly leg edema (+) and Based on sui testimony diagnosis, the treatment with boiogito (TJ-20) 7.5 g t.i.d. was initiated. Clinical course: two weeks after the administration of boiogito, knee joint pain was improved, and body weight reduced 2 kg (from 60 to 58 kg). One month after administration, she no longer needed the painkiller prescribed by her orthopedist.

In Case 1, the diagnosis was the hyperfunctioning type of febrile syndrome of the viscera (according to the four paired parameters of Kampo diagnosis) and the so-called "muscular type," which is associated with constipation and dizziness. Bofutsushosan was prescribed because of her marked obesity (BMI 37.4), and it proved to be very effective. In Case 2, the diagnosis was the hypofunctioning type of febrile syndrome of the viscera (according to the four paired parameters of

Kampo diagnosis) and the so-called "white complexion and flabby body type." She had edema and excessive sweating with weak stomach. We prescribed boiogito. Without body movement, no energy is consumed. The lack of exercise reduces the amount of muscle producing energy and, in turn, basal metabolism leading to resistance of the body to energy consumption. Notably, the lack of exercise impacts the reduction of basal metabolism more than it does with the reduction of energy consumption. It is generally accepted that environmental factors as well as genetic factors influence the development of obesity. Still, it is not easy to manage obesity. Lifestyle modifications, such as dietary and exercise interventions, are hard to follow. For obese subjects with knee problems, walking exercise is practically impossible. Thus, any suggestion by family members or others that exercise is needed could impose a mental burden. Based on the findings in the above-mentioned two cases, we suggest that the herbal treatment may trigger the awareness of weight loss. Majima et al. have reported the effect of the Japanese herbal medicine, Boiogito, on the osteoarthritis of the knee with joint effusion. boiogito have a possibility for a treatment modality for joint effusion with osteoarthritis of the knee [42].

5. Conclusion

Modern Western medicine is the official medicine practiced in every country. In Kampo medicine as well as other traditional medicines, different formulas have been prescribed for patients with the same disease, and diagnosis has been made by considering the constitution and condition of each patient. Such an individualized treatment has been successful in patients without any particular abnormalities of laboratory data. WHO is rigorously trying to incorporate complementary medicine into conventional medicine, emphasizing the importance of traditional medicine. Kampo is expected to be applied not only to therapeutics but also to disease prevention. In clinical practice, the usefulness of Kampo in combination with Western medicine is to be confirmed.

References

[1] G. M. Reaven and M. S. Greenfield, "Diabetic hypertriglyceridemia: evidence for three clinical syndromes," *Diabetes*, vol. 30, no. 2, pp. 66–75, 1981.

[2] H. Heine and M. Weiss, "Life stress and hypertension," *European Heart Journal*, vol. 8, pp. 45–55, 1987.

[3] J. Stamler, "Blood pressure and high blood pressure: aspects of risk," *Hypertension*, vol. 18, no. 3, pp. 95–107, 1991.

[4] I. Juhan-Vague, P. Vague, M. C. Alessi et al., "Relationships between plasma insulin triglyceride, body mass index, and plasminogen activator inhibitor 1," *Diabete et Metabolisme*, vol. 13, no. 3, pp. 331–336, 1987.

[5] K. Landin, L. Stigendal, E. Eriksson et al., "Abdominal obesity is associated with an impaired fibrinolytic activity and elevated plasminogen activator inhibitor-1," *Metabolism*, vol. 39, no. 10, pp. 1044–1048, 1990.

[6] I. Juhan-Vague and P. Vague, "Hypofibrinolysis and insulin-resistance," *Diabete et Metabolisme*, vol. 17, no. 1, pp. 96–100, 1991.

[7] C. R. Balistreri, C. Caruso, and G. Candore, "The role of adipose tissue and adipokines in Obesity-related inflammatory diseases," *Mediators of Inflammation*, vol. 2010, Article ID 802078, 19 pages, 2010.

[8] M. Spencer, B. S. Finlin, R. Unal et al., "Omega-3 fatty acids reduce adipose tissue macrophages in human subjects with insulin resistance," *Diabetes*, 2013.

[9] C. M. Phillips, A. C. Tierney, P. Perez-Martinez et al., "Obesity and body fat classification in the metabolic syndrome: impact on cardiometabolic risk metabotype," *Obesity*, vol. 21, no. 1, pp. E154–E161, 2013.

[10] W. C. Mina, R. W. Burns, and B. E. Terry, "The treatment of obesity," *Missouri Medicine*, vol. 100, pp. 248–255, 2003.

[11] M. L. Campbell and M. L. Mathys, "Pharmacologic options for the treatment of obesity," *American Journal of Health-System Pharmacy*, vol. 58, pp. 1301–1308, 2001.

[12] M. H. Noyan-Ashraf, E. A. Shikatani, I. Schuiki et al., "A glucagon-like peptide-1 analog reverses the molecular pathology and cardiac dysfunction of a mouse model of obesity," *Circulation*, vol. 127, pp. 74–85, 2013.

[13] L. M. Kaplan, "Pharmacologic therapies for obesity," *Gastroenterology Clinics of North America*, vol. 39, pp. 69–79, 2010.

[14] G. A. Bray and D. H. Ryan, "Drug treatment of obesity," *Psychiatric Clinics of North America*, vol. 34, pp. 871–880, 2011.

[15] A. Jindal, A. Whaley-Connell, and S. Brietzke, "Therapy of obese patients with cardiovascular disease," *Current Opinion in Pharmacology*, vol. 16, pp. 1471–4892, 2013.

[16] R. Christensen, P. K. Kristensen, E. M. Bartels, H. Bliddal, and A. Astrup, "Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials," *The Lancet*, vol. 370, no. 9600, pp. 1706–1713, 2007.

[17] M. Blüher, "Efficacy and safety of the weight-loss drug rimonabant," *The Lancet*, vol. 371, pp. 555–556, 2008.

[18] A. H. Sam, V. Salem, and M. A. Ghatei, "Rimonabant: from RIO to ban," *Journal of Obesity*, vol. 2011, Article ID 432607, 4 pages, 2011.

[19] D. H. O'Leary, A. Q. Reuwer, S. E. Nissen et al., "Effect of rimonabant on carotid intima-media thickness (CIMT) progression in patients with abdominal obesity and metabolic syndrome: the AUDITOR Trial," *Heart*, vol. 97, pp. 1143–1150, 2011.

[20] E. J. Topol, M. G. Bousser, K. A. Fox et al., "Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial," *The Lancet*, vol. 376, no. 9740, pp. 517–523, 2010.

[21] B. le Foll, D. A. Gorelick, and S. R. Goldberg, "The future of endocannabinoid-oriented clinical research after CB_1 antagonists," *Psychopharmacology*, vol. 205, no. 1, pp. 171–174, 2009.

[22] M. Downey, C. Still, and A. M. Sharma, "Is there a path for approval of an antiobesity drug: what did the sibutramine cardiovascular outcomes Trial find?" *Current Opinion in Endocrinology, Diabetes and Obesity*, vol. 18, pp. 321–327, 2011.

[23] H. Bays and C. Dujovne, "Anti-obesity drug development," *Expert Opinion on Investigational Drugs*, vol. 11, pp. 1189–1204, 2002.

[24] M. O. Dietrich and T. L. Horvath, "Limitations in anti-obesity drug development: the critical role of hunger-promoting neurons," *Nature Reviews Drug Discovery*, vol. 11, pp. 675–691, 2012.

[25] S. Hasani-Ranjbar, N. Nayebi, B. Larijani, and M. Abdollahi, "A systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity," *World Journal of Gastroenterology*, vol. 15, no. 25, pp. 3073–3085, 2009.

[26] T. Shimada, T. Akase, M. Kosugi, and M. Aburada, "Preventive effect of boiogito on metabolic sisorders in the TSOD mouse, a model of spontaneous obese type II diabetes mellitus," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 931073, 8 pages, 2011.

[27] T. Shimada, T. Kudo, T. Akase, and M. Aburada, "Preventive effects of bofutsushosan on obesity and various metabolic disorders," *Biological and Pharmaceutical Bulletin*, vol. 31, no. 7, pp. 1362–1367, 2008.

[28] M. Kanazawa, N. Yoshiike, T. Osaka et al., "Criteria and classification of obesity in Japan and Asia-Oceania," *Asia Pacific Journal of Clinical Nutrition*, vol. 11, pp. 732–737, 2002.

[29] Nikkei Medical Group, "Utilization survey of Kampo medicines," vol. 10, pp. 41–47, 2007.

[30] K. Terasawa, "Evidence-based reconstruction of kampo medicine: part I—is Kampo CAM?" *Evidence-Based Complementary and Alternative Medicine*, vol. 1, pp. 11–16, 2004.

[31] K. Terasawa, "Evidence-based reconstruction of Kampo medicine: part II—the concept of Sho," *Evidence-Based Complementary and Alternative Medicine*, vol. 1, pp. 119–123, 2004.

[32] K. Terasawa, "Evidence-based reconstruction of Kampo medicine: part III—how should kampo be evaluated?" *Evidence-Based Complementary and Alternative Medicine*, vol. 1, pp. 219–222, 2004.

[33] T. Nakayama, S. Suzuki, H. Kudo, S. Sassa, M. Nomura, and S. Sakamoto, "Effects of three Chinese herbal medicines on plasma and liver lipids in mice fed a high-fat diet," *Journal of Ethnopharmacology*, vol. 109, no. 2, pp. 236–240, 2007.

[34] T. Yoshida, N. Sakane, Y. Wakabayashi, T. Umekawa, and M. Kondo, "Thermogenic, anti-obesity effects of bofu-tsusho-san in MSG-obese mice," *International Journal of Obesity*, vol. 19, no. 10, pp. 717–722, 1995.

[35] S. Sakamoto, S. Takeshita, S. Sassa, S. Suzuki, Y. Ishikawa, and H. Kudo, "Effects of colestimide and/or Bofu-tsusho-san on plasma and liver lipids in mice fed a high-fat diet," *In Vivo*, vol. 19, no. 6, pp. 1029–1034, 2005.

[36] A. G. Dulloo, "Herbal simulation of ephedrine and caffeine in treatment of obesity," *International Journal of Obesity and Related Metabolic Disorders*, vol. 26, pp. 590–592, 2002.

[37] S. Akagiri, Y. Naito, H. Ichikawa et al., "Bofutsushosan, an oriental herbal medicine, attenuates the weight gain of white adipose tissue and the increased size of adipocytes associated with the increase in their expression of uncoupling protein 1 in high-fat diet-fed male KK/Ta mice," *Journal of Clinical Biochemistry and Nutrition*, vol. 42, no. 2, pp. 158–166, 2008.

[38] J. I. Yamakawa, Y. Ishigaki, F. Takano et al., "The kampo medicines orengedokuto, bofutsushosan and Boiogito have different activities to regulate gene expressions in differentiated rat white adipocytes: comprehensive analysis of genetic profiles," *Biological and Pharmaceutical Bulletin*, vol. 31, no. 11, pp. 2083–2089, 2008.

[39] J. I. Yamakawa, J. Moriya, T. Takahashi et al., "A kampo medicine, boi-ogi-to, inhibits obesity in ovariectomized rats," *Evidence-based Complementary and Alternative Medicine*, vol. 7, no. 1, pp. 87–95, 2010.

[40] H. Ogawa, F. H. Xu, K. Uebaba, O. Hideki, K. Kazuo, and M. Mikage, "Antioxidative potentiality of a Kampo formulation measured by an ex vivo study," *Journal of Alternative and Complementary Medicine*, vol. 15, no. 3, pp. 267–274, 2009.

[41] C. Hioki, K. Yoshimoto, and T. Yoshida, "Efficacy of bofu-tsusho-san, an oriental herbal medicine, in obese Japanese women with impaired glucose tolerance," *Clinical and Experimental Pharmacology and Physiology*, vol. 31, no. 9, pp. 614–619, 2004.

[42] T. Majima, M. Inoue, Y. Kasahara, T. Onodera, D. Takahashi, and A. Minami, "Effect of the Japanese herbal medicine, boiogito, on the osteoarthritis of the knee with joint effusion," *Sports Medicine, Arthroscopy, Rehabilitation, Therapy and Technology*, vol. 4, p. 3, 2012.

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Review Article

Significance of Kampo, Traditional Japanese Medicine, in Supportive Care of Cancer Patients

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The current standard treatment for cancer is a multidisciplinary therapy whereby various types of treatment are properly combined. Chemotherapy with multiple anticancer drugs is now common, and traditional, complementary, and alternative therapies are adopted as supportive measures. Medical care in Japan is distinguished by the ability for patients to access both Western and Kampo medical cares at the same time. There is a high degree of trust in the safety of Kampo therapies because they are practiced by medical doctors who are educated with fundamental diagnosis of Western medicine. Highly reliable clinical studies are being published, demonstrating that palliative or supportive care for cancer patients using Kampo preparations alleviates adverse effects of chemotherapy or radiotherapy. This paper reports the circumstances around cancer care in Japan where traditional therapeutic Kampo formulas are used for patients undergoing cancer treatment with cutting-edge chemotherapy, specifically to alleviate adverse effects of anticancer drugs.

1. Background

1.1. Historical Background of Cancer Treatment in Japan. Surgery, radiotherapy, and chemotherapy are the main medical treatments for cancer. Chief among those is surgery. In recent years, advances have been made in a range of treatments that target specific characteristics and stages of cancer. By its nature, cancer develops after gene mutations in the body's cells, and the difficulty in treating cancer lies in the fact that cells metastasize. Surgery and radiation are local therapies, which leave the problem of how to treat the invisible remaining cancer cells. What is then required is not a localized treatment but a systemic treatment such as chemotherapy.

But until progress was made in the development of anticancer drugs, there was no effective treatment against cancer once it had spread throughout the body. A combination of surgery with chemotherapy is generally used. And sometimes radiotherapy is also used. Nowadays, the standard treatment is "multidisciplinary treatment [1–5]," a comprehensive form of treatment that efficiently combines a variety of treatments.

1.2. Anticancer Drugs. Chemotherapy now occupies an important position in the treatment of cancer. Anticancer drugs have greatly changed cancer treatment. Excellent therapeutic effects have recently been achieved by combining radiation with anticancer drugs, even for solid cancers. The Achilles heel of anticancer drugs has been the strength of the adverse reactions [6–18]; however, these have been alleviated with the development of administration methods and supportive care to control nausea, vomiting, and so forth; therefore, patients do not suffer as much as before. Yet, the history of chemotherapy is still short. Surgery has been available for about 100 years and radiotherapy for about 50,

but anticancer drugs have only been used to treat cancer for the last 35 years.

Anticancer drugs have completely different effects depending on the type of cancer. While chemotherapy may be effective for some cancers, it is virtually ineffective for others. The effects of anticancer drugs also differ according to the way they are used. Potent effects are demonstrated when using drugs in combination, even if each anticancer drug does not promise sufficient effect when used alone. Nowadays, two to four types of anticancer drugs are used in combination to enhance their effectiveness, even at a modest amount. Such multidrug therapy is now being widely used and offers the hope of synergistic or additive effects.

1.3. Historical Background of Kampo Medicine. Traditional, complementary, and alternative therapies [19–25] are widely used and researched in the USA. Underlying this is the high cost of health care in that country and the common use of cheap folk remedies as well as traditional therapies and supplements against illness. The same situation exists in Europe and is becoming more widespread in Asia, where governments are promoting integrative medicine. There is a universal health insurance system which enables everybody in Japan to receive advanced health care at low cost. Therefore, alternative medicine did not attract attention. Japan's universal health insurance system [26, 27] is held in high regard across the country, and it means patients receive standard care for cancer at any medical service provider under this insurance system. However, if you prefer complementary or alternative therapies, you must pay a private provider out of your own pocket.

Yet, another characteristic of medical care in Japan is that patients can access Western and Kampo medical cares at the same time. Kampo medicine [28–30] is a unique medical system that originated from ancient China, was gradually imported to Japan since approximately 1500 years ago, and has been improved and refined by many excellent physicians especially since the 17th century (Edo periods in Japanese era). Now, most Kampo preparations (Japanese traditional herbal medicines) are available as extract formulations of high quality, which are greatly different from herbal medicines used in China, Taiwan, and Korea, where most preparations are herbal decoctions.

Four ethical Kampo extract formulations were approved in 1967 in Japan. Since then, the number of ethical Kampo extract formulations covered by health insurance has grown to 148. Much Japanese herbal extract preparation is used in Japan. Kampo extract preparation is mostly used in Japan. These Kampo extracts are the combination of herbal medicines from the viewpoint of Kampo theory. Standard examinations are done, and quality control of index ingredient is displayed. Kampo formulation for prescription is used for cancer medical treatment. Japan's universal health insurance system does allow simultaneous access to traditional Kampo preparations and Western medicines. However, doctors in Japan cannot be licensed without passing a board examination of Western medicine, which means patients in this country receive health care with a high degree of safety. This is another factor that distinguishes the health care system in Japan from other countries. In Japan, physicians who have studied Western medicine and Kampo medicine practice these approaches in their medical treatment of cancer with the aim of fusing Eastern and Western medicines into a unitary medical system, unlike the dual medical systems in China or Korea.

1.4. Supportive Care for Cancer Patients Using Kampo Preparations. Some people involved in the treatment of cancer reject Kampo therapy. The biggest reason they give is the scarcity of evidence. Kampo medicine is fundamentally a tailor-made type of treatment, and Kampo prescription is changed according to the patients' condition and symptoms. Therefore, the benefits of Kampo preparations cannot be fully evaluated using the criteria of the randomized clinical trials as in Western medicine. Objective data and proof of action mechanisms are required. Most of the studies on the actions of Kampo preparations have been animal trials and small-scale clinical trials. Little research has been done that offers highly reliable evidence, although progress has been made in this area recently [31–37]. The use of Kampo preparations for palliative and supportive care of cancer patients in combination with anticancer drugs or radiotherapy may offer alleviation of adverse effects and survival benefits, and the number of such research papers being published in international journals is increasing.

2. Kampo for Chemotherapy-Induced Peripheral Neuropathy

2.1. Cancer Chemotherapy-Induced Peripheral Neuropathy. A drawback of most anticancer drugs currently in use is that they are not cancer cell-specific: their actions affect all multiplying cells. They interfere with cancer cell division by interfering with DNA replication and the functioning of the proteins necessary for cell division, but they also damage normal cells. Myeloid cells, immune cells, gastrointestinal mucosal cells, and hair root cells are particularly susceptible to damage and are prone to adverse effects such as bone marrow suppression, immunodeficiency, digestive symptoms, and alopecia. Since nerve and muscle cells do not undergo cell division, they are thought to be robust against such damage. However, some anticancer drugs are known to cause peripheral neuropathy. While it is only certain anticancer drugs that has this side effect, we know that patients who take the following drugs develop peripheral neuropathy: taxane-based drugs [38–43] such as paclitaxel and docetaxel; vinca alkaloids such as vincristine sulfate; and platinum-based drugs [41, 44–55] including cisplatin and oxaliplatin. The causes involve injury to axonal microtubules and direct injury to nerve cells. Microtubules are necessary for the transfer of chromosomes when cells divide. If the formation of microtubules is disturbed, cell division is inhibited. In addition, microtubules are also found within axons, which transmit nerve cell signals, and are involved in axonal development and material transportation. Vinca alkaloids and taxanes, in particular, act on the microtubules within cancer cells but cause neuropathy because they simultaneously damage the

microtubules in normal nerve cells. Platinum-based drugs directly damage nerve cells and are thought to lead to nerve cell axon disorder.

2.2. Medical Treatment of Peripheral Neuropathy. Peripheral neuropathy symptoms include limb extremity numbness, as well as sensory motor ataxia, deep tendon reflex decline, and decreased muscle strength. There is great variation among sufferers of such complaints because sensation of these symptoms is extremely subjective. Patients may variously feel a tingling or stinging numbness or pain in the toes or fingers; an electric, shooting pain; loss of sense of touch; loss of heat/cold sensation; loss of power in the arms/legs; difficulty in grasping objects; or they may fall when walking. There are few effective remedies once peripheral neuropathy appears as a result of chemotherapy. In some cases the neuropathy may be almost irreversible. If symptoms are severe, the anticancer drug treatment must be discontinued or the prescription should be changed. In most cases, neuropathy persists as long as chemotherapy continues, and the symptoms do not disappear completely even after treatment ends, and complete recovery may take a long time. Treatment for peripheral neuropathy is not yet well established. Common medications including the combined use of calcium and magnesium or vitamin B6 and B12 have been reported to be effective to relieve numbness. The main symptomatic treatments for neuropathic pain include antidepressants, NSAIDs, or serotonin and norepinephrine reuptake inhibitors. If pain is severe, morphine and other narcotic analgesics may also be prescribed [56].

2.3. Indications and Evidence for Kampo Therapy for Chemotherapy-Induced Peripheral Neuropathy. The use of the Kampo preparation goshajinkigan [57–67] as drug therapy for peripheral neuropathy symptoms has been widely reported in Japan. Goshajinkigan extract preparation has been reported to relieve symptoms such as numbness or pain in 80% of cases in which it is used for peripheral neuropathy caused by paclitaxel for breast cancer [68]. Goshajinkigan also improves subjective symptoms of peripheral neuropathy due to the combined use of paclitaxel and carboplatin for ovarian or uterine cancers. Neuropathy is a characteristic adverse effect of oxaliplatin, the core drug for colorectal cancer. A high incidence of symptoms such as extremity numbness and cold sensation has been observed with the continued therapeutic use of oxaliplatin, especially at a cumulative dose over 500 mg/m^2. Treatment can be continued if symptoms are mild, but the dosage is decreased or the administration is discontinued in some severe cases. On the other hand, research has found that goshajinkigan can alleviate such symptoms. Nishioka et al. [69] and Kono et al. [70] conducted a retrospective comparison and examination of the effects of goshajinkigan for peripheral neuropathy associated with oxaliplatin in advanced or recurrent colorectal cancer patients. They found that the group which was administered goshajinkigan from the start of chemotherapy tolerated the largest dosage until onset of peripheral neuropathy. Goshajinkigan's efficacy differs according to the causal anticancer drug. It promises some effectiveness for numbness caused by paclitaxel, and so forth, but it is virtually ineffective for oxaliplatin. Since it might be effective for prevention of oxaliplatin-induced neuropathy, it would be better to administer goshajinkigan from the start of chemotherapy. It has been reported that administration of Kampo preparations promises an increase in the frequency of administration during the FOLFOX regimen, which centers on oxaliplatin, before onset of numbness as an adverse effect [58, 70].

Table 1: Goshajinkigan extract granules for ethical use.

Description	Goshajinkigan extract granules for ethical use	
Composition	7.5 g of TSUMURA goshajinkigan extract granules contains 4.5 g of a dried extract of the following mixed crude drugs:	
	JP *Rehmannia* root	3.0 g
	JP *Achyranthes* root	3.0 g
	JP *Cornus* fruit	3.0 g
	JP *Dioscorea* rhizome	3.0 g
	JP *Plantago* seed	3.0 g
	JP *Alisma* rhizome	3.0 g
	JP poria sclerotium	3.0 g
	JP moutan bark	1.0 g
	JP cinnamon bark	1.0 g
	JP powdered processed aconite root	5.0 g
	Inactive ingredients	
	JP magnesium stearate	
	JP lactose hydrate	
	Sucrose esters of fatty acids	

(JP: The Japanese Pharmacopoeia.)

2.4. Goshajinkigan. Goshajinkigan's Kampo constituents and HPLC fingerprint appear in Table 1 and Figure 1.

Goshajinkigan is indicated for the relief of the following symptoms in patients with decreased urine volume or polyuria, occasional dry mouth, proneness to fatigue, and sensitivity to cold in the extremities: leg pain, low back pain, numbness, blurred vision (elderly), pruritus, dysuria, and edema. Goshajinkigan consists of 10 constituent crude drugs (Table 1) and is a prescription with fortified effectiveness against swelling, numbness, and arthralgia, in addition to the beneficial effects of hachimijiogan. Specifically, goshajinkigan is a Kampo preparation that improves blood circulation, has a body warming analgesic action, and reduces swelling. It is used for patients with remarkable edema tendency, severe arthralgia, and persistent low back pain. It is frequently used for symptoms in which peripheral vascular disease is suspected of being involved, such as sciatica and diabetic neuropathy, and has demonstrated effectiveness for these conditions. The usefulness of goshajinkigan is conjectured to be aconitine [71]. Shakuyakukanzoto is a Kampo preparation used for various types of myalgia including menstrual pain and cramp [72]. Shakuyakukanzoto has been reported to demonstrate effectiveness for arthralgia and

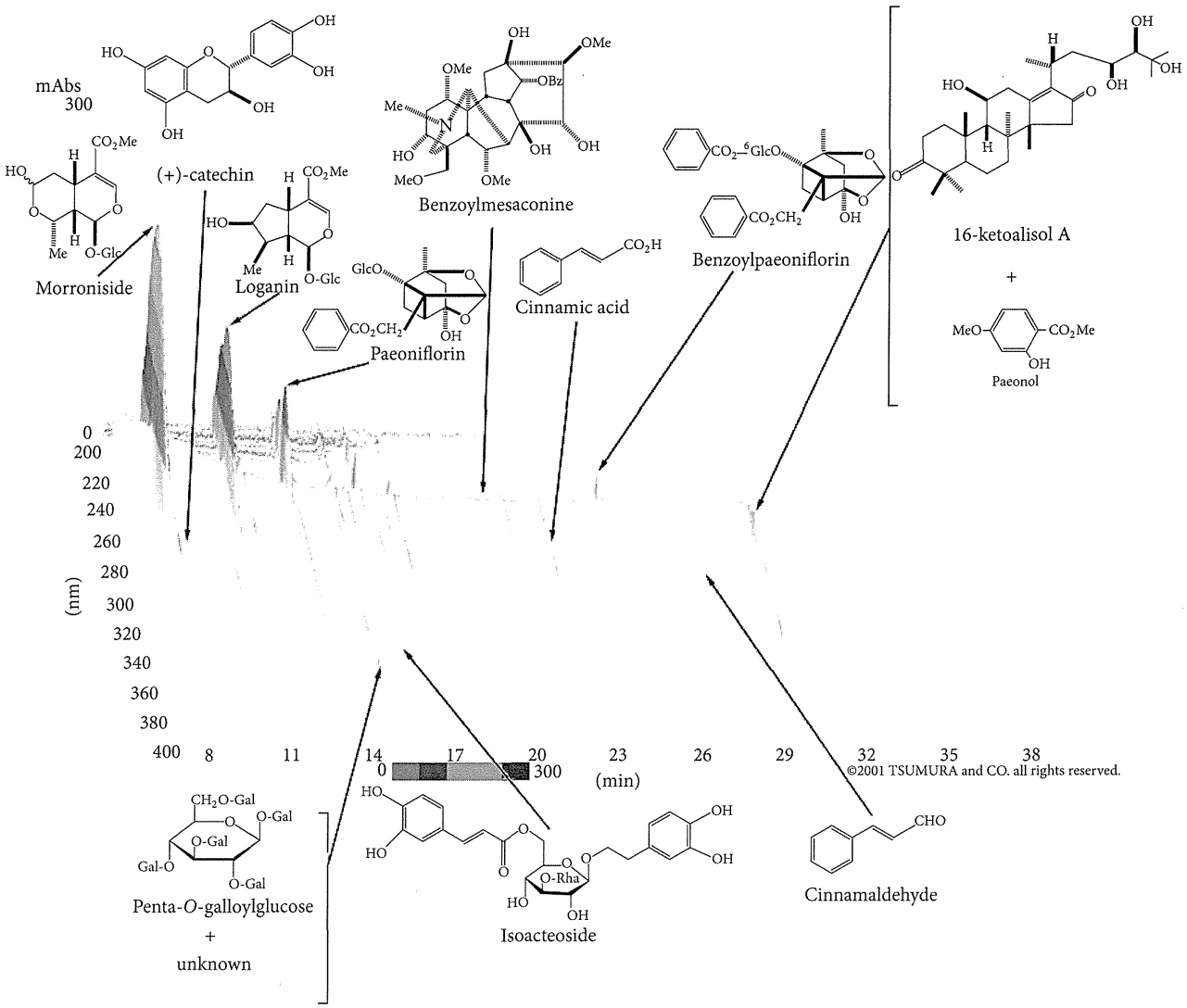

FIGURE 1: 3D-HPLC pattern of TJ-107 goshajinkigan (this 3D-HPLC was created in 2001 by TSUMURA and CO.).

myalgia due to paclitaxel [73]. While it is impossible to completely control peripheral neuropathy and myalgia caused by anticancer drugs, the combined use of goshajinkigan and shakuyakukanzoto may enhance improvement of subjective symptoms.

3. Kampo for Chemotherapy-Induced Diarrhea

3.1. Development of a Camptothecin Derivative—Irinotecan. Irinotecan is an anticancer drug classified as a plant alkaloid. It inhibits cancer cell proliferation by breaking DNA during cell division through its inhibition of the enzyme topoisomerase, which is required when DNA replicates. Wall et al. extracted and isolated camptothecin (CPT) in 1966 from *Camptotheca acuminate*, a plant native to China, and found that it has a powerful antineoplastic effect [74]. Subsequent development was undertaken by the National Cancer Institute (NCI) in the USA but was abandoned following the emergence of adverse effects. Pharmaceutical manufacturers in Japan vigorously pursued synthetic research into derivatives to preserve CPT's activity while reducing its toxicity, resulting in the CPT derivative irinotecan, which has been subsequently used as a potent anticancer drug. Irinotecan has demonstrated usefulness for various types of cancer, including colon and lung cancers, and its applications have been widening. Irinotecan suppresses the action of topoisomerase 1, which is involved in DNA replication, thereby demonstrating a strong antitumor effect; however, it can cause severe adverse effects including leukopenia and diarrhea [16, 17, 75–94].

3.2. Adverse Effects of Irinotecan and Their Frequency. The chief adverse effects are severe myelosuppression and intractable diarrhea. There have been reports of death following severe infection due to myelosuppression, intractable diarrhea, and intestinal perforation due to intestinal paralysis or bowel obstruction. Irinotecan undergoes metabolism