Pain Ther (2020) 9:161–170
https://doi.org/10.1007/s40122-020-00160-w

REVIEW

Kampo for the Treatment of Pain in Japan: A Review

Young-Chang Arai · Izumi Makino · Tatsunori Ikemoto · Hironori Saisu · Yuki Terajima · Keiko Owari

Received: January 15, 2020 / Published online: March 10, 2020

ABSTRACT

Kampo, a branch of traditional Japanese herbal medicine, has been the backbone of Japanese medicine for more than 1500 years. The health insurance system in Japan allows patients to access both Western and Kampo medical care at the same time in the same medical institution. Kampo has been used for the treatment of not only acute but also chronic pain in Japan. In this review, we will elaborate on the short history of Kampo, its basic concepts, and use for the treatment of pain.

Keywords: Kampo; Pain; Traditional Japanese herbal medicine

Key Summary Points

The authors try to summarize possible indications of Kampo for patients with common pain diseases.

Kampo has been used for the treatment of various pain conditions with or without combination of Western medicine.

Aspects of positive effects as well as adverse effects should be concerned to use Kampo herbs properly for treating pain symptoms.

THE HISTORY OF KAMPO IN JAPAN

Kampo is a unique, traditional Japanese herbal medicine system derived from traditional Chinese herbal medicine [1]. The Chinese herbal medicine system was first introduced into Japan from China in 552 AD. In the Tokugawa era, during the early to mid-18th century, Japan experienced a so-called renaissance [1, 2].

Kampo has been the backbone of Japanese medicine for more than 1500 years. After the Meiji Restoration of 1868, Japan decided to make efforts to achieve modernization, or Westernization. As part of its thorough efforts

Enhanced Digital Features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.11903220.

Y.-C. Arai · I. Makino · H. Saisu · Y. Terajima · K. Owari
Multidisciplinary Pain Center, School of Medicine, Aichi Medical University, Nagakute, Aichi 480-1195, Japan

T. Ikemoto (✉)
Department of Orthopedics, Aichi Medical University, 1-1 Yazako Karimata, Nagakute, Aichi 480-1195, Japan
e-mail: tatsunon31-ik@umin.ac.jp

to dispel many traditions as pre-modern, the Meiji government implemented the German system in official medical education and practice, and at the same time excluded the Kampo system as pre-modern [1, 2]. The Japanese government had long recognized Kampo, even as Kampo herbs were categorized as drugs separate from Western synthetic drugs. It took several more years for Kampo medicine to receive official attention around 1970 [1–3]. The time-tested herbal remedies of Kampo had regained the attention of the public at last. The National Health Insurance System, which enables everyone in Japan to receive advanced health care at a low cost, now allows patients to access Western and Kampo medical care at the same time in the same medical institution [4].

KAMPO'S BASIC CONCEPTS

Kampo consists of a system of essentially three dichotomies and three substance concepts [3–8]. The three dichotomies are: Yin-You (ying-yang), Kyo-Jitsu, and Netsu-Kan (translated into English as "positive–negative", "hollow-full", and "hot–cold", respectively). The three substance categories are Ki (Qi), Ketsu, and Sui. Ki (Qi) is energy fundamental to living things. In contrast to the Ki (Qi) concept, Ketsu and Sui are much closer to the common concepts of blood and bodily fluids, respectively. In Kampo, the healthy state of human beings means a well-balanced or non-deviated condition of the three dichotomies and the three substance concepts. The central concept of Kampo is Sho, a word that can most closely be translated into English as "symptom," [7, 8], but also has some connotation as "signs." When assessing disease due to deviation and Sho, four specific diagnostic procedures are used. According to Kampo theory, the most appropriate Kampo formula should be prescribed for each individual based on four diagnostic procedures (purely observational approaches): (1) visual observation, (2) listening to the sounds made by the patient's body, (3) smelling and touching the patient, and (4) listening to what they say.

It can be difficult for Western scientists and physicians to understand traditional Chinese medicine or Kampo until the full complexities of the three dichotomies and three substance concepts are grasped. The traditional Chinese medicine paradigm is very different from that of modern Western medicine. In addition, it is risky for Western physicians to use any Kampo or traditional Chinese medicine formulae outside the context of Kampo's cognitive paradigm. Since the full complexities of the three dichotomies, three substance concepts, and the context of Kampo's cognitive paradigm cannot be elaborated on easily or simply, for the purposes of this review they are not discussed.

COMPLIANCE WITH ETHICS GUIDELINES

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

KAMPO FOR TREATMENT OF PAIN

In Japan, the national health insurance system enables all citizens to receive advanced healthcare at a low cost. Kampo has long been used in Japan for the treatment of both acute and chronic pain. Moreover, some patients who cannot use adequate doses of certain Western medicines because of their side effects, such as opioids and antineuropathic drugs, can obtain moderate or high levels of satisfaction with a combination use including Kampo. Herein, we reviewed the available literatures and reports related to Kampo for treatment of pain in PubMed/MEDLINE and Google Scholar on websites up to December 2019. We summarize possible indications of Kampo medicine for patients with common pain diseases (Fig. 1). Each Kampo medicine consists of various herbal ingredients as shown in Table 1.

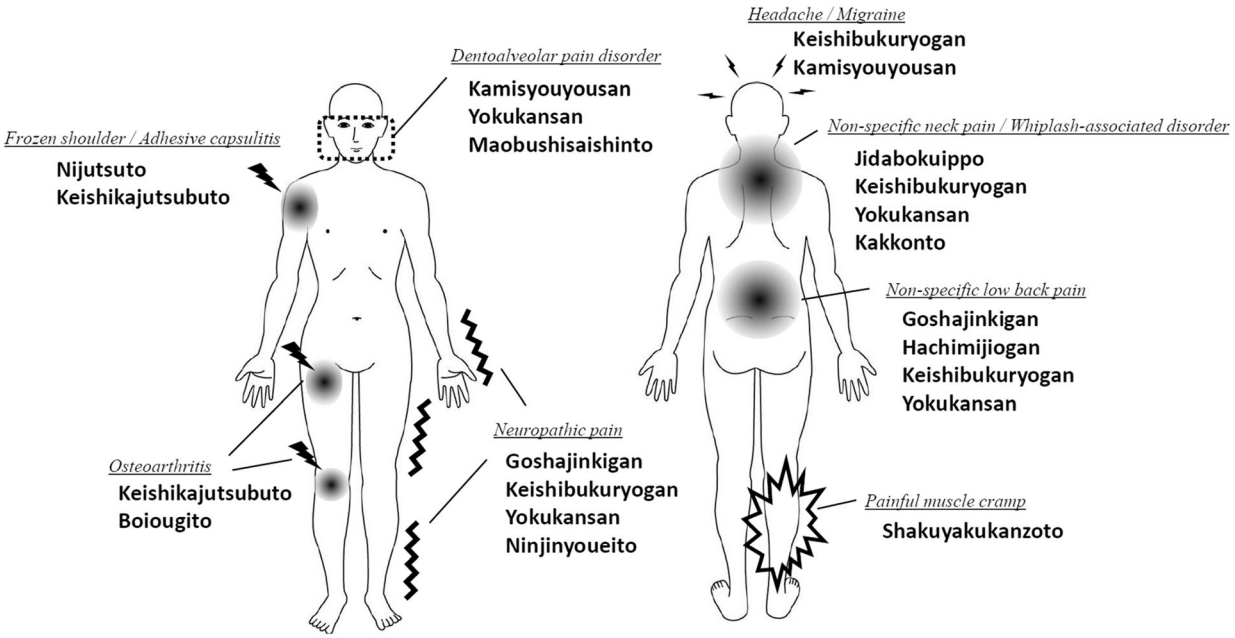

Fig. 1 Possible indications of Kampo medicine for treating common pain diseases

KAMPO FOR TREATMENT OF NEUROPATHIC PAIN

Kampo medicine has been reported to treat neuropathy. Neuropathy is one of the most frequent diabetic complications [9, 10]. Pain related to diabetic neuropathy, leading to neuropathic pain, has been hard to control irrespective of several recommendations of Western medicine [10]. Although tricyclic antidepressants and anticonvulsants are applied to manage the pain [11], these drugs often fail to provide satisfactory results due to adverse effects such as dizziness, drowsiness, nausea, somnolence, and sedation [12].

Goshajinkigan (a.k.a. Niu-Che-Sen-Qi-Wan), a Kampo medicine, has been used in Japan since ancient times to treat back pain and numbness. Goshajinkigan, which includes processed Aconiti tuber, was reported to improve subjective symptoms in diabetic patients [13], and a basic study of streptozocin-induced diabetic mice showed that the increased antinociceptive effect of Goshajinkigan was derived by stimulating spinal opioid receptors via the release of dynorphin [14]. Furthermore, another basic study showed that the antinociceptive effect of Goshajinkigan is derived from the peripheral action of increased nitric oxide [15, 16].

Moreover, neuropathy is one of the most frequent chemotherapy-related complications [17]. Chemotherapy-induced neuropathic pain is highly refractory to drugs such as opioids, tricyclic antidepressants, and anticonvulsants, as is diabetic neuropathic pain [18]. Kampo medicine has been successfully applied for the management and prevention of not just diabetic neuropathic pain but also chemotherapy-induced neuropathic pain in Japan, according to accumulating evidence shown in basic and clinical studies. Several articles have reported clinical effects of Goshajinkigan on chemotherapy-induced neuropathic pain [19–24]. A clinical retrospective survey showed that in addition to Goshajinkigan, Hachimijiogan (a.k.a. Ba-Wei-Di-Huang-Wan) and Keishibukuryogan (a.k.a. Gui-Zhi-Fu-Ling-Wan) were also effective Kampo medicines for chemotherapy-induced neuropathy. Their beneficial effects were observed independent of the timing of the treatment after cancer chemotherapy [18]. Basic studies have showed

Table 1 Ingredients in each Kampo medicine Modified from Arai, Y.P., Yasui, H., Isai, H. et al. The review of innovative integration of *Kampo* medicine and Western medicine as personalized medicine at the first multidisciplinary pain center in Japan. *EPMA Journal* **5,** 10 (2014). https://doi.org/10.1186/1878-5085-5-10

Japanese name	Synonym	Ingredients
Kampo medicine		
Boiogitou		Sinomenine, Astragalus, Atractylodes rhizome, Jujube, Glycyrrhiza, Ginger,
Goreisan		Alisma, Polyporus, Hoelen, Atractylodes rhizome, Cinnamon
Goshajinkigan	Niu-Che-Sen-Qi-Wan	Rehmannia, Cornus, Dioscorea, Alisma, Hoelen, Moutan, Cinnamon, Aconite, Achyranthes, Plantago Jukujio
Goshuyuto		Evodia, Ginseng, Ginger, Jujube
Hachimijiogan	Ba-Wei-Di-Huang-Wan	Rehmannia, Cornus, Dioscorea, Alisma, Hoelen, Moutan, Cinnamon, Aconite
Jidabokuippo		Cinnamon, Cnidium, Glycyrrhiza, Rhei rhizome, Quercus cortex, Caryophylli, Nupharis Rhizoma
Juzentaihoto		Ginseng, Astragalus, White atractylodes, Tang- kuei, Hoelen, Rehmannia, Cnidium, Peony, Cinnamon, Liquorice
Kakkonto		Pueraria, Ma-huang, Ginger, Jujube, Cinnamon, Peony, Liquorice
Kamishoyosan		Tang-kuei, Peony, Atractylodes rhizome, Hoelen, Bupleurum, Liquorice, Moutan, Gardenia, Ginger, Mentha
Keishibukuryogan	Guizhifulingwan	Cinnamon, Atractylodes rhizome, Aconite
Keishikajutsubuto	Gui-Zhi-Jia-Shu-Fu-Tang, Gyejigachulbutang	Cinnamon, Hoelen, Moutan, Persica, Peony
Kososan		Cyperus, Perilla, Citrus, Ginger, Liquorice
Maobushisaishinto		Ma-huang, Asarum, Aconite
Nijutsuto		White and blue atractylodes, Hoelen, Citrus, Arisaema, Cyperus, Scute, Clematis, Chianghuo, Pinellia, Liquorice, Ginger
Ninjinyoeito	Ren-Shen-Yang-Rong-Tang	Rehmannia, Japanese angelica, Atractylodes rhizome, Poria sclerotium, Ginseng, Cinnamon bark, Polygala, Peony, Citrus unshiu peel, Astragalus, Glycyrrhiza, Schisandra fruit
Shakuyakukanzoto	Shao-Yao-Gan-Cao-Tang	Glycyrrhiza, Peony, Liquorice
Tokishakuyakusan		Tang-kuei, Cnidium, Peony, Hoelen, Atractylodes rhizome, Alisma
Yokukansan	Yi-Gan-San	Tang-kuei, Gambir, Cnidium, Atractylodes rhizome, Holen, Bupleurum, Liquorice

that oxaliplatin induces mechanical allodynia and cold hypersensitivity, but not thermal hyperalgesia, and it reduced current perception thresholds of Aδ- and Aβ-fibers but not C-fibers. However, mechanical allodynia and other effects were counteracted by Goshajinkigan [22–24], the effectiveness of which was increased by using in combination with Bushi, a processed Aconiti tuber. Yokukansan (a.k.a. Yi-Gan-San), a Kampo medicine frequently used for various neurogenic symptoms, has been reported to have an analgesic effect on neuropathic pain by causing a blockade of glutamatergic neurotransmission [25] or the regulation of IL-6 levels [26]. In addition, a basic study showed that Shakuyakukanzoto (a.k.a. Shao-Yao-Gan-Cao-Tang), a Kampo medicine that has anticholinergic and prostaglandin-production-inhibiting actions, significantly relieved allodynia and hyperalgesia in rodents with neuropathic pain [27, 28]. Moreover, a basic study showed that Ninjinyoeito (a.k.a. Ren-Shen-Yang-Rong-Tang), a Kampo medicine, prevented and alleviated mechanical hyperalgesia induced by oxaliplatin in mice [29].

Post-herpetic neuralgia (PHN), a type of neuropathic pain, is the most common long-term complication of varicella-zoster virus reactivation. PHN, once established, can be refractory to treatment despite multimodal therapy. A combination of Bushi and Keishikajutsubuto (a.k.a. Gui-Zhi-Jia-Shu-Fu-Tang or gyejigachulbutang), a Kampo medicine, was reported to be a promising means of treating intractable neuralgia in cases of PHN aggravated by self-reported cold stimulation [30].

KAMPO FOR TREATMENT OF LOW BACK PAIN AND LUMBAR CANAL STENOSIS

Low back pain is a common health problem and often develops into a chronic condition. Cochrane systematic review reported that herbal medicine, namely Kampo medicine, could be effective on acute or chronic low back pain [31].

Although Western treatments are available, Goshajinkigan is commonly used to treat low back pain in Japan. A retrospective observational study of 28 patients was performed at a university hospital [32]. Routine daily administration of Goshajinkigan in patients without spinal disease led to the effects of the product on pain, compared with patients with spinal disease. Moreover, another retrospective cohort study of 151 patients with lumbar canal stenosis divided patient cases into two groups based on treatment with (n = 111) and without (n = 40) Kampo. In the first group, Goshajinkigan, Hachimijiogan, Shakuyakukanzoto, and Keishikajyutsubuto were prescribed in addition to other drugs such as pregabalin and opioids. The use of pregabalin and opioids decreased significantly in patients receiving treatment in conjunction with Kampo, and the number of patients who discontinued use of pregabalin or opioids was significantly larger in patients being treated with Kampo [33].

A retrospective survey conducted at the first multidisciplinary pain center in Japan showed that Kampo medicines were prescribed for 221 out of a total of 487 patients, based on patient-centered Kampo diagnosis, and of those 221 patients, 81 were prescribed Kampo to treat low back/lower limb pain [3]. Specifically, Goshajinkigan (22.2%, n = 18), Shakuyakukanzoto (17.3%, n = 14), Yokukansan (16.0%, n = 13), Keishikajutsubuto (14.8%, n = 12), Hachimijiogan (14.8%, n = 12), and Juzentaihoto (14.8%, n = 12) were prescribed. Two-thirds of the chronic pain patients who used Kampo medicine combined with Western medicine experienced further alleviation of pain. Furthermore, a randomized and non-blinded study compared the effectiveness of Shakuyakukanzoto for painful muscle cramps with that of eperisone hydrochloride, a muscle relaxant, in 30 patients with lumbar canal stenosis [34]. Shakuyakukanzoto reduced the frequency of painful muscle cramps to less than 50% in 13 of 16 patients. In contrast, eperisone hydrochloride reduced it to the same level in four of 14 patients.

KAMPO FOR HIP/KNEE OSTEOARTHRITIS

Osteoarthritis (OA) of the hip/knee is a common degenerative disease of leg joints, which leads to chronic pain as well as functional decline in elderly people. Sinomenin, which is extracted from the Chinese plant *Sinomenium acutum* and has been reported to have an anti-inflammatory effect [35, 36], has been used for rheumatic diseases for over 2000 years [36]. Research has reported that Boiogito [37, 38], a Kampo medicine, which includes sinomenin as a principle component, could reduce symptoms of osteoarthritis in humans [37, 39] and rodents [40]. Moreover, another study revealed the anti-inflammatory effects of Keishikajutsubuto [41]. This herbal medicine has been widely used in clinical practice not only for postherpetic neuralgia [30] but also several pain conditions such as chemotherapy-induced neuropathy [42], osteoarthritis [39], and dento-alveolar pain [43]. Recently, a randomized placebo-controlled clinical trial has begun to investigate the efficacy and safety of Keishikajutsubuto for the treatment of pain in patients with knee OA [44].

KAMPO FOR NECK AND SHOULDER PAIN

Neck pain around the shoulder girdle, which is often caused by cervical spondylitis, cervical disc herniation, whiplash-associated disorders, and frozen shoulder (adhesive capsulitis), is a common symptom encountered in clinical practice. According to data in our multidisciplinary pain center, prescriptions of Keishibukuryogan (34.5%, $n = 10$), Yokukansan (24.1%, $n = 7$), Jidabokuippo (17.3%, $n = 5$), Tokishakuyakusan (17.3%, $n = 5$), Kamishoyosan (13.8%, $n = 4$), Kakkonto (13.8%, $n = 4$), and Kososan (13.8%, $n = 4$) resulted in 34.5% of patients with a marked improvement, 20.6% with moderate improvement, 13.7% with some improvement, and 17.2% with no improvement for the management of neck/upper limb pain [3].

Nijutsuto is a Kampo formula used to effectively treat frozen shoulder [45]. A case series study showed that Nijutsuto combined with a 20-min exercise program improved pain intensity in 13 patients with frozen shoulder that had been unresponsive to long-term Western medical treatment [46].

KAMPO FOR VARIOUS REFRACTORY OROFACIAL PAIN

Glossodynia is a pathological condition characterized by persistent pain in the tongue not caused by any obvious organic change. Glossodynia is generally managed with psychosomatic therapy and the administration of psychomimetics and/or vitamins. A randomized study of 200 patients with Glossodynia analyzed the effect of a Kampo medicine, Saibokuto, compared with that of diazepam with vitamin B complex [47]. Clinical examinations evaluated the following subjective symptoms: pain, burning sensation, and discomfort. Effectiveness was evaluated as follows: "markedly effective," all three symptoms disappeared; "effective", pain improved; or "ineffective", no improvement in pain. The effectiveness rates were 70% after 1 month, 85% after 2 months, and 92% after 3 months of administration of Saibokuto and 74% after 1 month, 71% after 2 months, and 69% after 3 months of administration of diazepam with vitamin B complex.

Patients suffering from tooth pain, either dentoalveolar pain or nonodontogenic toothache of which the cause has yet to be identified, often seek pain treatment from several different kinds of medical practitioners in addition to dentists. Recently, persistent dentoalveolar pain disorder (PDAP) has been used to describe this kind of pain. Some reports have suggested that the pain disorder in the orofacial region including PDAP could be associated with psychological problems. Moreover, PDAP is reported to be partly somatoform pain and partly neuropathic pain. PDAP is effectively treated by using a unique exercise therapy for the improvement of jaw movement in combination with psychological intervention to reduce parafunctional activities. Kamishoyosan is a

Kampo formula used to effectively treat psychological symptoms such as anxiety, irritability, and depression [5]. A prospective study showed that Kamishoyosan improved the pain intensity in 14 out of 15 PDAP patients refractory to the original exercise therapy.

ADVERSE EFFECTS OF KAMPO MEDICINE

Physicians should note that previous studies have revealed not only clinical usefulness of Kampo medicines to improve several clinical manifestations but also possible adverse effects. A recent review article reports that frequent events caused by Kampo medicines include liver injury (28.2%) followed by lung injury (27.8%), psedoaldosteronism (21.0%), mesenteric phlebosclerosis (5.3%), drug eruption (4.4%), and others (13.3%) [48]. Since the classification of types of adverse reactions; acute, bizarre, chronic, or delayed onset, is applied both in Western drugs as well as Kampo herbs [49], it is important to note that pharmacotoxicity of Kampo herbs can occur at any timing.

Pseudoaldosteronism, which is related to peripheral edema, hypokalemia, and hypertension, is one of the significant adverse events when a Kampo treatment including Glycyrrhiza ingredients is administered [50–52]. Glycyrrhizae Radix is the most frequently used crude drug in Japan [51], as is included in 109 of 148 ethical Kampo extract formulations [52], and it is used for various symptoms. In particular, Shakuyakukanzoto was reported to be the most frequently prescribed Kampo formula in 2009 [4]. Since Shakuyakukanzoto and Yokukansan are often used for pain symptoms, clinicians should monitor for signs of pseudoaldosteronism in patients taking Kampo medicines.

LIMITATIONS

Pain is a common complaint between Kampo medicine and Western medicine, however, there are fundamental differences in basic concept between them. The concept of Kampo emphasizes the relationship between the human body and psychosocial environments [53]. Therefore, it is possible in Kampo medicine to prescribe different formulas for the same disease when the Sho (Kampo diagnosis) is different [e.g., balance in Ki (Qi), Ketsu, and Sui]. Thus, principal diagnostic techniques in Kampo such as Fuku shin (the abdominal exam) and Zetsu shin (the tongue exam) [54] would be required to use these herbs properly for anyone who is not familiar with Kampo concept. It would be desirable for Kampo beginners to prescribe regular dosages of a formula.

Kampo medicines are often a mixture of multiple herbs. For example, Goshajinkigan is a mixture of ten herbs. Although positive effects on pain symptom are not surprising with ten natural ingredients, identifying which herb and/or compound within the herbs are responsible is daunting. Nevertheless, a growing body of evidence demonstrates that effects of Kampo medicines on pain are convincing.

CONCLUSIONS

Kampo was the backbone of Japanese medicine for more than 1500 years, before being replaced by Western medical treatments. It then took about 100 years for Kampo medicine to experience a revival and receive official attention around 1970. In Japan, patients can now access Western and Kampo medical care at the same time in the same medical institution. Kampo has been used for the treatment of both acute and chronic pain in Japan. A growing body of evidence demonstrates that effects of Kampo medicines on pain are convincing.

ACKNOWLEDGEMENTS

We would like to acknowledge Mr. Matthew McLaughlin for his assistance in editing and proofreading the paper.

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Tatsunori Ikemoto is a member of the journal's Editorial Board. Young-Chang Arai, Izumi Makino, Hironori Saisu, Yuki Terajima, and Keiko Owari have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

REFERENCES

1. Terasawa K. Evidence-based reconstruction of Kampo medicine: part I–Is Kampo CAM? Evid Based Complement Alternat Med. 2004;1:11–6.

2. Moschik EC, Mercado C, Yoshino T, Matsuura K, Watanabe K. Usage and attitudes of physicians in Japan concerning traditional Japanese medicine (Kampo medicine): a descriptive evaluation of a representative questionnaire-based survey. Evid Based Complement Alternat Med. 2012;2012:139818.

3. Arai YC, Yasui H, Isai H, et al. The review of innovative integration of Kampo medicine and Western medicine as personalized medicine at the first multidisciplinary pain center in Japan. EPMA J. 2014;5:10.

4. Katayama K, Yoshino T, Munakata K, et al. Prescription of Kampo drugs in the Japanese health care insurance program. Evid Based Complement Alternat Med. 2013;2013:576973.

5. Arai YC, Makino I, Aono S, et al. Effects of Kamishoyosan, a traditional Japanese Kampo medicine, on pain conditions in patients with intractable persistent dentoalveolar pain disorder. Evid Based Complement Alternat Med. 2015;2015:750345.

6. Arai YC, Nishihara M, Inoue S, Makino I. Kampo diagnostic procedure, fuku shin, could be a useful diagnostic tool for psychopathological patients suffering from chronic pain. Evid Based Complement Alternat Med. 2013;2013:816216.

7. Terasawa K. Evidence-based reconstruction of Kampo medicine: part II-the concept of Sho. Evid Based Complement Alternat Med. 2004;1(2):119–23.

8. Watanabe S, Toyama T, Sato T, et al. Kampo therapies and the use of herbal medicines in the dentistry in Japan. Medicines (Basel). 2019;6(1):34.

9. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther. 2008;88(11):1254–64.

10. Viswanath O, Urits I, Jones MR, et al. Membrane stabilizer medications in the treatment of chronic neuropathic pain: a comprehensive review. Curr Pain Headache Rep. 2019;23(6):37.

11. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162–73.

12. Moulin D, Boulanger A, Clark AJ, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag. 2014;19(6):328–35.

13. Tawata M, Kurihara A, Nitta K, Iwase E, Gan N, Onaya T. The effects of goshajinkigan, a herbal medicine, on subjective symptoms and vibratory threshold in patients with diabetic neuropathy. Diabetes Res Clin Pract. 1994;26:121–8.

14. Suzuki Y, Goto K, Ishige A, Komatsu Y, Kamei J. Antinociceptive effect of Gosha-jinki-gan, a Kampo medicine, in streptozotocin-induced diabetic mice. Jpn J Pharmacol. 1999;79:169–75.

15. Suzuki Y, Goto K, Ishige A, Komatsu Y, Kamei J. Antinociceptive mechanism of Gosha-jinki-gan in streptozotocin-induced diabetic animals: role of nitric oxide in the periphery. Jpn J Pharmacol. 1999;79:387–91.

16. Hu X, Sato J, Oshida Y, Xu M, Bajotto G, Sato Y. Effect of Gosha-jinki-gan (Chinese herbal medicine: Niu-Che-Sen-Qi-Wan) on insulin resistance in streptozotocin-induced diabetic rats. Diabetes Res Clin Pract. 2003;59(2):103–11.

17. Jones MR, Urits I, Wolf J, et al. Drug-induced peripheral neuropathy, a narrative review. Curr Clin Pharmacol. 2019. https://doi.org/10.2174/1574884714666190121154813.

18. Kimata Y, Ogawa K, Okamoto H, Chino A, Namiki T. Efficacy of Japanese traditional (Kampo) medicine for treating chemotherapy-induced peripheral neuropathy: a retrospective case series study. World J Clin Cases. 2016;4:310–7.

19. Kono T, Hata T, Morita S, et al. Goshajinkigan oxaliplatin neurotoxicity evaluation (GONE): a phase 2, multicenter, randomized, double-blind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy. Cancer Chemother Pharmacol. 2013;72(6):1283–90.

20. Yamanaka T, Kono T, Tomita N, et al. Preventive effect of Goshajinkigan on peripheral neurotoxicity of FOLFOX therapy (GENIUS trial): a placebo-controlled, double-blind, randomized phase III study. Int J Clin Oncol. 2015;20(4):767–75.

21. Kuriyama A, Endo K. Goshajinkigan for prevention of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Support Care Cancer. 2018;26(4):1051–9.

22. Ushio S, Egashira N, Sada H, et al. Goshajinkigan reduces oxaliplatin-induced peripheral neuropathy without affecting anti-tumour efficacy in rodents. Eur J Cancer. 2012;48:1407–13.

23. Mizuno K, Shibata K, Komatsu R, Omiya Y, Kase Y, Koizumi S. An effective therapeutic approach for oxaliplatin-induced peripheral neuropathy using a combination therapy with goshajinkigan and bushi. Cancer Biol Ther. 2016;17:1206–12.

24. Cascella M, Muzio MR. Potential application of the Kampo medicine goshajinkigan for prevention of chemotherapy-induced peripheral neuropathy. J Integr Med. 2017;15:77–87.

25. Suzuki Y, Mitsuhata H, Yuzurihara M, Kase Y. Antiallodynic effect of herbal medicine yokukansan on peripheral neuropathy in rats with chronic constriction injury. Evid Based Complement Alternat Med. 2012;2012:953459.

26. Ebisawa S, Andoh T, Shimada Y, Kuraishi Y. Yokukansan improves mechanical allodynia through the regulation of interleukin-6 expression in the spinal cord in mice with neuropathic pain. Evid Based Complement Alternat Med. 2015;2015:870687.

27. Hidaka T, Shima T, Nagira K, et al. Herbal medicine Shakuyaku-kanzo-to reduces paclitaxel-induced painful peripheral neuropathy in mice. Eur J Pain. 2009;13:22–7.

28. Lee KK, Omiya Y, Yuzurihara M, Kase Y, Kobayashi H. Antinociceptive effect of paeoniflorin via spinal α_2-adrenoceptor activation in diabetic mice. Eur J Pain. 2011;15(10):1035–9.

29. Suzuki T, Yamamoto A, Ohsawa M, Motoo Y, Mizukami H, Makino T. Effect of ninjin'yoeito and ginseng extracts on oxaliplatin-induced neuropathies in mice. J Nat Med. 2017;71:757–64.

30. Nakanishi M, Arimitsu J, Kageyama M, et al. Efficacy of traditional Japanese herbal medicines-Keishikajutsubuto (TJ-18) and Bushi-matsu (TJ-3022)-against postherpetic neuralgia aggravated by self-reported cold stimulation: a case series. J Altern Complement Med. 2012;18:686–92.

31. Gagnier JJ, Oltean H, van Tulder MW, Berman BM, Bombardier C, Robbins CB. Herbal medicine for low back pain: a Cochrane review. Spine. 2016;41(2):116–33.

32. Hamaguchi T, Yoshino T, Horiba Y, Watanabe K. Goshajinkigan for low back pain: an observational study. J Altern Complement Med. 2017;23:208–13.

33. Oohata M, Aoki Y, Miyata M, Mizobe H, Suzuki KS. Japanese traditional herbal medicine reduces use of pregabalin and opioids for pain in patients with lumbar spinal canal stenosis: a retrospective cohort study. JA Clin Rep. 2017;3:60.

34. Takao Y, Takaoka Y, Sugano A, et al. Shakuyaku-kanzo-to (Shao-Yao-Gan-Cao-Tang) as treatment of painful muscle cramps in patients with lumbar spinal stenosis and its minimum effective dose. Kobe J Med Sci. 2015;61:E132–7.

35. Liu L, Riese J, Resch K, Kaever V. Impairment of macrophage eicosanoid and nitric oxide production by an alkaloid from *Sinomenium acutum*. Arzneimittelforschung. 1994;44(11):1223–6.

36. Liu L, Resch K, Kaever V. Inhibition of lymphocyte proliferation by the anti-arthritic drug sinomenine. Int J Immunopharmacol. 1994;16(8):685–91.

37. Majima T, Inoue M, Kasahara Y, Onodera T, Takahashi D, Minami A. Effect of the Japanese herbal medicine, Boiogito, on the osteoarthritis of the knee with joint effusion. Sports Med Arthrosc Rehabil Ther Technol. 2012;4:3.

38. Yamakawa J, Moriya J, Takeuchi K, Nakatou M, Motoo Y, Kobayashi J. Significance of Kampo, Japanese traditional medicine, in the treatment of obesity: basic and clinical evidence. Evid Based Complement Alternat Med. 2013;2013:943075.

39. Kogure T, Tatsumi T, Shigeta T, Fujinaga H, Sato T, Niizawa A. Effect of Kampo medicine on pain and range of motion of osteoarthritis of the hip accompanied by acetabular dysplasia: case report and literature review. Integr Med Insights. 2011;6:13–7.

40. Fujitsuka N, Tamai M, Tsuchiya K, et al. Boiogito, a Kampo medicine, improves hydrarthrosis in a rat model of knee osteoarthritis. BMC Complement Altern Med. 2015;15:451.

41. Nogami T, Hiroshi O, Fujimoto M, et al. Two cases of postherpetic neuralgia recurring after withdrawal of Kampo medicine including uzu. Kampo Med. 2011;62:369–73.

42. Schröder S, Beckmann K, Franconi G, et al. Can medical herbs stimulate regeneration or neuroprotection and treat neuropathic pain in chemotherapy-induced peripheral neuropathy? Evid Based Complement Alternat Med. 2013;2013:423713.

43. Chiba M. Neuropathic pain in the alveolar process of the mandible after pulpectomy treated with Keishikajutsubuto and Neurotropin®. J Jpn Soc Pain Clin. 2007;14:410–3.

44. Sul JU, Kim MK, Leem J, et al. Efficacy and safety of gyejigachulbutang (Gui-Zhi-Jia-Shu-Fu-Tang, Keishikajutsubuto, TJ-18) for knee pain in patients with degenerative knee osteoarthritis: a randomized, placebo-controlled, patient and assessor blinded clinical trial. Trials. 2019;20(1):140.

45. Otsuka K. Kampo: a clinical guide to theory and practice. Edinburgh: Churchill Livingstone; 2010.

46. Arai YC, Shimo K, Inoue M, et al. Integration of a Kampo medicine, Nijutsuto, and Western medical treatment in the treatment of long-term frozen shoulder refractory to Western medical treatment: a case series. J Evid Based Complementary Altern Med. 2015;20(2):157–61.

47. Bessho K, Okubo Y, Hori S, Murakami K, Iizuka T. Effectiveness of Kampo medicine (sai-boku-to) in treatment of patients with glossodynia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86:682–6.

48. Shimada Y, Fujimoto M, Nogami T, Watari H. Adverse events associated with ethical Kampo formulations: analysis of the domestic adverse-event data reports of the Ministry of Health, Labor, and Welfare in Japan. Evid Based Complement Alternat Med. 2019;2019:1643804.

49. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255–9.

50. Conn JW, Rovner DR, Cohen EL. Licorice-induced pseudoaldosteronism. Hypertension, hypokalemia, aldosteronopenia, and suppressed plasma renin activity. JAMA. 1968;205(7):492–6.

51. Nose M, Tada M, Kojima R, et al. Comparison of glycyrrhizin content in 25 major kinds of Kampo extracts containing Glycyrrhizae Radix used clinically in Japan. J Nat Med. 2017;71(4):711–22.

52. Makino T. 3-Monoglucuronyl glycyrrhretinic acid is a possible marker compound related to licorice-induced pseudoaldosteronism. Biol Pharm Bull. 2014;37(6):898–902.

53. Yu F, Takahashi T, Moriya J, et al. Traditional Chinese medicine and Kampo: a review from the distant past for the future. J Int Med Res. 2006;34(3):231–9.

54. Arai YC, Aono S, Makino I, Nishihara M, Ikemoto T, Owari K. Observational study of the association between tongue exam and the Kampo diagnostic procedure of Fuku Shin (abdominal exam) in blood stasis. J Evid Based Complementary Altern Med. 2017;22(4):879–82.