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CHAPTER 14

Kampo Medicines for Infectious Diseases

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Introduction

Numerous Kampo medicines and Oriental herbs have been used for the treatment of infectious diseases for several reasons, such as genetic background, economical reasons, fewer adverse effects, and so on. This chapter describes Kampo medicines and related Oriental herbs that are effective or promising in the treatment of infectious diseases at the clinical level and/or in animal models. In addition, effective Kampo medicines tested in vitro in cultured-cell studies are also included in this chapter. Each section is categorized by infectious disease and according to the popularity of the Kampo medicine.

Influenza Virus Infection

Influenza virus infection causes annual epidemics and recurring pandemics that have a serious impact on public health and the global economy. Antiinfluenza agents such as oseltamivir and zanamivir have been very effective, but neuraminidase-resistant viruses due to cumulative mutation of neuraminidase have been found (Moscona, 2009; Weinstock and Zuccotti, 2009), and these drugs can be expensive for low-income countries. Several Kampo medicines have been proposed to be effective complementary and alternative medicines against viral infections by stimulating host immune systems or directly acting on virus growth.

Shoseiryuto

Shoseiryuto is used for symptoms such as runny nose, cough, allergic rhinitis, bronchitis, and so on (Ikeda et al., 1994). It has been reported that shoseiryuto possesses antiinfluenza activity in vivo. It was first described that replication of the virus in the nasal cavity and spread of the virus to the lung are efficiently inhibited in intranasal infection with a mouse-adapted influenza strain, A/PR/8/34, in BALB/c mice when shoseiryuto is orally administered (Nagai and Yamada, 1994). Shoseiryuto increases the antiviral IgA antibody in nasal and bronchoalveolar washes of infected mice. It did not stimulate type I interferon (IFN) induction in this study (Nagai and Yamada, 1994); however, other in vitro studies with

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human cell lines have suggested that shoseiryuto shows type I IFN–mediated inhibition of other viruses such as ganciclovir-resistant human cytomegalovirus (Murayama et al., 2006) and human respiratory syncytial virus (Chang et al., 2013). Regarding influenza virus infection, there have been no reports on inhibitory effects on viral growth by shoseiryuto in a cultured-cell system. Antiinfluenza activity of shoseiryuto is most likely through immunostimulative adjuvant-like activity but not direct action on the virus in any case. Therefore, it is proposed that shoseiryuto is useful for the treatment of influenza virus infection with a history of influenza virus infection and/or as an influenza vaccine adjuvant (Nagai and Yamada, 1998; Yamada and Nagai, 1998). In fact, the same group explored the active ingredient in shoseiryuto and tested for influenza adjuvant activity. Oral administration of one of the ingredients, pinellic acid, to mice with influenza hemagglutinin (HA) vaccine enhanced antiviral IgA antibody in nasal and bronchoalveolar washes, suggesting that pinellic acid may provide a safe and potent oral adjuvant for nasal influenza HA vaccine (Nagai et al., 2002).

Juzentaihoto

The involvement of adjuvant activity of another Kampo medicine has also been investigated for human subjects who are in a high-risk group for influenza infection. Juzentaihoto is a Kampo medicine traditionally used for patients with anemia, anorexia, or fatigue and also has an ability to accelerate recovery from hematopoietic injury induced by radiation and the anticancer drug mitomycin C (Hisha et al., 1997). The influenza adjuvant activity of juzentaihoto was tested using 91 subjects with a minimum age of 65 years by measuring the antibody titer after influenza vaccination (Saiki et al., 2013). The investigation indicated a significant increase in hemagglutination inhibition titer against A/Victoria/210/2009 (H3N2) among the tested vaccine strains, A/California/7/2009 (H1N1), H3N2, and B/Brisbane/60/2008. However, the mechanisms underlying the specificity of juzentaihoto for the H3N2 strain remain to be discovered, although a study has reported that juzentaihoto stimulates the IFN-α response by affecting the responsible transcription factors, IRF-3/7 (Munakata et al., 2012).

Hochuekkito

An antiinfluenza Kampo medicine that affects cytokine and antimicrobial peptide production has been reported. Hochuekkito is a Kampo medicine that is used for treating functional conditions such as general fatigue, compromised state, and gastrointestinal motility disorder (Yanagihara et al., 2013). Hochuekkito administered orally before, on the day of, or after influenza virus infection is found to increase survival rate, suppress viral growth in bronchoalveolar lavage fluid, and inhibit the lung index in mice. Administration of hochuekkito in mice elevates the concentration of IFN-α in bronchoalveolar lavage fluid and decreases

inflammatory cytokines such as interleukin (IL)-1α, IL-6, and granulocyte–macrophage colony stimulation factor, but not tumor necrosis factor α (TNFα) and IFN-γ (Mori et al., 1999). Furthermore, it has been reported that hochuekkito enhances the expression of antimicrobial peptides, defensins, in mice compared to control subjects (Dan et al., 2013). Synergistic antiinfluenza effects of hochuekkito with oseltamivir phosphate also have been reported in mice (Ohgitani et al., 2014). Furthermore, a clinical study has indicated that preoperative administration of hochuekkito may ameliorate an excessive postoperative inflammatory response and prolonged immunosuppressed state, resulting in fewer postoperative infectious complications (Iwagaki and Saito, 2013).

Shahakusan

Another antiinfluenza Kampo medicine, shahakusan, has been reported to affect cytokine mRNA expression levels in mandibular lymph node or lung in an influenza-infected mouse model. This Kampo medicine is prescribed in the late phase of infection that causes inflammation in the lung. Shahakusan administered orally from 7 days before to 4 days after infection with the influenza A/PR/8/34 strain in the upper respiratory tract significantly decreases the virus titer in nasal lavage fluid and lowers IL-4, IL-1β, and IL-10 mRNA. In contrast, IL-12 mRNA is increased in infected mice under the same conditions. In addition, shahakusan decreases infiltration of inflammatory cells in the bronchiole and stimulates natural killer (NK) cell activity. However, shahakusan has no direct effect on influenza growth or life cycle (Hokari et al., 2012).

Maoto

Several studies of Kampo medicines that directly act on the influenza life cycle have been reported. The herbal extract of *Ephedra* has an inhibitory effect on the growth of influenza virus (Mantani et al., 1999). For entry of influenza virus into host cells, acidification of lysosomes and endosomes is a well-known factor (Yoshimura et al., 1982). The extract of Ephedrae herba inhibits acidification of endosomes and lysosomes in Madin–Darby canine kidney (MDCK) cells, leading to growth inhibition of the influenza virus A/PR/8/34 when treated immediately or 5–10 min after infection. Chemical inhibition experiments suggest that tannin is one of the active components of inhibition in the extract.

Maoto, which contains *Ephedra*, is used for the early phase of influenza infection, and its efficacy against influenza virus infection has been demonstrated. Oral administration of maoto 4–52 h postinfection significantly reduces virus titers in both nasal and bronchoalveolar lavage fluids of A/J mice (Nagai et al., 2014). The treatment increases antiinfluenza virus IgM, IgA, and IgG1 antibody titers in nasal fluid, bronchoalveolar lavage fluid, and serum,

respectively, showing effects similar to those of shoseiryuto. Clinical and randomized studies have also claimed that maoto may be effective in cases of influenza with low sensitivity to oseltamivir and younger patients under 5 years of age (Kubo and Nishimura, 2007; Toriumi et al., 2012).

Cinnamomi Cortex

Trans-cinnamaldehyde (CA), one of the principal components of essential oil derived from Cinnamomi cortex, has antiinfluenza activity in vitro and in vivo (Hayashi et al., 2007). Micromolar levels (20–200 μM) of CA significantly inhibit viral growth in MDCK cells infected with influenza A/PR/8/34 virus. Inhalation in mouse cages (50 mg/cage per day) and intranasal administration of CA (250 μg/mouse per day) significantly increase the survival rate of influenza virus-infected mice. Virus yield in bronchoalveolar lavage fluids is 10 times lower in inhalation treatments of CA compared to control treatments. These findings suggest that Cinnamomi cortex—containing Kampo medicines are effective for acute respiratory infectious diseases.

Hepatitis C Virus Infection

Hepatitis C virus (HCV) infection is a significant worldwide problem in public health. The standard care for HCV is a combination therapy with PEGylated IFN-α and ribavirin, but ribavirin/IFN treatment is not effective enough for some HCV genotypes and shows serious side effects, such as influenza-like symptoms, mental health problems, and hematological abnormalities. Although the IFN-free ledipasvir–sofosbuvir medication had an enormous impact and is very effective for the treatment of chronic HCV genotype 1 (Smith et al., 2015), this therapy could still be expensive for low-income countries with a high prevalence of HCV. Several Kampo medicines and/or natural products have been reported as anti-HCV-agent complementary and alternative medicines.

Ninjinyoeito/Gomisin A

Ninjinyoeito is a Kampo medicine that is used for the treatment of athrepsia due to surgery, anorexia, cold constitution, and anemia. An active component, gomisin A, in *Schisandra* fruit, among the herbs included in ninjinyoeito, has been reported to have inhibitory effects on HCV and protective effects on immunological hepatopathy against HCV infection (Cyong et al., 2000). Ninjinyoeito is reported to have antiinflammatory properties by suppressing phagocytosis of alveolar macrophages (Aoki et al., 1994) and to increase NK activity in healthy individuals (Kamei et al., 1998). It also has antioxidant and hepatoprotective activities in a cell culture system (Kamei et al., 1998) and an in vivo model (Egashira et al., 2003). Based on these findings, Cyong et al. (2000) have identified an active anti-HCV component in ninjinyoeito as gomisin A in a cultured-cell system and an animal model of immunologically

induced acute hepatic failure. The study also demonstrated clinical effects of using ninjinyoeito to treat chronic HCV; however, the results were not conclusive and further studies are needed to assess the promise of ninjinyoeito for the treatment of chronic HCV (Azzam et al., 2007), as it may reduce viral load or contribute to delaying HCV progress.

Shosaikoto

Shosaikoto has been used for patients with liver diseases in Japan because of its suppressive effect against cancer development in the liver and its macrobiotic effects. To assess its mechanistic aspects, an in vitro study has tested the effects of shosaikoto on the production of IL-12 in circulating mononuclear cells from liver cirrhosis patients (Yamashiki et al., 1999). The group determined IL-12 levels in the monocyte/macrophage fraction and the lymphocyte fraction of peripheral blood obtained from 11 HCV-positive liver cirrhosis patients and 12 healthy subjects and found that IL-12 produced by the patients was significantly lower than that produced by healthy subjects. Shosaikoto stimulation of the monocyte/macrophage fraction or the lymphocyte fraction increased the levels of IL-12 about threefold, which was almost the same level as that of healthy subjects. The study concluded that one of the possible mechanisms of the macrobiotic effects of shosaikoto in liver cirrhosis patients may be the improvement in IL-12 production.

A phase II trial of shosaikoto was conducted in HCV patients who were not candidates for IFN-based therapy to determine the effectiveness for further study (Deng et al., 2011). In the trial, 24 chronic HCV patients were orally administered 2.5 g shosaikoto three times daily for 12 months. Improvement of aspartate aminotransferase and alanine aminotransferase was observed in 16 (67%) and 18 (75%) patients in the study, respectively. Viral load was reduced in 7 patients, increased in 10 patients, and not affected in 7 patients. The study concluded that shosaikoto may improve liver pathology in selected HCV patients who are not candidates for IFN-based treatment, but larger and controlled studies are necessary.

Oxymatrine

Oxymatrine is one of the major alkaloid components of *Sophora flavescens*. It was first described to have anti-HCV and anti-hepatitis B virus (HBV) effects in a cell culture model (Chen et al., 2001b) and an animal model (Chen et al., 2001a). A mouse study indicated that oxymatrine has hepatoprotective activity against acute liver injury induced by allyl alcohol (Liu et al., 1994). Antifibrotic activity of oxymatrine in D-galactosamine-induced rat liver fibrosis has been predicted to be partly through inhibition of lipid peroxidation. Immune-stimulative activity that changes the immune response of HBV-transgenic mice from a Th2 (IL-4 and IL-10) to a Th1 (IFN-γ and IL-2) response has been also reported (Dong et al., 2002; Yang et al., 2002). Because these animal studies and cell-based experiments showed promising effects against HCV infection, several clinical studies have been

conducted (Li et al., 1998; Mao et al., 2004). A review paper has evaluated the efficacy of several natural products reported in the treatment of chronic HCV subjects. The paper concluded that the results are promising and indicate the need for further evaluation in HCV cases (Azzam et al., 2007).

Maoto and Daiseiryuto

Maoto and daiseiryuto have been used for the common cold in Japan. Clinical studies have been conducted to assess whether maoto and daiseiryuto reduce the adverse effect of IFN-β in the treatment of chronic HCV patients. In these studies, patients were treated with a combination of IFN-β and either maoto or daiseiryuto and the combinations with Kampo were compared to treatment with IFN-β alone (Kainuma et al., 2002a,b). Adverse effects of IFN-β were evaluated based on the severity of symptoms self-classified into four categories using a questionnaire consisting of 29 items. Scores of symptoms such as discomfort were significantly lower with the combination therapy of IFN-β and Kampo compared to IFN-β alone and none of the patients needed to interrupt therapy because of side effects of IFN-β. Biochemical parameters such as serum alanine aminotransferase and serum hyaluronic acid levels were better compared to IFN-β alone. The authors proposed that administration of these Kampo medicines together with IFN-β treatment could increase the sustained biochemical response rate and reduce liver fibrosis.

Other Herbal Mixtures

There are two studies of the effects of herbal mixtures on HCV infection. EH202 is a mixture of four herbal extracts that have IFN-inducing effects, although information about the ingredients of EH202 is not clearly indicated. A group has conducted an uncontrolled clinical study on E202 in 35 patients with chronic HCV (Kaji et al., 2004). The study claimed that after 3 months of daily EH202 administration, HCV RNA levels in patients were decreased, and improvements in malaise, bloating sensation in the abdomen, and nausea and vomiting were observed in a significant number of patients without showing any serious adverse effects. The authors concluded that EH202 may be safe and useful for the treatment of chronic HCV, although further investigations need to be performed to obtain a definitive conclusion. Another study has reported anti-HCV activity of extracts of *Citrus unshiu* peel (Aurantii nobilis pericarpium) through inhibition of viral absorption in the human acute lymphoblastic leukemia cell line MOLT-4 (Suzuki et al., 2005).

Human Immunodeficiency Virus Infection

Shosaikoto has been widely used for patients with chronic hepatitis and cirrhosis in Japan (Shimizu, 2000). A study has examined the inhibitory effect of shosaikoto on human immunodeficiency virus type 1 (HIV-1) replication in peripheral blood mononuclear cells

(Piras et al., 1997). In the study, the anti-HIV activity of shosaikoto was tested when combined with known anti-HIV drugs such as zidovudine (AZT), lamivudine (3TC), or a combination of AZT/3TC. In vitro experiments indicated that shosaikoto enhanced anti-HIV activity of 3TC among the tested combinations. The authors suggested that a combination therapy of shosaikoto and 3TC has potential as a chemotherapeutic modality for HIV-1 infection. Because it has been reported that shosaikoto inhibits the reverse transcriptase of murine leukemia virus and HIV in vitro (Ono et al., 1990), this activity may be the underlying mechanism of its anti-HIV activity. Another in vitro study has reported that *Polyporus* sclerotium, gardenia fruit, *Atractylodes lancea* rhizoma, *Cnidium* rhizoma, and Japanese *Angelica* root have some anti-HIV activity (Kato et al., 2012). However, no clinical trials of shosaikoto or other Kampo medicines against HIV infection have been reported so far.

Hepatitis B Virus Infection

Shosaikoto was initially tested in 1992 for anti-HBV infection in vitro and in clinical studies. The in vitro study tested peripheral blood mononuclear cells (PBMCs) from patients with chronic active hepatitis and indicated that shosaikoto increased IFN-γ and anti-HBV antibodies produced in PBMCs in a dose-dependent manner (Kakumu et al., 1991). The clinical study investigated the efficacy of shosaikoto in children with chronic HBV infection and with sustained liver disease (Tajiri et al., 1991). Seven of 14 patients (50%) became negative for hepatitis B antigen within a year in the study. The hepatitis B antigen clearance rate in the shosaikoto-treated group was higher than the control annual hepatitis B antigen clearance rate (22.7%) in 22 untreated patients. Other groups also have confirmed similar effects of shosaikoto on HBV infection (Akbar et al., 1999; Chen et al., 2001a; Dong et al., 2002). In addition, a 2007 study demonstrated that shosaikoto directly inhibits viral growth in a HepG2 cell model (Chang et al., 2007). Therefore, the group has proposed shosaikoto as a supplementary to nucleotide analogs to minimize the recurrence of viremia after its discontinuation.

Herpes Simplex *Virus Type 1 Infection*

The effects of kakkonto against cutaneous herpes simplex type 1 (HSV-1) infection in mice have been described (Nagasaka et al., 1995). Kakkonto, at a dose corresponding to that in humans, reduces the mortality of HSV-1-infected mice and reduces localized skin lesions. Kakkonto does not inhibit viral growth in vitro and does not affect cytokine production, NK cell activity, natural cytotoxic killer cell activity, or the population of T-cell subsets in spleen cells of infected mice. Because the delayed-type hypersensitivity (DTH) response to HSV-1 antigen is stronger in kakkonto-treated mice than in untreated mice, the authors attributed the reduction in the mortality of kakkonto-treated mice to an induction of a strong DTH to HSV-1.

Another study has investigated the protective effects of hochuekkito on mitomycin C–immunosuppressed mice. An HSV-1 lethal infection caused by mitomycin C treatment in mice was prevented by oral hochuekkito administration. The authors concluded that hochuekkito may be beneficial for the treatment of infectious diseases in immunocompromised patients receiving chemotherapeutic drugs (Kido et al., 2000). No clinical trials of hochuekkito against HSV-1 infection have been reported.

Severe Acute Respiratory Syndrome Coronavirus Infection

Two in vitro studies of the inhibitory effects of herbal extracts against severe acute respiratory syndrome coronavirus (SARS-CoV) infection have been reported. Extract from a vegetable, the tender leaf of *Toona sinensis* Roem, inhibits growth of SARS-CoV in vitro (Chen et al., 2008). Another study also demonstrated that six herbal extracts from Gentianae radix (long dan; the dried rhizome of *Gentiana scabra*), *Dioscoreae* rhizoma (shan yao; the tuber of *Dioscorea batatas*), Cassiae semen (jue ming zi; the dried seed of *Cassia tora*), and Loranthi ramus (sang ji sheng; the dried stem with leaf of *Taxillus chinensis*) and two from Cibotii rhizoma (gou ji; the dried rhizome of *Cibotium barometz*) inhibit replication of SARS-CoV at 25 to 200 μg/mL concentrations in Vero E6 cells (Wen et al., 2011). Interestingly, extracts from Dioscoreae Rhizome and Rhizome Cibotii were found to inhibit SARS-CoV 3CL protease activity among the extracts tested.

BK Virus–Associated Hemorrhagic Cystitis

BK virus–associated hemorrhagic cystitis (BKV-HC) is a common problem arising occasionally after hematopoietic stem cell transplantation. A group examined the efficacy of choreito for treating BKV-HC in children who underwent allogeneic hematopoietic stem cell transplantation (Kawashima et al., 2015). The duration until complete resolution of hematuria was significantly shorter in the choreito-treated group (median 9 days, range 4–17 days) compared to the nonchoreito group (median 17 days, range 15–66 days; $p = .037$). The BKV load in urine was decreased a month after choreito treatment and no adverse effect was observed. Therefore, the authors suggest that choreito may be a safe and promising therapy for the hemostasis of BKV-HC after hematopoietic stem cell transplantation.

Human Papillomavirus Vaccine Adjuvant

The human papillomavirus (HPV) E7, an oncoprotein ubiquitously expressed in the precursor lesion of cervical cancer, is a target for HPV therapeutic vaccines. A study has demonstrated that juzentaihoto and hochuekkito have adjuvant activity for oral vaccination with recombinant *Lactobacillus casei* expressing HPV-16 E7 (LacE7) in mice (Taguchi et al., 2012). Oral

immunization of mice with LacE7 with mucosal adjuvant, heat-labile enterotoxin T subunit (LTB), promotes systemic E7-specific type 1 T-cell responses and a similar effect was observed with juzentaihoto or hochuekkito as an adjuvant. Oral administration of LacE7 plus either of these Japanese Kampo medicines and LTB enhances mucosal E7-specific type 1 T-cell response by approximately threefold more than after administration of LacE7 alone. Secretion of IFN-γ and IL-2 into the intestinal lumen is enhanced by juzentaihoto or hochuekkito and LTB in oral administration of LacE7. Finally, these Kampo medicines enhance the mucosal type 1 immune responses to orally immunized antigen synergistically with *Lactobacillus* and LTB. Therefore the authors suggest that juzentaihoto or hochuekkito may be an excellent adjuvant for oral *Lactobacillus*-based vaccines and may have the potential to elicit extremely high E7-specific mucosal cytotoxic immune response to HPV-associated neoplastic lesions.

Candida albicans *Infection*

C. albicans causes the majority of the opportunistic fungal infections observed in patients under treatment with immune-suppressive drugs and others, such as HIV patients. A group has suggested that several Kampo medicines might be effective as therapeutic agents against candidiasis in immunosuppressed patients. The protective effects of juzentaihoto and its ingredients against *Candida* infection were investigated using immunosuppressed mice (Abe et al., 1998, 1999). ICR mice injected with prednisolone or cyclophosphamide were orally administered 1 g/kg juzentaihoto daily and intravenously infected with a lethal dose of *C. albicans*. Juzentaihoto treatment prolonged the life span of infected mice compared to control mice. A similar protective effect was obtained by treatment with its ingredients ginseng radix, *Glycyrrhiza* radix, *A. lancea* rhizoma, or *Cnidium* rhizoma. Ninjinyoeito also had a similar effect on mice immunosuppressed with cyclophosphamide (Abe et al., 2000).

Listeria monocytogenes *Infection*

A foodborne pathogen, *L. monocytogenes* causes illness mainly in pregnant women, newborns, elderly, and immunocompromised people. Two Kampo medicines have been indicated to be effective against *L. monocytogenes* infection in mice. Shosaikoto was first described as preventing the lethal effect of *L. monocytogenes* by an intraperitoneal (ip) injection. Growth of *L. monocytogenes* in the peritoneal cavity and liver was suppressed from day 1 after the infection. The bactericidal activity of peritoneal macrophages from shosaikoto-treated mice was maintained from 1 to 3 days after ip injection of killed *L. monocytogenes*, whereas the activity of control mouse macrophages was decreased. The authors suggest that augmented accumulation of macrophages and maintenance of their bactericidal activity may be the main mechanisms of the resistance in shosaikoto-treated mice.

The effect of hochuekkito against *L. monocytogenes* infection has been reported in mouse models. Mice orally administered hochuekkito for 10 days (1 g/kg per day) were intravenously (iv) or ip infected with *L. monocytogenes*. Survival rates in mice infected iv at day 1 or infected ip at day 4 after the last administration were increased. The number of bacteria in spleen and liver was increased to kill iv-infected mice by day 5 in the nonadministered group, whereas the number of bacteria in the hochuekkito-pretreated mice was increased relatively slowly by day 3 and decreased from day 3 to day 8. A similar effect was observed in ip-infected mice. Peritoneal macrophages from hochuekkito-treated mice showed an enhanced activity to kill *L. monocytogenes* in vitro within 60 min after ingestion of bacteria. A similar effect was observed in mice undergoing restraint stress treatment and in infant mice (Yamaoka et al., 2000, 2001). In infant mice, IFN-γ-producing $CD4^+$ T cells were increased with hochuekkito treatment independent of the deficiency in the antigen-presenting function.

Propionibacterium acnes *Infection*

P. acnes is a gram-positive commensal bacterium that causes acne on the skin. *P. acnes* releases lipase that produces fatty acids by digesting sebum, creating inflammation of the skin. Several Kampo medicines and their ingredients have been described for their inhibitory effect on the growth of bacteria. Reports have described that orengedokuto and its ingredients, Coptidis rhizoma and Phellodendri cortex (Higaki et al., 1990, 1995, 1996a,b), jumihaidokuto (Higaki et al., 2000, 2001), unseiin (Higaki and Morohashi, 2003), and keigairengyoto (Higaki et al., 1997, 2004) inhibit the growth of *P. acnes* and lipase activity. Therefore, these Kampo medicines have been used for acne.

Helicobacter pylori *Infection*

H. pylori is a gram-negative bacterium that infects the stomach and whose infection is a major cause of gastroduodenal diseases in humans. Eradication of *H. pylori* by antibiotics is a very effective treatment; however, the variable prevalence of resistant organisms has been developing (Fakheri et al., 2014). A study has investigated the antibacterial effect of hochuekkito against *H. pylori* infection in vivo and in vitro (Yan et al., 2002). The in vitro experiments demonstrate that hochuekkito inhibits the growth of antibiotic-resistant strains of *H. pylori* as well as antibiotic-sensitive strains at a dose of 2.5 mg/mL. The in vivo experiments with mice orally administered hochuekkito for 7 days before or after inoculation of *H. pylori* showed that the bacterial load in the stomach was significantly reduced in the hochuekkito group compared with the control group. Hochuekkito administration induced IFN-γ in the gastric mucosa and there were no significant differences in bacterial load between the control and the hochuekkito-treated group in IFN-γ gene-deficient mice. Therefore, the authors suggest that the antibacterial effect of hochuekkito is partly due to IFN-γ induction and its possible clinical use for treatment of *H. pylori* infection.

Vibrio cholerae *Infection*

Infection with the bacterium *V. cholerae* in the small intestine causes severe diarrheal diseases such as cholera. The causative agent of cholera is cholera toxin (CT), the virulence factor secreted by *V. cholerae*. A study has indicated that daiokanzoto inhibits CT activities such as ADP-ribosylation and Chinese hamster ovary cell elongation and identified the active compounds in this Kampo medicine (Oi et al., 2002). Among several components purified from daio extract, rhubarb galloyl-tannin, a compound characterized by a polygallate structure, is the most effective one. Synthesized gallate analogs similar to rhubarb galloyl-tannin inhibit all CT activities, including ADP-ribosylation, elongation of Chinese hamster ovary cells, and fluid accumulation in ileal loops. Therefore, the authors claim that the Kampo formulations or their gallate components might be effective adjunctive therapies with oral rehydration solution for the severe diarrhea of cholera.

Porphyromonas gingivalis *and Other Oral Microorganism Infections*

P. gingivalis is a gram-negative bacterium that is implicated in certain forms of periodontal disease. Several Kampo medicines have been reported to inhibit *P. gingivalis* growth and suggested to be effective for controlling periodontal disease. A group has tested several Kampo medicines for *P. gingivalis* growth, adherence to epithelial cells, and proteinase activity (Liao et al., 2013). Among the Kampo medicines tested, sanoshashinto has the strongest inhibitory effect, and the test identified the responsive compounds present in the Chinese rhubarb, one of the major components of sanoshashinto, to be anthraquinones such as aloe emodin and rhein. These anthraquinones also inhibit the adherence of *P. gingivalis* to oral epithelial cells and reduce its proteinase activity. The strongest antiadherence activity was observed with a Kampo medicine, mashiningan extract granules, that contains rhubarb. Therefore, the authors claim that Kampo medicines containing rhubarb and its anthraquinone derivatives may be effective for controlling periodontal disease through their capacity to inhibit *P. gingivalis* growth and virulence properties.

Certain oral microorganisms are implicated in intensifying the inflammatory process and aggravating the ulcer formation of oral mucositis (OM) in cancer patients under chemotherapy or radiotherapy. A Kampo medicine, hangeshashinto (HST), has been investigated for antimicrobial activity against several bacteria and fungi (Fukamachi et al., 2015). HST extract inhibits the growth of gram-negative bacteria, including *Fusobacterium nucleatum*, *P. gingivalis*, *Porphyromonas endodontalis*, *Prevotella intermedia*, *Prevotella melaninogenica*, *Tannerella forsythia*, *Treponema denticola*, and *Porphyromonas asaccharolytica*, and less inhibitory effects on gram-positive bacteria and the fungal strains were observed. The active ingredients in HST are identified to be baicalein, berberine, coptisine, 6-shogaol, and homogentisic acid. The authors suggest that HST may be a useful treatment for OM in patients undergoing anticancer treatment.

Streptococcus pyogenes *Infection*

S. pyogenes infection causes necrotizing fasciitis and streptococcal toxic shock syndrome. The efficacy of a Kampo medicine, hainosankyuto, for the treatment of *S. pyogenes* skin infection has been investigated in in vivo experiments using mice (Minami et al., 2011). Oral administration of hainosankyuto to infected mice for 4 consecutive days increased the survival rate and reduced the size of local skin lesions compared to control mice. Hainosankyuto attenuated the bacterial load in the blood, with increased macrophage phagocytic activity in mice, and increased the levels of IL-12 and IFN-γ and decreased the level of TNFα in the serum of *S. pyogenes*-infected mice. The authors conclude that hainosankyuto may be useful for the treatment of *S. pyogenes* infection more prophylactically than therapeutically.

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