Integrating Kampo and Evidence-Based Medicine (7) – From Reports of Medical Cases from 200 Years Ago –

The Effect of Maoto on Influenza

Hiromichi Yasui[1)], Tetsuhiro Yoshino[2)], Ryutaro Arita[2)], Yuko Horiba[2)], Hiroshi Koike[2)], Takuya Hamaguchi[2)], Miwako Ohgishi[2)] and Kenji Watanabe

1) Japan Institute of TCM Research

2) Center for Kampo Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

From medical cases about 200 years ago

This is a story of an experience by a boy born in a doctor's family in a rural area in Japan about 200 years ago.

One day, the people of the neighborhood came to this doctor's house saying they wanted him to examine a patient. At this time, the doctor was not at home, and the grandfather, who was already retired, told the doctor's younger brother to "go and examine the patient". And so the boy went and examined the patient. The grandfather asked the boy what kind of sickness the patient had, and the boy answered, "The patient's disease is Shang-han, he has splitting pain in his head, chills, fever, labored breathing, pain all over his body, and his pulse was floating and strong." To this the grandfather replied, "What kind of prescription do you think to give him?" The boy answered, "how about maoto?" Then the grandfather smiled and said, "Good job", so he prop 3 doses of maoto and ordered him to "give him these doses warm, and make him sweat a lot" and sent the messenger back. When he went back the next morning, the patient had sweat a lot and said that his suffering had quickly been alleviated. He still had a slight fever, so he changed the prescription to shosaikoto, and he recovered in barely more than a day.

This is a story experienced by Dr. Yodo ODAI (1799-1870) at age 13, who was praised as a great doctor in his later years, and he wrote of this as being his "first challenge" [1)].

These records continued to be read even to this day. Among them, the ailment that he wrote as "Shang-han lun" seems to be almost the same as the "Shang-han lun" which is listed in the " Shang-han lun", the original text in which described maoto. And seen from our modern eyes, this was probably influenza.

Maoto is currently widely used for influenza. This is because this experience of Dr. Yodo ODAI was earnestly recorded in his "Essay of Medical Technique".

The composition of maoto

"Shang-han lun" lists the compounding and dosing method of maoto as follows.

Mix ephedra (3 liang, remove stem node), apricot seed (70 pieces, remove skin tip), cinnamon twig (2 liang, remove skin), and liquorice (2 liang, scorch) with 9 sheng of water, first boil the ephedra, reduce by 2 sheng, remove foam, add the other medicines, boil down by 2.5 sheng, remove scum, and take 8 ne warm. In other words, the boiled liquid will be divided into 3 equal parts.

Currently, the following crude drugs are boiled in the following gram amounts to prepare one day's dose. The formulation divides this into 3 times.

Ephedra 3～5g, apricot seed 4～5g, cinnamon twig 2～4g, liquorice 1～1.5g

Because the amounts are slightly different at each pharmaceutical company, there is a range. Lactose is often used as an excipient, with some formulations using starch.

Maoto as a remedy for influenza

Use of maoto is generally limited to the early stages of acute fever such as influenza. As stated above, the indication is the combination of symptoms such as chills, fever, headache, joint pain, and floating pulse, with no sweating.

When administering maoto for influenza, I conduct the following dosing guidance based on the description in the "Shang-han lun".

Patients take an extract formulation of maoto in hot water. After taking, keep the body warm to help induce sweating. After the first dose, take 1 dose every 2 hours taking 1 day's worth (3 doses) in 4 hours. Subsequently, take some every 3-4 hours, and continue until sweating onsets. After sweating starts, stop taking at that point. In the original text it is stated that you must not induce too much sweating, but in actuality as long as you quickly change clothes, keep warm, and intake an appropriate amount of water.

In some cases the fever may temporarily rise before subsequently falling. For example, in some case a body temperature of 38.5℃ may rise to 39.3℃ 1 hour after dosing. Normally, the fever will go back down after this. In rare cases, palpitation or tachycardia may occur after dosing. In these cases temporary stop taking the medicine.

When the fever starts to go down, there is often large amounts of sweating, but in a few dozen percent of patients, the fever can go down with frequent urination (urination may occur about 5 times in 2 hours). In these cases, there is not much sweating. In extremely rare cases, reduction of fever may occur with nosebleeds. When effective, the fever will drop to about 37.0℃ in 18-36 hours from the start of dosing.

The amount to use for children depends on their age and body weight or body surface area

Furthermore, in the series of maoto research below, the standard method of dosing one day's worth separated into 3 times is most common.

The diseases for which maoto is indicated in the text of the "Shang-han lun" belong to taiyang diseases among diseases called "Shang-han", and they are "headache and fever, sheng teng lower back pain, bone pain, chills, and panting without sweat". Thought of in the context of modern notions of ailments, these descriptions of "Shang-han" seem to be influenza or associated ailments. In recent years, research from this point of view has progressed and there has been a great deal of clinical research produced showing that maoto is effective against influenza.

There are also many medical reports, the prototypical of which is published by Oribe in Vol.1 No. 1 of this journal.

Caution when using

Maoto is a formulation with ephedra as its main ingredient, and the main component of ephedra is ephedrine. For this reason, use in combination with other ephedra-containing compounds and catecholamine formulations requires caution. Side effects caused by ephedrine can be seen including coronary artery disease, arrhythmia, excessive perspiration and urinary retention. Also seen are digestive symptoms such as a heavy feeling in the stomach and epigastric pain.

It has also been shown that the absorption of ephedrine raises in pH of the alimentary canal, so absorption is higher when taken internally after meals, and it also has the potential to increase the likelihood of side effects due to sympathetic nerve stimulation. For the same reason, taking together with antacid drugs also requires caution [3].

Research into maoto for influenza

Influenza virus infection often shows evidence of maoto, and there have been many reports regarding the effects of administering maoto. Classified broadly, we see studies which examine the effects when adding maoto to commonly used anti-viral medicines, studies which compare maoto alone with anti-viral medicines alone, and also case series and comparative studies which investigate the side effects and administration methods in addition to what happens before and after maoto is administered.

In Japan, continuing from the rapid testing of influenza viral antigens, in February 2001 the

National Health Insurance drug prices of oseltamivir (Tamiflu®) and zanamivir (Relenza®) were listed, after which their use expanded explosively. In the case of oseltamivir especially, 70-80% of its consumption in the world is in Japan, and as a unique phenomenon in Japan it as acquired the status of the standard treatment in a short period of time. Consequently, early-stage clinical research into the results of maoto against influenza virus infection has no option to not administer the standard treatment anti-viral medicine, and has started generally as an examination of the effects of maoto on top of the other medicine.

As the use of oseltamivir expanded, in 2004 a postscript was added to the package insert of oseltamivir regarding mental and nervous disorders, furthermore about the abnormal behavior of the teenage patient, Japan's Ministry of Health, Labour and Welfare came to urgently perform a delivery of safe information in 2007, and the report that compared the independent groups given *maoto* with the oseltamivir came to attract attention. In basic researches using rats, the simultaneous administration of ethanol and oseltamivir has been reported to promote excitability, and similar phenomena are predicted in ephedrine as well [4]. For this reason there are opinions that prudence is required when using oseltamivir and maoto together.

Furthermore, in 2009 the effectiveness of maoto against new strains of influenza was investigated, and this continues today. Compared to oseltamivir, the National Health Insurance drug cost of maoto is overwhelmingly low, and it is receiving attention in terms of health economics as well regarding whether or not administering maoto alone has the same effects as oseltamivir.

Note: In Japan, the prices of medicines used with health insurance are controlled by the nation. The drug price of oseltamivir phosphate is about 640 yen per one day's worth, while maoto is about 60 yen. Arita et al. preliminarily calculated that using maoto instead of oseltamivir would result in a reduction in health care costs of 3,000 yen per person or 9 billion yen in Japan overall [5].

In recent years there have also been reports of viruses that are resistant to oseltamivir, and furthermore oseltamivir-resistant viruses have shown cross-resistance with peramivir, a injectable medicine, as well. There are no reports of resistance to maoto, and viewed from the point of view of resistant virus control as well as from the point of view of drug assurance to prepare for pandemics, the significance of the existence of Kampo medicine such as maoto would seem to be great.

Studies of maoto with standard therapy

Research by Kuroki, et al.

In a comparative study by Kuroki, et al., oseltamivir was administered to 83 children with influenza, and in 44 of the 83 cases maoto 0.1-0.15g/kg/day x 3 was simultaneously administered. In the group administered oseltamivir alone, no complications were seen except 1 case of febrile convulsions. The time from the first day of fever until the alleviation of fever was 3 days in the maoto + oseltamivir group, and 2 days in the oseltamivir only administration group. The reason maoto was prescribed was not stated, and it is unclear what the fever period indicates [6].

Research by Kimoto, et al.

In an open labeled quasi-randomized-controlled trial (RCT) conducted subsequently by Kimoto, et al., with the same group, 19 patients diagnosed with influenza through clinical condition and rapid testing from January to March 2004 which did not meet exclusion criteria were divided into a group of 10 patients (4 men, 6 women, age 24.1±7.72) who were administered oseltamivir and maoto (7.5g/day×3 days) in the order of examination, and a group of 9 patients (5 men, 4 women, age 29.1±4.52) who were administered oseltamivir with Western medicine (cyproheptadine hydrochloride and clenbuterol hydrochloride or carbocysteine), and their body temperature, appetite, fatigue, and dizziness after treatment were compared via a questionnaire filled out by the patients. All of the cases were type-A influenza. 12 hours after the start of treatment, their body temperature showed a tendency to be lower in the maoto combination group than in the Western medicine combination group. The date when the maoto group's fatigue, dizziness and lack of appetite scores improved significantly compared to before treatment was sooner compared to the Western medicine group. Not examples if increased CRP were observed in the maoto group, but in the Western medicine group 3 cases of CRP increase were observed. In the Western medicine group reduced WBC, increased RBC, Hb, hematocrit and significant increase in ALT and γ-GTP were observed. A decrease in albumin was also observed in the maoto group. Including 8 weeks of follow-up observation, no serious adverse events were observed in either group [7].

Research by Fukutomi, et al.

In an open labeled RCT by Fukutomi, et al., 22 patients diagnosed with influenza through rapid testing within 24 hours of the onset of symptoms were divided into a group of 12 patients administered oseltamivir only (the single administration group) and a group of 10 patients who were administered oseltamivir with maoto (combined administration group) with the combined administration group being administered maoto (7.5g/day), and the number of days the patients continued to experience a fever of 38℃ or higher, headaches, and full-body fatigue was investigated. The method of assignment into the groups was not stated. The number of days the fever continued was 1.7±0.8 days in the single administration group and 1.9±0.6 days in the combined administration group, showing a significant difference. The number of days the headache continued was 2.4±1.0 days in the single administration group and 1.3±0.5 days in the combined administration group, while the full-body fatigue was 2.3±1.2 days in the single administration group and 1.3±0.5 days in the combined administration group, showing a significant difference. It appeared to be clinical influenza, but in the 6 cases where maoto was administered without a diagnosis via an influenza rapid testing kit, no significant difference in number of days fever, headache, and full body fatigue continued was found compared to the combined administration group. No serious side-effects were observed [8].

Research by Kubo, et al.

In an open labeled RCT by Kubo, et al., 60 case of patients (5 months to 13 years of age) experiencing fevers of 38℃ or higher, 2 or more of the symptoms headache, chills, and fatigue, and coughing and nasal inflammation all appearing within 48 hours were first classified into 2 groups: the group which was 1 year old or older with a positive rapid testing result, and the group which was 1 year or less with a positive rapid testing result or a negative rapid testing result regardless of age. Additionally, the group of 1 year and older with positive rapid testing results was further assigned randomly into 2 groups, with 19 patients being administered oseltamivir (4mg/kg/day) and 17 patients being administered oseltamivir and maoto (0.06g/kg/day). The group of 24 patients 1 year or less in age with a positive rapid testing result or a negative rapid testing result regardless of age was administered maoto only.

Antipyretics were requested not to be internally administered. The definitive diagnosis of influenza was conducted with viral culture or PCR, and among the negative rapid testing group those diagnosed with type A influenza were the only targets of analysis. The method of randomization was not stated. 3 of the patients with positive rapid testing results assigned combined administration of oseltamivir and maoto did not internally take maoto and were therefore excluded from analysis. The 2 groups which took maoto orally had significantly shorter periods of fever after examination compared to those who did not take maoto orally. All patients resumed their normal lives and no side effects from maoto were observed. No patients required hospitalization [9].

Research by Takeya, et al.

In RCT by Takeya, et al., the fever period from start of treatment until alleviation of fever was compared in two groups--a group that was administered both maoto and oseltamivir (23 type A and 17 type B) and a group that was administered only oseltamivir (59 type A and 86 type B)--targeting 185 patients (age 0-14) selected from children examined at 7 hospitals and clinics in Shimane prefecture who had not received influenza vaccination and who were shown to be type A or type B influenza virus antigen-positive in rapid testing. The results showed a shorter trend in the combined administration group compared to the oseltamivir only group, but no significant difference was observed [10].

Research by Yamamoto, et al.

In a retrospective comparative study by Yamamoto, et al., 167 cases were investigated via responses to questionnaires out of 329 cases of children where were diagnosed with new strains of influenza who were administered maoto. A questionnaire was administered to the guardians of the target patients regarding the state of oral ingestion, day of fever alleviation, and side effects or lack thereof, and the results of these were compared with the patient information in the electronic charts to confirm the patient backgrounds such as age and gender, fever period, and administration of anti-viral medicine and antibiotics or lack thereof. The results showed that in the younger ages there was more administration of maoto alone, while in the higher ages there was administration together with anti-influenza drugs. The average fever period by treatment method was 1.39±0.96 days in the maoto-only group and 1.60±1.20 days in the anti-influenza drugs combined use group, with no significant difference observed between the 2 groups. Side effects were observed in 21 patients (13.1%), and a breakdown observing duplicate responses was that 13 patients experienced lack of appetite, 5 experienced nausea/vomiting (including while taking orally), 3 experienced rashes, 2 experienced diarrhea/watery stools, and 1 each experienced bad temper and edema, respectively, with no significant difference observed between the groups [11].

Research by Tsuji, et al.

Comparative research by Tsuji, et al. targeted 81 cases of child influenza patients whose families consented in participation in the study. They were separated into 3 groups--an anti-influenza medicine only group (oseltamivir 4mg/kg/day or zanamivir 8mg/day), a maoto-only group (0.2g/kg/day), and an anti-influenza + maoto group--and investigated. The method of assignment into the groups was not stated. No significant difference was observed in the periods of fever continuation or clinical symptoms continuation among the 3 groups, however the fever continuation period and clinical symptoms continuation period were both shortest in the combined administration group. Furthermore, treatment with anti-influenza medicine, clarithromycin (10mg/kg/day), and maoto combined with clarithromycin was conducted targeting a total of 288 other child patients diagnosed with influenza (the maoto-only group and antipyretic group administered group were excluded due to a low

number of cases). The results showed no statistically significant difference between the groups in the fever continuation or clinical symptom continuation groups [12].

Studies comparing maoto administered alone and anti-viral medicines administered alone

Research by Kawamura

Although it was not random assignment, Kawamura, who is proactively proceeding with comparative research, has come to imply the possibility that the differences in results and side effects between maoto and oseltamivir are small. 139 child patients with influenza examined in the spring of 2007 were divided into a maoto (0.08 ～ 0.19g/kg/day, maximum of 7.5g in 3 divided doses) administration group and an oseltamivir (4mg/kg/day , maximum 150 ㎎ in 2 divided doses)administration group as per their parents' requests, the time of fever alleviation and fever period, etc. were investigated. The administration period was 2-8 days in the maoto group and 2-5 days in the oseltamivir group, with fever alleviation or improvement of symptoms as criterion in the case of both medicines. Antihistamine, antitussives, and expectorants were also additionally administered as necessary. In the type A patients no significant difference was observed in age, maximum body temperature, ingested dose of maoto, time from outbreak of illness to start of ingestion, time from ingestion until alleviation of fever, time from ingestion until alleviation of general symptoms, and time of continuation of general symptoms. In the type B patients, the time of starting ingestion was significantly later in the maoto group, the time from ingestion until alleviation of fever and time until alleviation of general symptoms was significantly faster in the maoto group, and the length of general symptoms was significantly shorter in the maoto group [13]. In the B group patients, the time from ingestion until alleviation of fever and time until alleviation of general symptoms was significantly shorter in the maoto group, but the time until the start of ingestion was longer, so it is difficult to come to a conclusion based solely upon this report.

In a subsequently published report by Kawamura with almost the same contents targeting 129 child influenza patients, in addition to similar contents to the preceding study, the study also investigated the time passed after onset of fever and after onset of illness until the start of ingestion, the fever period, the symptom continuation period, and the correlation between the amount of maoto ingested and the fever period and symptom continuation period. By and large no correlation was observed, but a positive correlation between the time of starting ingestion after onset of fever and fever period was observed in the type A influenza oseltamivir group and in the type B influenza maoto group. No significant difference in abnormal behavior such as sleep-talking, auditory hallucinations, and visual hallucinations was observed between these two groups [14].

In comparative research conducted by Kawamura conducted in the following season (2007/08), the time of disappearance of the influenza virus form the pharynx with maoto and oseltamivir was examined, and the study implied the efficacy of maoto. 172 patients with type A influenza in the 2007/2008 season were divided into 3 groups--64 patients with Teikoku's maoto (0.16g/kg/day, maximum 7.5g/day in 3 divided doses), 61 patients with Tsumura's maoto (0.16g/kg/day, maximum 7.5g/day in 3 divided doses), and 47 patients with oseltamivir (average 3.9 mg/kg/day, maximum 150 mg/day in 2 divided doses) by the request of the patients (their parents)--with maoto administered with 1-6 days with fever alleviation as the target, and oseltamivir administered with fever alleviation or 5 days being the criterion. The average time after ingestion until fever alleviation was 45.73±35.51 hours, 53.90±39.42 hours, and 30.36±20.96 hours, with the oseltamivir group being significantly shorter compared to the 2 companies' maoto groups. Similarly, the average fever time was average 67.27±37.88 hours,

69.57±39.76 hours, and 45.79±21.05 hours, and the time from onset of illness until disappearance of symptoms was 70.47±41.99 hours , 73.95±43.01 hours, and 48.47± 26.90 hours, significantly shorter. No significant difference was observed in the 3 groups in the time after onset of illness until the influenza virus was removed, the time from alleviation of fever was significantly shorter in the 2 companies' maoto groups compared to the oseltamivir group. In a comparison of the Teikoku and Tsumura maotos, a significant difference was observed in the fever alleviation time, fever time, general symptoms time, and elimination of A type influenza virus from the pharynx [15].

In comparative research by Kawamura, et al. conducted from January to March 2009, each subtype of influenza was investigated. 147 patients who came to a hospital within 48 hours of the onset of illness, were diagnosed with type A influenza via rapid testing kits using nasal swabs and diagnosed with a subtype (Soviet A-type H1N1, Hong Kong A-type H3N2) were divided into the symptomatic treatments of oseltamivir 4mg/kg/day and Teikoku maoto extract 0.2g/kg/day as per the request of the patients. 1-5 days of oral administration was conducted depending on the continuing time of the symptoms, and a comparative investigation of the continuation period of fever of 37.5℃ or higher and the continuation period of general symptoms such as headaches, fatigue, and lack of appetite was conducted. In Soviet A-type, there was an oseltamivir group of 15 patients (6 male patients, 9 female patients, age 11.20±16.22), an maoto group of 63 patients (33 male patients, 30 female patients, age 7.66±7.25), and a conservative of 8 patients (1male patients, 7 female patients, age 4.53±2.38), and in Hong Kong A-type there was an oseltamivir group of 18 patients (9 male patients , 9 female patients, age 12.86±16.20), an maoto group of 34 patients (18 male patients, 16 female patients, age 9.24±11.41),and a conservative of 9 patients (2 male patients, 7 female patients, age 7.86±9.40). In Soviet A-type, the conservative was significantly younger than the maoto group. Also, although the fever period was significantly longer in the conservative compared to the maoto group, there was also no significant difference observed between the groups in the time until coming to the hospital and the time until alleviation of fever after ingestion. In Soviet A-type, the time until coming to the hospital as well as the time after ingestion until alleviation of fever and fever time were all significantly shorter in the oseltamivir group compared to the maoto group. Also, although the fever period was significantly longer in the conservative compared to the oseltamivir group, there was also no significant difference observed between the groups in the time until coming to the hospital and the time until alleviation of fever after ingestion. Furthermore, the Soviet A-type had significantly longer fever time and time until fever alleviation after ingestion compared to the Hong Kong A-type. No significant difference was observed between the groups in the time until general symptoms were alleviated after ingestion [16].

Research by Fukutomi, et al.

In the preceding comparative study by Fukutomi, et al. which reported the efficacy of combined administration of maoto, 112 patients of less than 10 years of age diagnosed with influenza via rapid testing within 24 hours after the onset of illness was divided into 2 groups--54 patients (average age 4.7±2.1) administered oseltamivir and 68 patients (average age 5.2±2.7) administered Tsumura maoto extract (7.5g/day) as per the request of the patients--and their body temperatures on consecutive days were examined. In both groups, the 2nd day of illness showed a significant decrease in body temperature compared to the 1st day of illness, and no difference was observed between the groups. No serious side-effects were observed [17]. It was furthermore reported in a comparative study conducted targeting 41 cases in a different season that no difference was observed between the groups. The oseltamivir group was 20 patients (average age 4.1±1.8, 10 type A

patients/10 type B patients, fever of 39.0±0.3℃ when coming to hospital), and the maoto group was 21 patients (4.1±2.6 age, 12 type A patients・9type B patients, 39.0±0.4℃). In a questionnaire regarding the results of maoto conducted 3 days after the administration of maoto, 66% rated the results very good or good. On the other hand, a large number of respondents at 70% responded that it was difficult to drink. In spite of the common opinion that it was difficult to drink, only about 3% responded that they could not drink it [18].

Research by Mori, et al.

In a retrospective comparative study by Mori, 19 patients (12 men, 7 women, average age 11±11) out of 22 patients from amount 291 patients diagnosed with type A influenza between October and December 2009 were administered maoto extract, and the time it took for their temperature to drop to 36.9℃ from examination was investigated. They ingested 3 packets of Kampo medicine every 2 hours, and subsequently ingested every 3 hours until sweating was induced. By comparison, a group of 19 patients (7 men, 12 women, average age 16.5±16.1) administered oseltamivir and a group of 21 patients (11 men, 10 women, average age 15.4±8.7) administered zanamivir were also set up. Regarding the time for the fever to drop to 36.9℃ after administration, although the fever dropped significantly faster in the maoto group compared to the zanamivir group, no significant difference was observed between the maoto and oseltamivir groups[19].

Research by Toriumi, et al.

In the comparative research by Toriumi, et al., 86 patients (aged 5 months to 15 years) who were observed to have fevers of 37.5℃ or more and who tested positive for type B influenza were separated into 3 groups--a group between 1 and 10 years of age who desired oseltamivir, a group age 6 and older who desired zanamivir, and a group age 1 year or younger or who didn't desire neuraminidase inhibitors but desired maoto. Moreover, the patients who desired maoto from among the group which desired neuraminidase inhibitors were additionally administered maoto. Furthermore, an investigation was conducted into the patients who were administered neither anti-viral medication nor maoto. The amount of each drug administered was 4mg/kg/day for oseltamivir, 10mg/day for zanamivir, and 0.06g/kg/day for maoto. 16 patients were omitted, and only 70 patients were analyzed. No significant difference was observed in time from ingestion to alleviation of fever or time from onset of illness to alleviation of fever between the groups administered the drugs in ANOVA. The time from onset of illness to alleviation of fever was significantly shorter in all the groups administered drugs compared to the group administered no drugs.

All patients resumed their normal lives and no side effects from maoto were observed. No patients required hospitalization. Although there were 2 patients in the oseltamivir-only and zanamivir-only administration groups reported abnormal behavior respectively, no serious side effects were observed [20].

Research by Saita, et al.

In open labeled RCT by Saita, et al., 45 adult patients (average age 32.4±11.5) who tested positive for type A influenza in rapid testing were divided into 3 groups--a group of 11 maoto patients (7.5g/day), a group of 14 oseltamivir patients, a group of 9 zanamivir patients and a group of 11 patients who took maoto in combination with oseltamivir. 2 patients in the maoto and combined administration groups, 1 patient in the oseltamivir group, and 3 patients in the zanamivir group were omitted. No significant difference was observed between the groups in fever after coming to the hospital. The symptoms of joint pain, muscle pain, headache, cough, and fatigue were evaluated on a 5-point scale, with the product of the difference between the maximum and minimum values of each patient and the number of days taken to reach the minimum value from the maximum value as the

symptom score, which when compared among the groups was shown to be significantly lower in the maoto group than the oseltamivir group. 1 patient developed nausea due to the odor of the maoto, but no serious side-effects were observed [21) 22)].

Research by Nabeshima, et al.

In comparative research by Nabeshima, et al., 20 adult patients who developed a fever of 38 degrees or higher within 48h and tested positive for type A influenza in rapid testing were divided into a group of 12 patients who desired maoto (7.5g/day) and 8 patients who desired oseltamivir. No significant difference was observed between the maoto and oseltamivir groups in the fever continuation time after coming to the hospital and the symptoms continuation time. The average body temperature and headache score on the evening of the first day of treatment was significantly lower in the maoto group [23)]. In open labeled RCT subsequently conducted by Nabeshima, et al., 33 adult patients age 20-64 who developed a fever of 38 degrees or higher within 48h and tested positive in rapid testing were randomly divided into a group of 11 patients who were administered maoto (7.5g/day), a group of 10 patients who were administered oseltamivir, and a group of 12 patients who were administered zanamivir. Ischemic heart disease patients, patients with hyperthyroidism, enlargement of the prostate, and chronic infections, patients taking steroid/immunosuppressant drugs, anti-viral drugs, or Kampo medicine, and patients testing positive for new strains of influenza were excluded. 1 patient from the maoto group, and 2 patients from the oseltamivir and zanamivir groups respectively were omitted. The median value of the fever continuation time since coming to the hospital, which was the primary outcome, was 29h in the maoto group, 46h in the oseltamivir group, and 27h in the zanamivir group. A significant difference was observed between the maoto and oseltamivir groups. No significant difference was observed between the 3 groups in the influenza symptoms score. There was no significant difference in the virus isolation positive ratio or the serum cytokine concentration on the 5th day after the start of administration among the 3 groups. Mild liver dysfunction was observed in 1 patient from the maoto and oseltamivir groups respectively, but this improved quickly [24)].

Research by Yamagishi, et al.

Although retrospective, Yamagishi, et al., reported research comparing 130 pregnant women who had contracted influenza by whether they had been administered maoto or now. The assignment was by the patients' requests, with 90 patients being administered maoto and 40 patients being administered no drugs. The group administered maoto comprised 70 type A patients and 20 type B patients, while the group administered no drugs comprised 32 type A patients and 8 type b patients. The maoto was administered at 7.5g/day in 3 divided doses (administration period not stated, antitussives and expectorants administered in combination). In the maoto group, both the type A and type B patients had their fevers alleviated significantly faster than the group administered no drugs. Furthermore their symptoms such as headache, full-body fatigue and lack of appetite were observed to improve significantly faster [25)].

Research by Yaegashi, et al.

In open labeled RCT by Yaegashi, 14 patients aged 18 and older who had been diagnosed with type A influenza within 48 hours of developing fever were randomly divided into 2 groups--a group administered maoto and shosaikoto in combination (6 patients: 7.5g of maoto extract granules and 7.5g of shosaikoto granules/day in combination, taken for 3 days) and a group administered oseltamivir (8 patients: 150mg/day, taken for 5 days). The fever period from onset of illness, time from onset of illness until start of treatment, time from start of treatment until alleviation of fever, maximum body temperature, amount of antipyretics used, and amount of antitussives used were compared. The

method of assignment into the groups was not stated. No significant difference was observed between the groups [26].

Research by Yamauchi, et al.

In comparative research by Yamauchi, et al., child patients aged 15 and younger diagnosed with influenza were administered either anti-influenza drugs (oseltamivir or zanamivir) (166 patients) or maoto (80 patients) based mainly on the preference of their guardians, after which their frequency of follow-up treatment was investigated. The patients were administered 4mg/kg/day of oseltamivir in 2 divided doses, 20mg of zanamivir in 2 divided doses, and 0.2g/kg/day of maoto in 2-3 divided doses. The anti-viral medicine group and maoto group were further stratified by age (younger than 10, and between 10 and 15), history of bronchial asthma or lack thereof, rate of follow-up treatment for respiratory organ complications, and rate of use of concomitant drugs for respiratory organs (expectorants, bronchodilators, anti-allergy drugs, and antitussives). The rate of patients requiring follow-up treatment for respiratory organ complications was 34 out of 166 (20.5%) in the anti-viral drug group and 9 out of 80 (17.8%) in the maoto group, showing no significant difference. In the patients without a history of bronchial asthma, the rate of patients requiring follow-up treatment was 19 out of 107 (17.8%) in the former group and 4 out of 67 (6%) in the latter group, significantly higher in the anti-viral drug group. In the patients with a history of bronchial asthma younger than age 10, the rate of patients requiring follow-up treatment was 15 out of 57 (26.3%) in the anti-viral drug group and 4 out of 5 (80%) in the maoto group, showing a significantly high rate requiring follow-up treatment in the maoto group, although the number of cases was small. The rate of use of concomitant drugs for respiratory organs in all of the cases was 64 out of 166 (38.6%) in the anti-viral drug group and 12 out of 80 (15%) in the maoto group, significantly lower in the maoto group. In the patients without a history of bronchial asthma as well, the rate of use of concomitant drugs for respiratory organs was 34 out of 107 (31.8%) in the anti-viral drug group and 9 out of 13.4 (13.4%) in the maoto group, significantly lower in the maoto group. The rate of use of concomitant drugs for respiratory organs was lower in the maoto group. Furthermore, in spite of the fact that the rate of use of concomitant drugs for respiratory organs was significantly lower the maoto group in patients without a history of bronchial asthma, the need for follow-up treatment for respiratory organ complications was low [27].

Research by Suzuki, et al.

In an open labeled quasi RCT by Suzuki, et al., child patients age 1-10diagnosed with type A influenza were divided into a group administered maoto (0.15g/kg/day, in 3 divided doses) and a group administered oseltamivir (4mg/kg/day, in 2 divided doses) for 5 days in alternating order of examination. Furthermore, the subjects of the study were limited to those with a maximum body temperature of 38.4 ～40.1℃ before administration, and who also could be administered one of the drugs within 24 hours after the onset of fever. Child patients who could not be administered maoto were also excluded. A comparison of the body temperatures was conducted at each 6 hour interval. The oseltamivir group comprised 46 patients, while the maoto group comprised 40 patients. No significant differences in age, gender, rate of vaccination before contracting the illness, maximum body temperature before treatment, and body temperature at the time of starting administration were observed between the 2 groups. At 12-30 hours after the start of administration, the temperature in the maoto group was on average 0.15～0.26℃ lower, showing a significantly lower body temperature. Subsequently, the median value of the body temperatures of the two groups crossed at the 36th hour, after which the oseltamivir group's body temperature conversely became clearly lower. With having a fever is defined as "37.5℃ or higher", the average ± standard

deviation of the fever period was 84.8±36.8 hours in the maoto group and 67.0±24.4 hours in the oseltamivir group, showing a significant difference between the 2 groups. With "a fever of 37.5℃ or higher continuing for 24 hours or more after a normal temperature for between 12 and 72 hours " defined as diphasic fever, the ratio becomes 4.3% in the oseltamivir group and 20.0% in the maoto group, significantly higher in the former. The average value of the number of days of administration was 5.3±1.59 days in the maoto group and 4.6±0.75 days in the oseltamivir group. Depending on the progress, in the case of maoto, when the fever continued for 5 days or more, there were also cases where the administration was longer. Conversely, in oseltamivir, there were many cases where the fevers were alleviated quickly, with a short administration period not requiring 5 days of administration [28].

Case series and comparative studies investigating side effects, administration methods, etc.

Research by Iwaki, et al.

In a case series by Iwaki, et al., 41 patients (17 men, 24 women, age 40.5±13.6) age 20-72 diagnosed influenza positive (type A and type B) via rapid testing kits, who had fevers of 38.0℃ or higher before or when coming to the hospital, and who had been experiencing influenza symptoms for 48 hours or less were administered maoto, and the time from administration until alleviation of fever (fever alleviation time), virus survival time and transition of clinical symptoms were investigated. The results showed that the overall average fever alleviation time was 27.4 hours, of which it was 25.9 hours with type A and 33.7 hours with type B. Furthermore, the fever alleviation times of type A by subtype were 24.9 hours with H1N1 and 26.5 hours with H3N2. The survival rate of the viruses 5 days after administration was 22.6%, with type A H1N1 having a survival rate of 30.0%, type A H3N2 0%, and type B 20.0%. Regarding the progress of the clinical symptoms, upon calculating the average body temperatures and symptom scores from the patient reports, all symptoms showed improvement. Side effects appeared in 2 patients (4.9%), which were diarrhea and rashes respectively [29]. Iwaki also conducted a similar case series regarding the 2009 pandemic, in which 12 type A influenza patients (4 men, 8 women, average age 21.9±11.6) were administered Tsumura maoto extract granules in doses of 7.5g per day for adults and 0.2g/kg per day for children for a period of 5 days. Results of virus examination via viral isolation and RT-PCR using nasal swabs and throat swabs as specimens showed that all cases were the 2009 pandemic virus (H1N1). The average time from onset of illness until initial dosing was 15.7 hours, with temperatures at the time of arrival at hospital of 38.2℃ and a post-administration fever alleviation time of 18.5 hours. Regarding the symptoms, upon calculating the average symptom scores (0-3) from the patients' journals, comparing the pre- and post-administration symptoms showed significant improvement in "sore throat", "muscle and joint pain", fatigue and tiredness" and "headache". An examination of the virus survival rate conducted on average on the 5th day after the start of administration showed 6 patients positive, for a survival rate of 50.0%. Harmful events observed were 1 case each of abnormal behavior and diarrhea, with the abnormal behavior starting on the first day of administration and ending the following day and being deemed "unrelated" to the maoto [30].

Research by Ihashi, et al.

Although it is not comparative research, the case series by Ihashi et al. contains reports of results of seriously ill child patients with new strains of influenza and pneumonia requiring hospitalization who were administered maoto in combination with neurominidase inhibiters. The subjects were 70 child patients (average age: 7.3±3.7; gender: 46 male and 24 female; bronchial asthma: 25 with and 45 without; administration of anti-influenza drugs as outpatients: 21 yes and 49 no) who were hospitalized with new strains of influenza and pneumonia from

June 2009 to January 2010 with no serious underlying illnesses. The anti-influenza drugs selected for treatment after hospitalization were oseltamivir for 64 patients and zanamivir for 6 patients. Regarding the administration of maoto, the administration dose was 0.2g/kg in 3 divided doses, the administration method was every 2-3 hours on the first day and 3 divided doses from the 2nd day onwards (before or after morning, noon, and evening meals), and the administration period was 5.0 days on average (95%CI : 4.7～5.2 days). The main subject of the paper was to suggest the importance of administering neuraminidase inhibiters before hospitalization via multiple regression analysis, but even regarding treatments where maoto was administered to seriously ill patients, no side effects were observed [31].

Research by Mori

Mori's open labeled quasi RCT, which examined unique administration methods of maoto, divided cases of maoto administration from November 2007 through March 2008 into 2 groups and examined the administration methods. Group Ⅰ (group administered maoto every 3 hours): Patients with evidence of maoto up to January 31were dosed with maoto every 3 hours when the maoto administration was started (no administration during sleep). Group Ⅱ (group administered maoto every 2 hours): Patients with evidence of maoto After February 1 were dosed with maoto every 2 hours when the maoto administration was started, taking 1 day worth (3 packets) every 3 hours, and subsequently continued to take it every 3 hours until the onset of sweating (no administration during sleep). After they started sweating, the dosing was halted (Hiromichi Yasui's method). Among those treated with Kampo, group Ⅰ was 17 patients (average age 6.7) and group II was 11 patients (average age 6.7). Furthermore, 13 patients treated with oseltamivir who did not use antipyretics served as the control group. Examining group II and the group treated with oseltamivir shows that it took significantly less time for group II's fevers to drop to 36.9℃ after administration. There are no statements regarding comparisons between group Ⅰ and the control group, or between group Ⅰ and group II. No serious side-effects due to Kampo treatment were observed[32].

Research by Mori, et al.

In a case series by Mori, et al., where early-stage administration of Kampo medicine was conducted before seeing a doctor, treatment via early-stage administration of Kampo medicine was conducted on 10 patients (5 men, 5 women, average age 13.2±12.1) who exhibited flu-like symptoms between October to December 2009 and for whom treatment with the Kampo internal medicine on hand was insufficient, after which they went to hospitals and were diagnosed with type A influenza, and the results thereof were examined. Upon arrival at the hospital the evidence was reconfirmed, and in cases where it fit it was continued, while in cases where it differed the method was changed. During fevers, a dose of 1.5-2 times the normal does was administered frequently (every 2-3 hours), with the treatment being ended at the point when the fever, general condition, and respiratory tract symptoms improved. The results showed that the time from coming to the hospital until alleviation of fever was 17.0±17.0 hours, the number of days from coming to the hospital until recovery was 1.8±0.6 days, and the number of days from early-stage administration until recovery was 2.5±0.7 days. The early-stage Kampo administered before going to the hospital was keishi-to maoto for 4 patients, keishito for 3 patients, maoto for 2 patients, and saiko keishito shoken-chu-to for 1 patient, with 1-5 administrations, with 5 patients' Kampo fitting the evidence and 4 of the remaining 5 leaving early-stage administration prescriptions and combining with other compounds. Furthermore, in a comparison of the Kampo medicine/anti-viral medicine combined administration group and the Kampo-only group, no significant difference was

observed in the number of days from start of administration before going to the hospital until recovery, but the Kampo-only group had a significantly shorter fever alleviation time and number of days from going to the hospital until recovery [33].

Research by Nishimura, et al.

In a case series by Nishimura, et al., wherein there is a unique report of using a maoto suppository, a comparison is conducted on the body temperatures before administration and until 24 hours after administration of a maoto suppository in pediatrics department between June 2006 and April 2007 on 21 patients (from 10 days old to 9 years and 9 months old) with fevers of 38.9℃ or greater. There were 17 patients whose body temperature were possible to track. The temperature of these patients decreased significantly. No side-effects were observed [34].

Research by Tabata, et al.

In open labeled comparative research by Tabata, et al., in addition to the clinical results of maoto and zanamivir, the influence of interfused flavoring agent guidance by pharmacists as an idea to increase patient compliance in taking medicine was compared over 2 seasons. (1) In the 2006-2007 season, maoto was administered to 63 child influenza patients (37 type A, 26 type B). (2) In the 2007-2008 season, maoto was prescribed for all cases of children 5 years or younger, while for children of 5 years or older either maoto or zanamivir were administered after informed consent and the parents choosing one of them, with 49 patients (all type A patients) being administered maoto and 32 patients (31 type A patients and 1 type B patient) being administered zanamivir. The time until alleviation of fever was scored, and the compliance with taking the medicine was also examined split into a good group and poor group. maoto was taken 0.18g/㎏/day in 3 divided doses for 3 days, and zanamivir was inhaled 2 blisters (10mg) per time, twice per day for 5 days. In the good medication compliance group of type A influenza in (1) in the group from age 0 to 2, the good group was about 32 hours while the poor group was about 48 hours, showing a significant difference. In the type B influenza, the fever alleviation time of the good compliance group was about 28 hours while the poor compliance group was about 56 hours, showing a significant difference. In (2), the fever alleviation time of the maoto administration group was about 26 hours, which was significantly shorter than in (1) where it was about 40 hours. In the zanamivir administration group it was about 32 hours. However, in (2), a pharmacist proactively conducted interfused flavoring agent guidance for the maoto. The results were that milk coffee, cocoa, orange juice, Calpis and other flavors resulted in good medication compliance, with (2) being the good medication compliance group significantly increasing from (1)'s 69.9% to 93.9%, while in the age 0 to 5 group the good medication compliance group significantly increased from (1)'s 59.4% to 100% [35].

This concludes the discussion of the state of maoto's use in Japan as a treatment for influenza and the current state of its research. It is currently commonly used in combination with anti-viral medications, but in some circumstances it is also used alone. It is used especially often in the field of pediatrics.

The fact that the text cited in the first paragraph which was written in "Shang-han lun" is connected to the treatment by a 13 year old boy almost 200 years ago is a testament to the very high level of research that "Shang-han lun" was in Japan. The Kampo medicine of Japan even today continues to carry on this tradition.

Note: One way of looking at maoto is that veterinary surgeons are focusing on the prescription. They discovered maoto's effect on avian influenza during their research. Currently they are aggressively proceeding with the study [36]. A vast amount of research reports in future.

Reference Literature

1) Yodo Odai: 『Hogi zasshi』(Essay of Medical Technique) 1871. (in Japanese)
2) Kazuhiro Oribe: *Maoto* Demonstrated as Highly Effective for the Treatment of Influenza, *The Journal of KAIM,* vol.1 No.1, 18-19, 2006.
3) Yasufumi Sawada: Change of pH – Diet (antacid) and maoto, *The Journal of Practical Pharmacy Additional Volume*, 55: 115, 2004. (in Japanese)
4) Yukitoshi Izumi et al.: Neuroexcitatory actions of Tamiflu and its carboxylate metabolite Neuroscience Letters, 426 (2007) 54-58
5) Arita R, et al. National cost estimation of maoto, a Kampo medicine, compared with oseltamivir for the treatment of influenza in Japan, *Kampo and Traditional Medicine,* vol. 3, no. 1 pp. 59-62, 2016.
6) Haruro Kuroki, Hiroshi Kimoto: Experiences with East-West integrated medicine for pediatric influenza and rubeola, *Journal of the CHIBA MEDICAL ASSOCIATION*, vol. 55, no.10, pp 1209-1212, 2003 (in Japanese)
7) Hiroshi Kimoto, Haruro Kuroki: Effects of oseltamivir phosphate combination therapy with *maoto* for influenza, comparison of effects in adults when combined with western drugs, Science of *Kampo Medicine*, vol. 29, no. 4, pp. 166-169, 2005 (in Japanese)
8) Osamu Fukutomi, Toshiyuki Fukao, Eiji Matsukuma. et al.: Experiences where the use of *maoto* effectively alleviated influenza symptoms, *Science of Kampo Medicine*, vol. 29, no. 5, pp. 228-230, 2005. (in Japanese)
9) Kubo T, Nishimura H: Antipyretic effect of Mao-to, a Japanese herbal medicine, for treatment of type A influenza infection in children, *Phytomedicine,* vol. 14, no. 2-3, pp. 96-101, 2007.
10) Takeshi Taketani, Jyoji Hayashi, Takeshi Kasai, et al.: Investigation of the effectiveness of *maoto* for pediatric influenza, *Child Health,* vol. 11, no. 2, pp. 114-118, 2008. (in Japanese)
11) Katsusuke Yamamoto, Takehisa Yamamoto, Yoshimi Mizoguchi, et al.: Effects of *maoto* administration for new influenza types in pediatric outpatients, *Kampo and Immunology / Allergy,* vol. 24, pp. 55-59, 2011. (in Japanese)
12) Yuichiro Tsuji, Kohji Morita, Izumi Ichihashi, Kazuo Itabashi: Effects of *maoto* in combination therapy for pediatric influenza, *Science of Kampo Medicine*, vol. 35, no. 2, pp. 158-160, 2011. (in Japanese)
13) Kenichi Kawamura: Investigation of the effectiveness of *maoto* for influenza patients, *Journal of the Japan Physicians Association,* vol. 22, no. 4, pp. 435-438, 2007. (in Japanese)
14) Kenichi Kawamura: Investigation of the effectiveness of *maoto* for influenza patients, *Japanese Journal of Pediatrics,* vol. 61, no. 5, pp. 1057-1062, (in Japanese)
15) Kenichi Kawamura: Investigation of the time until elimination of type A influenza virus from the throat, *Journal of the Japan Physicians Association,* vol. 23, no. 4, pp. 418-422, 2008. (in Japanese)
16) Kenichi Kawamura, Yoshinobu Miwa: Investigation of the effectiveness of oseltamivir and *maoto* in patients with type A influenza (Soviet type A, Hongkong type A), *Journal of the Japan Medical Association,* vol. 138, no. 7, pp. 1391-1396, 2009. (in Japanese)
17) Osamu Fukutomi, Hideo Kaneko, Hidenori Onishi, et al.: Investigations of the effects of *maoto* for pediatric influenza and the choice of therapy, *Kampo and Immunology / Allergy,* vol. 22, pp. 23-33, 2008. (in Japanese)
18) Osamu Fukutomi, Takahide Teramoto, Michio Koseki, et al.: Investigations of the usefulness of *maoto* for the treatment of pediatric influenza, *Journal of Japan Pediatric Oriental Medicine Society,* vol. 24, pp. 11-15, 2010. (in Japanese)
19) Yoshio Mori: Experiences with Kampo treatment for a new type of influenza, *Journal of Kampo Medicine,* vol. 57, no. 10, pp. 1655-1662, 2010. (in Japanese)
20) Yoshitaka Toriumi, Kohji Murata, Tsutomu Kamei: Investigation of the effects of *maoto* for the treatment of pediatric type B influenza, *Research Report for 2009*. The Japanese Society for Complementary and Alternative Medicine (in Japanese)
21) Mizue Saita, Toshio Naito, Soushin Boku, et al.: The efficacy of ma-huang-tang (maoto) against influenza, *Health,* vol. 3, no. 5, pp. 300-303, 2011
22) Mizue Saito, Toshio Naito, Soshin Boku, et al.: Investigation of the effectiveness of *maoto* for

influenza, *Kampo and Immunology / Allergy,* vol. 23, pp. 17-26, 2010. (in Japanese)

23) Nabeshima S, Kashiwagi K, Ajisaka K, et al.: A comparison of oseltamivir with maoto, a traditional herbal medicine, for the treatment of adult seasonal influenza A, *Journal of Traditional Medicines,* vol. 27, no. 4, pp. 148-156, 2010.

24) Nabeshima S, Kashiwagi K, Ajisaka K, et al.: A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza, *J Infect Chemother,* vol. 18, no. 4, pp. 534-543, 2012

25) Yuka Yamagishi, Koji Izumi, Hiroshige Mikamo: Effects of *maoto* in women suffering from influenza during pregnancy, *Recent Progress of KAMPO MEDICINE in Obstetrics and Gynecology,* vol. 04, no. 27, pp. 89-92, 2010. (in Japanese)

26) Hironobu Yaegashi: Efficacy of Coadministration of *maoto* and Shosaikoto, a Japanese Traditional Herbal Medicine (Kampo Medicine), for the Treatment of Influenza A Infection, In Comparison to Oseltamivir, *Japanese Journal of Complementary and Alternative Medicine* vol. 7, no. 1, pp. 59-62, 2010. (in Japanese)

27) Toshihiko Yamauchi, Akio Kanno, Keiichi Ichimura; Effectiveness of *maoto* in the treatment of pediatric influenza, *Kampo Medicine,* vol. 62, no. 4, pp. 556-558, 2011. (in Japanese)

28) Eitaro Suzuki, Kiyoshi Ichihara: Comparison of the effects of oseltamivir and *maoto* in the treatment of type A pediatric influenza as seen in changes of the fever pattern, *The Journal of Ambulatory and General Pediatrics of Japan,* vol. 14, no. 3, pp. 248-253, 2011. (in Japanese)

29) Norio Iwaki, Naoki Kawai, Osamu Tanaka, et al.: The Japanese Journal of Clinical and Experimental Medicine, The Japanese Journal of Clinical and Experimental Medicine, *The Japanese Journal of Clinical and Experimental Medicine*, vol. 86, no. 12, pp. 1713-1718, 2009. (in Japanese)

30) Norio Iwaki, Yutaka Wakasa, Osamu Tanaka, et al.: Investigation of the therapeutic effectiveness and safety of *maoto* during the pandemic (H1N1) in 2009, *The Japanese Journal of Clinical and Experimental Medicine*, vol. 87, no. 12, pp. 1789-1793, 2010. (in Japanese)

31) Mai Ito, Takehisa Yamamoto, Katsusuke Yamamoto, et al.: The influence of a combination therapy with oseltamivir and *maoto* during hospitalization because of influenza pneumonia on the clinical course in children after discharge, *Kampo and Immunology / Allergy,* vol. 24, pp. 60-68, 2011. (in Japanese)

32) Yoshio Mori: Experiences with Kampo therapy over the period from 2003 until 2008, *Kampo & Newest therapy,* vol. 18, no. 4, pp. 313-320, 2009. (in Japanese)

33) Katsumi Mori, Mizuaki Miyazaki: Early initiation of Kampo monotherapy for a new influenza type, *Journal of Kampo Medicine,* vol. 57, no. 8, pp. 1295-1307, 2010. (in Japanese)

34) Nishimura N, Doi N, Uemura T, et al. [Pharmaceutical analysis and clinical efficacy of Kampo medicine, maoto, extract suppository against pediatric febrile symptoms], *Yakugaku Zasshi Journal of the Pharmaceutical Society of Japan,* vol. 129, no. 6, pp. 759-766, 2009.

35) Yuichi Tabata, Yuji Arasiki: Investigation of the clinical effects of oseltamivir and *maoto* on pediatric influenza infection; investigation of the two seasons 2006/2007 and 2007/2008, *Japanese Journal of Pediatrics,* vol. 62, no. 10, pp. 2219-2225, 2009 (in Japanese)

36) Miyazaki T.: Pathogenesis of Influenza and Effects of Herbal Medicines on the Inhibition of Influenza Virus Replication, *Kampo Medicine*, 63(6), 363-368, 2012.