Commentary

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Complementary and alternative medicine is expected to make greater contribution in controlling the prevalence of influenza

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Summary **Influenza pandemics are a serious threat to public health in today's world. In the past 10 years, the outbreak of three forms of severe influenza – H5N1, H1N1, and H7N9 – has caused tremendous loss of life and property. In order to better cope with pandemics, antivirals such as oseltamivir are being stockpiled in great quantities, placing a substantial burden on government budgets and potentially resulting in massive waste because of the uncertainty as to when an influenza pandemic will strike and whether emerging virus strains will be resistant to the stockpiled drugs. Complementary and alternative medicine (CAM) is generally available, affordable, and commonly used in China and many other countries and CAM has a long track record of fighting influenza. The Chinese Government appropriated funds to intensively investigate herbal medicines in accordance with the principles of evidence-based medicine in order to identify effective, inexpensive, and easily stockpiled medicines. Thus far, several drugs including Shufeng Jiedu capsules, Lianhua Qingwen capsules, Maxing Shigan decoction, Yinqiao powder, and Jinhua Qinggan granules have demonstrated effectiveness in fighting influenza. In the future, CAM is expected to make greater contribution in controlling the prevalence of influenza pandemics.**

Keywords: Complementary and alternative medicine (CAM), influenza, H5N1, H1N1, H7N9

Influenza virus infection is a serious public health problem because of its significant mortality in humans. As an example, pandemic human influenza A (H1N1) caused 18,449 laboratory-confirmed deaths worldwide in one and a half years from early April 2009, when the first case of infection appeared, to August 2010, when the end of the pandemic was announced (*1,2*). Due to the great adaptability and ready variation of the influenza virus, frequent outbreaks of highly pathogenic avian influenza H5N1 and H7N9 during the past 10 years sounded the alarm regarding the pressing need to control human influenza pandemics in the near future.

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Currently, neuraminidase inhibitors including zanamivir, oseltamivir, laninamivir, and peramivir are widely used clinically to treat influenza. In order to efficiently deal with possible influenza pandemics, the World Health Organization (WHO) implemented regulations on antiviral stockpiles (*1*). As a result of this policy, the drug oseltamivir was promptly delivered to affected countries and regions, where it played an important role in controlling the prevalence of H1N1. However, large antiviral stockpiles require substantial expenditures because of the expense of antiviral drugs, potentially imposing a massive economic burden on less developed countries. In addition, when an influenza outbreak occurs is uncertain, so stockpiled drugs may lose their effectiveness, thus causing massive waste. Most importantly, evidence shows that clinical isolates of viruses are rapidly becoming more resistant to

neuraminidase inhibitors currently in use (*3,4*). These factors necessitate the development of effective, easily accessible, and inexpensive anti-influenza regimens.

Complementary and alternative medicine (CAM) is characterized by unique concepts that differ from those of Western medicine. Around the world, traditional medicines are generally available, affordable, and commonly used in large parts of Asia, Africa, and Latin America (*5*). Traditional Chinese medicine (TCM) is a typical CAM that has been widely used in China for thousands of years and TCM has a long record of treating influenza (*6*). After the H1N1 outbreak in China in 2009, the Beijing Municipal Government allocated a special fund of 10 million RMB to launch one preclinical study and one clinical trial, *i.e.* a "Study to Screen and Evaluate Effective Traditional Chinese Medicines to Prevent and Treat H1N1 Influenza" and a "Prospective Multicenter Randomized Controlled Trial of TCM to Prevent and Treat H1N1 Influenza" (*7*). Based on the characteristics and advantages of TCM and the principles of evidence-based medicine, the study and trial seek to discover safe, effective, inexpensive, and easily stockpiled traditional Chinese medicines and develop corresponding therapeutic regimens (*7*). Researchers screened approximately 40 traditional Chinese medicines that were previously used to treat the common cold, flu, severe acute respiratory syndrome (SARS), and avian influenza to identify potential drugs to fight H1N1 virus infection. Thus far, several drugs including Shufeng Jiedu capsules (SFJDC), Lianhua Qingwen capsules (LHQWC), Maxing Shigan decoction (MXSGD), Yinqiao powder (YQP), and Jinhua Qinggan granules (JHQGG) have been found to possess potent action against influenza (Table 1).

SFJDC is usually used to treat patients with an acute upper respiratory infection and symptoms of fever, sore throat, headaches, runny nose, and coughing. SFJDC's efficacy against the H1N1 virus has been investigated in both normal and immunocompromised mice (*8*). Models of pneumonia were created by giving those mice nasal drops containing H1N1 virus strain FM1 or PR8. In normal mice with pneumonia, treatment with SFJDC for 4 days markedly reduced the viral load and increased the level of interferon γ in the lung tissue. In immunocompromised mice with pneumonia, treatment with SFJDC significantly decreased the mortality of mice infected with the FM1 strain and increased the survival time for mice infected with the PR8 strain. In addition, the viral load and lung index both dramatically decreased in mice treated with SFJDC. These findings suggest that SFJDC may have the potential to clinically treat H1N1 virus infection. In a subsequent clinical study of 130 patients with an acute viral upper respiratory tract infection (43 patients with H1N1 infection) at Jiangsu Provincial Hospital of TCM (Nanjing, Jiangsu Province), Nanjing Hospital of TCM (Nanjing, Jiangsu Province), Hebei Provincial Hospital of TCM (Shijiazhuang, Hebei Province), The Second Hospital of Nanjing (Nanjing, Jiangsu Province), and the People's Hospital of Maizhokunggar County (Lhasa, Tibet Autonomous Region), administration of SFJDC caused fever to abate within 4 h in 39 patients (30.0%) and within 72 h in 118 patients (90.8%) (*9*). This medicine caused fever to abate in an average time of 20.5 h. A point of note is that body temperature started to drop in 30% of patients 4 h after the medicine was administered, suggesting that SFJDC usually has rapid and effective antipyretic action (*9*). Currently,

Table 1. Traditional Chinese medicines to treat influenza

Drug	Indication	Formulation
Shufeng Jiedu capsule	Acute upper respiratory infection (wind-heat cold)	Rhizoma Et Radix Polygoni Cuspidati; Fructus Forsythiae; Radix Isatidis; Radix Bupleuri; Herba Berbenae; Rhizoma Phragmitis; Radix Et Rhizoma Glycyrrhizae
Lianhua Qingwen capsule	Influenza with symptoms including fever, aversion to cold, muscular soreness, nasal congestion, runny nose, cough, headache, *etc*.	Fructus Forsythiae; Flos Lonicerae Japonicae; Herba Ephedrae; Semen Armeniacae Amarum; Gypsum Fibrosum; Radix Isatidis; Rhizoma Dryopteridis Crassirhizomatis; Herba Houttuyniae; Herba Pogostemonis; Radix Et Rhizoma Rhei; Radix Et Rhizoma Rhodiolae Crenulatae; Mentholum; Radix Et Rhizoma Glycyrrhizae
Maxing Shigan decotion	Pneumonia, chronic bronchitis, bronchial asthma	Herba Ephedrae; Semen Armeniacae Amarum; Gypsum Fibrosum; Radix Et Rhizoma Glycyrrhizae
Yinqiao powder	Anemopyretic cold with symptoms including fever, headache, cough, sore throat, scanty dark urine	Flos Lonicerae Japonicae; Fructus Forsythiae; Radix Platycodonis; Radix Et Rhizoma Glycyrrhizae; Spica Schizonepetae; Semen Sojae Praeparatum; Fructus Arctii; Rhizoma Phragmitis
Jinhua Qinggan granule	Influenza with symptoms including pharyngalgia, nasal congestion, runny nose, cough, *etc*.	Flos Lonicerae Japonicae; Gypsum Fibrosum; Herba Ephedrae; Semen Armeniacae Amarum; Radix Scutellariae; Fructus Forsythiae; Bulbus Fritillariae Thunbergii; Rhizoma Anemarrhenae; Fructus Arctii; Herba Artemisiae Annuae; Mentholum; Radix Et Rhizoma Glycyrrhizae

Information is from corresponding drug labels.

the Guidelines for Diagnosis and Treatment of H1N1 Infection issued by the Chinese Ministry of Health (MOH) recommend SFJDC as a treatment for H1N1 virus infection.

LHQWC is used to treat influenza in individuals with symptoms of a fever, muscle soreness, nasal congestion, runny nose, coughing, headaches, *etc*. The effects of this medicine in treating H1N1 infection were reported at the International Scientific Symposium on Influenza A (H1N1) Pandemic Response and Preparedness held by the Chinese MOH, the WHO, and the journal Lancet on August 21, 2009 (*10,11*). Studies by the Academy of Military Medical Sciences and Beijing Ditan Hospital found that LHQWC markedly suppresses the H1N1 virus (*11*). The results of those studies indicated that LHQWC is comparable to oseltamivir in clearing the H1N1 virus from the blood of patients. However, fever abated significantly sooner in patients treated with LHQWC compared to those treated with oseltamivir. Moreover, treatment with LHQWC cost just one-eighth of treatment with oseltamivir. These advantages of LHQWC indicate that this medicine may have great promise in controlling the prevalence of influenza pandemics.

MXSGD and YQP are traditionally used to treat febrile infectious diseases in China. Studies directed by Beijing Chao-Yang Hospital investigated the efficacy of these two traditional Chinese medicines in the treatment of H1N1 influenza infection (*12*). The study of 410 adult patients with mild symptoms sought to examine the fever-reducing action of MXSGD and YQP. Results indicated that the control group had a fever for 26 h, patients treated with oseltamivir had a fever for 20 h, patients treated with TCM had a fever for 16 h, and patients treated with oseltamivir plus TCM had a fever for 15 h. Thus, MXSGD and YQP were able to effectively shorter the duration of fever in patients with H1N1 influenza infection. These two medicines had efficacy that was comparable or slightly superior to that of oseltamivir. In order to develop more effective drugs to fight H1N1 virus infection, experts in TCM developed JHQGG based on the formulations for MXSGD and YQP (*13*). In one preclinical study, JHQGG was found to possess potent action at decreasing mortality, increasing surviving time, and reducing the severity of pulmonary lesions in mice infected with the H1N1 virus (*13*). In another study, JHQGG was able to reduce fever in a rabbit model of fever (*13*). A clinical study showed that JHQGG markedly reduced the duration of fever and alleviated symptoms in patients with H1N1 influenza infection (*13*). Thus far, JHQGG has been approved and used to treat influenza in hospitals. The cost for a course of treatment (5-7 days) is approximately 80-110 RMB, which is one-fourth of the cost of oseltamivir, thus significantly reducing the economic burden for patients (*13*).

The results cited thus far indicate that TCM could be an option in situations where neuraminidase inhibitors such as oseltamivir are in insufficient quantity or strains of influenza are resistant to those drugs. Of 845 patients infected with H1N1 influenza who admitted to hospitals in Beijing by September 1, 2009, 326 were cured by TCM alone (*14*). Given the potential efficacy of TCM, the Beijing Government allocated 70 million RMB to stockpile 2 million doses of TCM to prevent a possible influenza pandemic (*14*). This revision of the policy on drug stockpiling means that more types of drugs are available and a greater number of people benefit.

The outbreak of H7N9 avian influenza in China in 2013 caused public alarm about a new influenza pandemic. By August 31, 2013, a total of 134 confirmed cases had been reported in mainland China; 45 of the patients died while 86 recovered (*15*). Laboratory testing showed that the virus is sensitive to the neuraminidase inhibitors oseltamivir and zanamivir. In addition, the MOH's Guidelines for Diagnosis and Treatment of H7N9 Infection recommend SFJDC and LHQWC to cope with symptoms like a high fever, coughing, and chest tightness induced by H7N9 infection. Although no evidence to date has indicated that the virus has increased transmissibility or is spreading from person to person, cross-over of genes between the avian and human influenza viruses may result in a more dangerous form of the flu in the future.

Clearly, potent antivirals should be developed, but the potential of CAM to deal with the challenge of influenza pandemics should also be closely investigated. Compared to antivirals, these medicines offer various advantages such as their low cost, accessibility, and the ease with which they can be stockpiled. In instances where influenza has developed resistance to drugs or those drugs cause serious adverse reactions, CAM could help to treat patients. In this sense, CAM is expected to make greater contribution in controlling the prevalence of influenza in the future.

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