

## Researchers of chronic obstructive pulmonary disease gathered at the 2017 Japan-China Joint Medical Workshop on Aging and Health

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### Summary

As the number of elderly and the size of the total population increase, population aging will become a major problem because of an increase in diseases associated with aging, such as chronic obstructive pulmonary disease (COPD). The 2017 Japan-China Joint Medical Workshop on Aging and Health was held at The University of Tokyo on December 2, 2017 with a focus on management of COPD. More than 50 experts in the fields of respiratory medicine, emergency medicine, traditional Chinese medicine, and Kampo (traditional Japanese medicine) from Japan and China presented the results of their research and shared their experiences treating COPD from different perspectives. Guidelines for diagnosis and management of COPD in different countries were described at the workshop, and advances in recent research into the treatment of COPD with Kampo and traditional Chinese medicine were fully discussed. The results of the workshop should help to improve GOLD guidelines and they should greatly help to optimize COPD treatment.

**Keywords:** Chronic obstructive pulmonary disease, traditional Chinese medicine, Kampo, ShuFengJieDu Capsules

The 2017 Japan-China Joint Medical Workshop on Aging and Health was held at The University of Tokyo on December 2, 2017. The workshop started with introductory remarks by the workshop chairs, Drs. Kazuhisa Sekimizu (Teikyo University, Japan) and Wei Zhang (Shandong University of Traditional Chinese Medicine, China). Next were a series of speeches by 11 experts from Japan and China. Closing remarks were given by Dr. Wei Tang (The University of Tokyo, Japan). The theme of this workshop was the management of chronic obstructive pulmonary disease (COPD). More than 50 experts in the fields of respiratory medicine, emergency medicine, traditional Chinese medicine, and Kampo (traditional Japanese medicine) from Japan and China discussed related topics in depth and they shared their experiences

treating COPD.

COPD is a progressive disease that causes chronic bronchitis and emphysema in older people. As of 2016, 251 million people worldwide had COPD, and COPD is currently the fourth leading cause of death. The World Health Organization (WHO) has predicted that the COPD will become the third leading cause of death by 2030 (1-4). In order to facilitate COPD management, more than 50 experts from China and Japan discussed the treatment of COPD from different perspectives at the workshop. The guidelines for diagnosis and management of COPD in different countries were described. In addition, advances in recent research into treatment of COPD with Kampo and traditional Chinese medicine were discussed in depth.

Dr. Yasuhiro Yamauchi from Respiratory Medicine, The University of Tokyo Hospital described clinical guidelines for COPD diagnosis and care in Japan. According to annual reports from the Ministry of Health, Labor, and Welfare, the mortality of patients with COPD in Japan has decreases since 2010. Over 16,000 patients died from COPD in 2011. Deaths

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decreased to 15,000 (5,6) prior to 2016. According to Dr. Yamauchi, "This is due to the increased use and improvement of COPD guidelines in Japan; the dissemination of clinical guidelines on COPD has greatly helped to decrease the mortality of COPD".

Dr. Wei Zhang of the Shandong University of Traditional Chinese Medicine Hospital described treatment of COPD with traditional Chinese medicine in China. COPD can be graded based on the extent of air flow limitation and the severity of the symptoms. Patients are divided in four groups: A, B, C, and D (7). Group A have low-risk COPD and few symptoms. Group B has low-risk COPD but more symptoms. Groups C has high-risk COPD but few symptoms. Group D has high-risk COPD and more symptoms. As Dr. Zhang explained, "In traditional Chinese medicine, the ABCD assessment can be described as a righteous qi or an evil qi". Group A, for example, has an abundance of righteous qi but a slight amount of evil qi, so broad-spectrum antivirals such as ShuFengJieDu Capsule (SFJDC) are recommended. A clinical study on COPD has indicated that a combination of SFJDC and conventional therapy can improve lung function and reduce the duration of hospitalization (8).

Dr. Masayuki Hojo of the NTT Medical Center, Tokyo described the prevalence and features of eosinophilic COPD in Japan. According to guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), an inhaled corticosteroid (ICS) is recommended for severe to very severe COPD when frequent exacerbations are not adequately controlled by optimized long-acting bronchodilation (9). According to Dr. Hojo, fewer patients in Japan receive a regimen including an ICS than in Western countries. Post hoc analysis of the FLAME trial indicated that an ICS is just one of many options and that an ICS is not always the most appropriate treatment for a patient who had more than two exacerbations a year (10).

Dr. Xiaolan Cui of the Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences described the substances in and the efficacy of SFJDC. SFJDC contain rhizoma *Polygoni cuspidati*, fructus *Forsythiae*, radix *Bupleuri*, herba *Patriniae*, herba *Verbenae*, rhizoma *Phragmitis*, and radix *Glycyrrhizae*. An *in vitro* study by Dr. Cui and his colleagues indicated that SFJDC have broad-spectrum antiviral activity against viruses such as respiratory syncytial viruses, the Sendai virus, the Coxsackie virus, the H1N1 influenza virus, and the H3N2 influenza virus as well as antibacterial activity against bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus albus*, *Escherichia coli*, *Pseudomonas aeruginosa*, beta hemolytic *Streptococcus*, *Candida albicans*, *Proteus spp.*, and *Neisseria gonorrhoeae* (11). The study by Dr. Cui and his colleagues indicated that SFJDC can reduce the incidence of respiratory infections leading to lung damage.

Dr. Jing Yu of the Faculty of Pharmacy, Yokohama University explained how Kampo medicine is used to treat COPD. He also described the general concept of Kampo, its history, and Kampo medicines used in Japan. As Dr. Yu explained, Kampo originated from traditional Chinese medicine and developed in Japan after the 7th century (12,13). Japanese practitioners of Kampo developed their own unique formulations and treatments. In Japan, Kampo is strictly managed and assessed. Crude drugs must be identified and assessed to produce Kampo medicines. Crude drugs must undergo many processes such as morphological evaluation, chemical evaluation, molecular biological evaluation, serum pharmacological evaluation, biological evaluation, and 3D-HPLC (14). Hochuekkito is prescribed to treat COPD in Japan. Hochuekkito contains radix *Astragali*, rhizoma *Atractylodis lanceae*, radix *Panacis ginseng*, radix *Angelicae*, radix *Bupleuri*, fructus *Zizyphi*, pericarpium *Aurantii nobilis*, radix *Glycyrrhizae*, rhizoma *Cimicifugae*, and rhizoma *Zingiberis*. Studies on Hochuekkito have indicated that it has anti-inflammatory and anti-viral action and that it aids the digestive system and immune system, alleviating a patient's symptoms (15,16).

Dr. Wei Zhang of the Shuguang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine described the clinical use of traditional Chinese medical in pulmonary rehabilitation for patients with COPD. In China, traditional Chinese medicine is used to prevent and relieve pulmonary symptoms of patients with COPD. In a study by Dr. Zhang and his colleagues, the respiratory function of patients with COPD improved after 4 months of traditional Chinese breathing training (17).

Dr. Zhijun Jie of Respiratory Medicine, the Fifth People's Hospital of Shanghai described the mechanism, treatment of viral infection, and management of acute deterioration of COPD (AECOPD) in China. AECOPD is a phenomenon whereby patients with COPD have an aggressive airway obstruction, difficulty breathing, and increased sputum in a short amount of time. Patients with AECOPD have a higher rate of infection with respiratory viruses and atypical clinical manifestations; this is especially true for patients over the age of 65 (18,19). Studies by Dr. Jie and his colleagues have examined the pharmacological action of Chinese medicine against influenza. SFJDC markedly reduced the inflammation caused by influenza viruses through the ERK-NK-kB pathway (20,21). Although research on antiviral therapy for AECOPD is still underway, traditional Chinese medicine may benefit patients with AECOPD.

Dr. Tiejun Zhang of the Tianjin Institute of Pharmaceutical Research, State Key Laboratory of Drug Delivery Technology and Pharmacokinetics, Tianjin Engineering Laboratory of Quality Control Technology of Traditional Chinese Medicine described mechanisms of action of SFJDC as a treatment for pulmonary

inflammation. In a study on SFJDC by Dr. Zhang and his colleagues, HPLX-Q/TOF-MS identified 94 chemical components of SFJDC. Forty-six compounds were identified as potential bioactive constituents (8 flavonoids, 4 anthraquinones, 4 stilbenes, 2 iridoids, 2 lignans, 2 naphthalenes, 1 phenylglycoside, 1 triterpenoid saponin, 3 other compounds, and 19 metabolites). Moreover, 28 compounds in SFJDC acted on 22 pathways through 41 related targets and 10 active components acted on 3-phosphoinositide dependent protein kinase-1 (PDK1), mitogen-activated protein kinase 10 (MAPK10), and inflammatory response pathways including mitogen-activated protein kinase (MAPK), extracellular regulated protein kinases (ERK), and arachidonic acid metabolism. *In vivo* studies using a rat and mouse model of pneumonia, a rat model of pharyngitis, a mouse model of peritonitis, and a rat model of fever have indicated that SFJDC have anti-inflammatory and antipyretic action.

Dr. Jufeng Xia of the Graduate School of Medicine, The University of Tokyo described how the anti-tumor, anti-inflammatory, and anti-viral action of SFJDC can be used. In a study by Dr. Xia and his colleagues, SFJDC markedly inhibited the proliferation of HepG2.2.15 cells, which are derived from a hepatoma cell line and transfected with the HBV genome, and they inhibited the Akt/mTOR, and Ikba/NF- $\kappa$ B pathways. These results indicate that SFJDC may serve as a potential component of anti-tumor therapy. In addition, Drs. Atmika Paudel and Suresh Panthee of the Graduate School of Pharmaceutical Sciences, The University of Tokyo described the pharmacokinetic analysis of therapeutically effective antimicrobials using a silkworm model of infection and use of *in vivo* transcriptomic analysis to identify virulence factors in *Staphylococcus* (22). Studies have indicated that this new antimicrobial has promise as a novel approach for COPD management.

As has been indicated by the topics mentioned here, more than 50 experts from China and Japan discussed the management of COPD in depth at the Japan-China Joint Medical Workshop. Information shared at the workshop will help to further refine the clinical guidelines on COPD in both countries and it should help to improve treatment for patients with COPD.

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