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A PRACTICAL APPLICATION OF RELIEF EFFECT BY ORIENTAL MEDICINES ON DRY COUGH OF A PATIENT

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ABSTRACT

A dry or involuntary cough is an involuntary and explosive exhalation movement in the respiratory without any phlegm. This study investigated the degree of cough relief with various plants that help relieve cough in Korea. The medicines used are Herbal medicines in clouding *Liriope platyphylla, Luffa aegyptiaca, Platycodon grandiflorum, Zingiber officinale, Dioscorea polystachya, Pseudocydonia sinensis, Pyrus ussuriensis, Schizandra chinensis, Ziziphus jujube,* and *Glycyrrhiza uralensis*. The average number of coughs per hour (CPD) before taking herbal medicine was 46.8 times per hour. The CPD on the 12th day after taking herbal medicine decreased to 12.2 times which was decreased 73.9% compared to the first day. The average number of times woke up from sleep (WUS) was 5.2 times before taking herbal medicine. Compared to the first day, WUS decreased by 57.7% on the 13th day. The number of coughing times was significantly decreased compared to the 1st and 4th days ($p<0.01$). Nitric oxide (NO) radical scavenging activities on 50 mg/L and 100 mg/L were evaluated 7.8% and 15.9%, respectively. The inhibitory effect was 43.8% on 1200 mg/L. There was significant difference among four concentrations (50, 100, 200, 400, 800, and 1200 mg/L) ($p < 0.05$). The effect of suppression by herb medicines was clearly seen using the TNF-α level of RAW264.7 cells. TNF-α in 200 and 400 mg/L samples decreased by 3.1% and 4.3%, respectively. Herbal medicines in clouding *L. platyphylla* may be contained useful compounds for studies connected with dry cough.

KEYWORDS:- Herbal medicines, Involuntary **c**ough, Number of coughs per hour (CPD), TNF-α.

INTRODUCTION

A tickling sensation in the throat can make you have a dry cough. A dry or unproductive cough is an involuntary and explosive exhalation movement in the respiratory, laryngeal, and pharyngeal muscle activity and serves both preventative and corrective roles in pulmonary health.[1] Generally, coughs can be associated with a cold or flu, but dry coughs have nothing to do with them. Meanwhile, asthma is a condition in which your airways swell and become narrow. Asthma-related coughs can be both productive and nonproductive, though they're frequently nonproductive. Gastroesophageal reflux disease (GERD) is a type of chronic acid reflux. It happens when stomach acid regularly flows back up into your esophagus, which connects your mouth to your stomach. Post-nasal drip can sometimes cause a cough. Coughs can also be caused by viral or bacterial respiratory infections, such as pneumonia, whooping cough, and croup. Many of the same things that cause a cough during the day cause a cough at night.

Liriope platyphylla Wang et Tang is widely used as one of the 50 fundamental herbs in traditional Oriental medicine.[2] Liriope Tuber is the roots of this plant. These plants grows commonly in the shady forests of East Asia including China, Korea and Japan at elevation of 100 to 1400 m. *L. platyphylla* is used for treatment asthma and bronchial and lung inflammation.[3]

Luffa cylindrica (L.) M. Roemer is an annual species of vine cultivated for its fruit, native to South and Southeast Asia in temperate regions. Unlike the young fruit, the fully ripened fruit is strongly fibrous and inedible, and is used to make scrubbing bath sponges. Due to the use as a scrubbing sponge. *L. cylindrica* is a candidate for the prevention and dietetic treatment of chronic diseases and for the development of functional food.[4]

Platycodon grandiflorum (Jacq.) A. DC. is a species of herbaceous flowering perennial plant of the family Campanulaceae. The species is an herbaceous flowering perennial plant of the family Campanulaceae. In Korea, the plant as well as its root are referred to as doraji. Doraji is good for people who have weak immune systems that are vulnerable to respiratory diseases, as well as for asthma, which can be called respiratory

illness.[5]

Zingiber officinale Roscoe (Zingiberaceae) is commonly known as ginger, is a spice consumed worldwide for culinary and medicinal purposes. The plant has a number of chemicals responsible for its medicinal properties, such as antiarthritis, antiinflammatory, antidiabetic, antibacterial, antifungal, anticancer, etc. A study showed that a mixture containing the roots of ginger have medicinal properties that could help the symptoms of a cold or sore throat.[6]

Pseudocydonia sinensis (Thouin) C.K. Schneid. is called Chinese quince. The fruits of the species were widely used in traditional Chinese medicine for the treatment of asthma, colds, sore throat, mastitis, rheumatoid arthritis, and tuberculosis.[7] In Europe, *P. sinensis* is only grown in botanical gardens.

Yams (San-yak: Dioscoreae Rhizoma) are perennial rhizome plants, which belong to Dioscoreaceae family and Dioscorea genus has been used widely in Korean herbal medicines.[8]

Pyrus communis, the common pear, is a species of pear native to central and eastern Europe, and western Asia. *Pyrus pyrifolia* (Makino) Nakai is a species of pear tree native to East Asia. The tree's edible fruit is known by many names, including: Asian pear, Japanese pear, Chinese pear, Korean pear, Taiwanese pear, apple pear, and so on.[9] *Pyrus pyripolia* var. *culta* or Korean pear is a cultivar of the *P. pyripolia*. *Pyrus pyrifolia* var. *culta* or Korean pear is a cultivated species of pear tree (*Pyrus pyripolia*). *Pyrus ussuriensis* Maxim. grow naturally in mountainous areas or valleys with an elevation of less than 1,500m nationwide to Korea, China, and the Ussuri River area of far eastern Russia. It is considered the hardiest of all pears. So, the fruits are not the tastiest of pears to humans. Fruit is used for medicinal purposes rather than food, and young trees are used for grafting pear trees.

Schizandra chinensis (Turcz.) Baill. is a vine plant native to forests of Northern China, the Russian Far East and Korea.[10] Its Chinese name comes from the fact that its berries possess five basic flavors: salty, sweet, sour, pungent (spicy), and bitter. In Korean, the berries are known as omija (hangul, five flavours). Its berries are used in traditional medicine. Chemical constituents include the lignans schisandrin, deoxyschizandrin, gomisins, and pregomisin.[11]

Ziziphus jujuba Mill. is a small deciduous tree or shrub reaching a height of 5–12 m, usually with thorny branches. The fruit and its seeds are used in Chinese and Korean traditional medicine, where they are believed to alleviate stress, and traditionally for anti-fungal, anti-bacterial, anti-ulcer, anti-inflammatory purposes and sedation, antispastic, antifertility/contraception, hypotensive and antinephritic, cardiotonic, antioxidant, immunostimulant, and wound healing properties.[12-13]

Glycyrrhiza uralensis Fisch. ex Dc. is perennial herb, about 30-70cm tall, rarely 1 meter tall. The roots of *Glycyrrhiza* spp. have been utilized in Traditional Chinese medicine (TCM) for thousands of years.[14] It is used in Chinese medicine to harmonize other herbs and to reduce the harsh effects of other herbs.[15] *Z. jujuba* and *G. uralensis* weren't used as cough medicines.

Unlike western medicine, the balance and interaction of all the ingredients are considered more important than the effect of individual ingredients. Traditional Chinese medicine is based on the thought that every medicinal substance has its strengths and shortcomings, and that each ingredient in the formula should be carefully balanced in quality and quantity. The aim of this study was to evaluate relief effects on dry cough using several medicinal plants.

MATERIALS AND METHODS

Composition (g/kg) of the experimental herbs

The composition of the sample is shown in Table 1. Since the juice of *Luffa aegyptiaca* is a liquid, the undiluted solution was taken and used in an experiment.

Table 1: The composition of ten species for chinese medicines.

Species	Amount (g or ml)
Liriope platyphylla	50 g
Luffa cylindrica	100 ml
Platycodon grandiflorum (Jacq.) A. DC.	100 g
Zingiber officinale	100 g
Dioscorea polystachya Turcz	50 g
Pseudocydonia sinensis	100 g
Pyrus ussuriensis	100 g
Schizandra chinensis	50 g
Ziziphus jujuba	100 g
Glycyrrhiza uralensis	50 g

Sample extract for herb medicines

The solid materials except liquid (*L. cylindrica*) were treated with hot distilled water. The mixture of boiling group was further stirred with a magnetic bar at 100℃

for one day. The sample was treated with ultrasound at 60℃ for two hours. The ultrasound extraction was carried out using an ultrasonic bath (5510, Branson, USA) and a grinding mixer. Extracted sample was filtered. The sample and *L. cylindrica* were evaporated to remove solvent under reduced pressure and controlled temperature by using rotary vacuum evaporator (N-1001S-W, Eyela, Tokyo, Japan). To get dry powder, samples placed in a low temperature vacuum chamber.

Antitussive effective assay

The number of coughs generated was measured at intervals of 5 seconds for 15 minutes.

Measurements of cough efficacy

Cough efficacy measured by means of the gastric pressure (Pga) which used commercially available latex balloon catheter (Farrell Valve System, Halyard, USA). The balloon catheter is connected to a manometer and the subject is asked to perform 3-5 coughs, starting from maximal inspiration.

Assay of Nitric oxide scavenging activity

Nitric oxide (NO) radical scavenging activity was determined according to the method reported by Marcocci et al.[16] using Griess IlIosvoy reaction. The compound sodium nitroprusside is known to decompose in aqueous solution at physiological pH (7.2) producing NO.[17] Under aerobic conditions, NO reacts with oxygen to produce stable products (nitrate and nitrite). The quantities of NO concentration was measured by using Griess reagent system. For the experiment, sodium nitroprusside (5 mM) in phosphate buffer saline (PBS) was mixed with 3.0 ml of different concentrations (0.1–5 mg/ml) of the Suaeda maritime extract and incubated at 25ºC for 150 min. The samples were added to Greiss reagent (1% sulphanilamide, 2% H_3PO_4 and 0.1% napthylethylene diamine dihydrochloride). The absorbance of the chromaphore formed during the diazotization of nitrite with sulphanilamide and subsequent coupling with napthylethylenediamme was read at 546 nm using the Microplate Reader (VersaMax, Califonia, USA) and referred to the absorbance of standard solutions of catechin treated in the same way with Griess reagent as a positive control. The degree of inhibition was linearized against the concentrations of each extract and standard antioxidant.

Assay of TNF-alpha ELISA

Raw 264.7 cells were adjusted to 5×10^4 cells/ml using a DMEM medium, inoculated on a 96-well plate, and cultured 24 hours ago in a 5% CO_2 incubator. Cells were treated with 10 μg/ml of LPS, and after 1 hour, herb medicines were treated with various concentrations and cultured for 24 hours. The TNF-alpha ELISA kit (AuthentiKine™ Human TNF-alpha ELISA Kit, Proteintech Group, Inc., IL., USA) was used to detect and quantify protein levels of endogenous TNF-α. In order to measure the degree of TNF-α released by the culture medium in each sample, the culture medium was captured during the experiment and stored at -70°C until the measurement. In order to suppress the non-specific reaction, PBS containing 0.05% Tween-20 was washed twice. The sample was treated on a 96-well plate coated with mouse monoclonal antibody to TNF-α for 1 hour on a negative control, positive control, and a 96-well plate according to the manufacturer's usage method. For signal development, horseradish peroxidase (HRP)-conjugated antibody is added, followed by Tetramethyl-benzidine (TMB) reagent. Solution containing sulfuric acid is used to stop color development and the color intensity which is proportional to the quantity of bound protein is measurable at 450 nm with the correction wavelength set at 630 nm. The TNF-α concentration of the sample was calculated using a standard concentration curve for absorbance.

RESULTS

The numbers of coughs per hour which was shown in the maxium frequecy among day time or night (CPD) were shoen in Table 2. Measuring cough within a day was set as the number of times per hour that coughs the most, as cases of omission may occur. It was mainly in the morning at that time. The average CPD before taking herbal medicine was 46.8 times per hour. Three days after taking the herbal medicine, there was a decrease in CPD by about 16.2%. Six and nine days after taking the herbal medicine, there was a decrease in CPD by 49.1% and 63.2%, respectively. The number of coughs on the 12th day after taking herbal medicine decreased to 12.2 times (73.9%).

The average number of times woke up from sleep (WUS) was 5.2 times before taking herbal medicine (Table 2). Three days after taking the herbal medicine, there was a decrease in WUS by about 13.4%. Nine days after taking herbal medicine, the value of WUS decreased by about half (50.0%). Compared to the first day, WUS decreased by 57.7% on the 13th day. Before taking herbal medicine, the degree of pain in the neck while coughing was very severe (+++), but on the 12th day after taking herbal medicine, it turned into a slight pain (+). There was a lot of the amount of sputum discharged through coughing until the 4th. From day six, the amount of sputum discharged through coughing was moderate or more. As a result of this study, taking herbal medicine for at least one week is effective for coughing and sleeping.

Table 2: Clinical symptoms progress by date Before and After taking herbal medicines.

Date (January)	No. of cough/hour (reduction rate, %)	No. of times woke up during sleeping (reduction rate, %)	A sore throat	Sputum
1	46.8±5.2 (0.0)	5.2±1.2 (0.0)	+++	A lot

4	33.4±4.4 (16.2)	4.5±0.8 (13.4)	+++	A lot
7	23.8±1.2 (49.1)	3.2±1.0 (38.5)	++	Moderate or more
10	17.2±3.2 (63.2)	2.6±0.5 (50.0)	++	Not a lot
13	12.2±2.9 (73.9)	2.2±0.7 (57.7)	+	Little or few

The number of coughing times while sleeping was shown in Fig. 1. Before taking herbal medicine, it averaged 12.2 times. The 12th day of taking the herbal medicine averaged 1.9 times. It was significantly decreased compared to the 1st and 4th days (p<0.01).

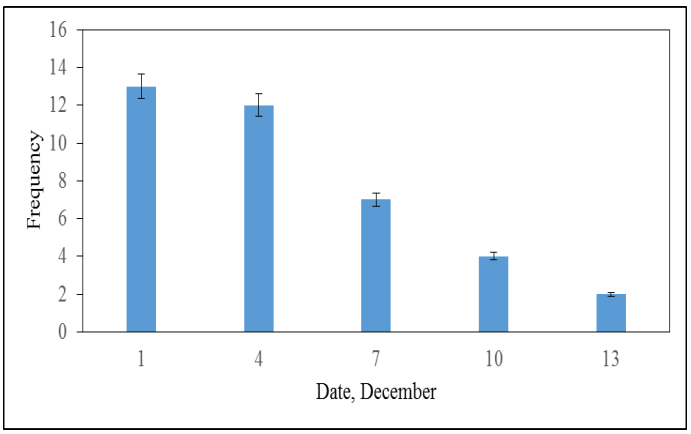

Figure 1: The frequency of coughing for 1 day at night after taking medication.

The average time spent sleeping deeply was 3.5 hours before taking the herbal medicine (Fig. 2). The average time of deep sleep during sleep was 5.5 hours after 12 days after taking the herbal medicine. Compared to the first day, time spent sleeping deeply increased by 57.1% on the 13th day.

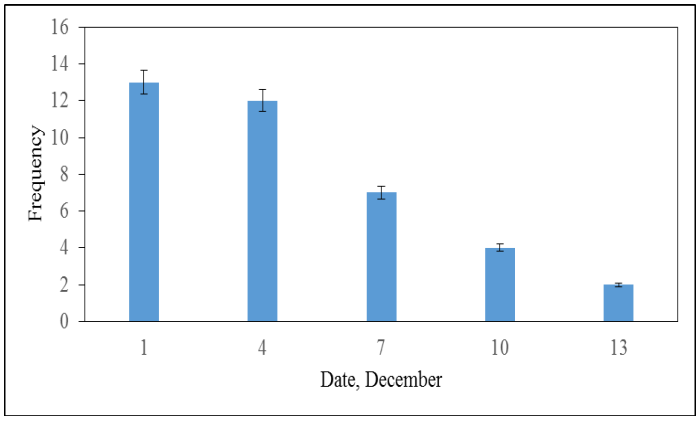

Figure 2: The change of good night's sleeping hours for one day after taking the medication. 1 December is not taken the medication.

In the normal subjects, only occasional coughs were ranged from 0 to 16 coughs per day. Coughs occurred mostly in the daytime, peaking between 6 a.m. and 10 a.m. (53.6%), and in the night before sleeping (23.0% between 8 p.m. and 10 p.m.) (Fig. 3). The patient had a cough when he woke up, but it showed that he couldn't sleep deeply.

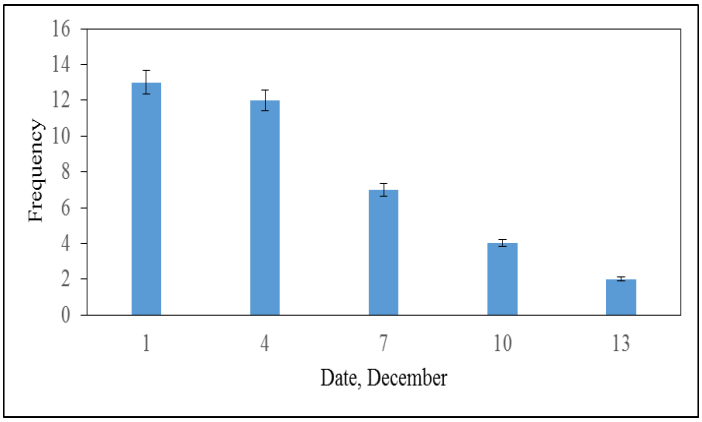

Figure 3: A 24-hour cough frequency in a patient with chronic cough.

In this study, the inhibitory effects of herbal medicines for nitric oxide (NO) radical scavenging activities were increased with enhancements in concentration of herbal medicines in the assay mixture (Table 3). NO radical scavenging activities on 50 mg/L and 100 mg/L were evaluated 7.8% and 15.9%, respectively. The inhibitory effect was 43.8% on 1200 mg/L. There was significant difference among four concentrations (50, 100, 200, 400, 800, and 1200 mg/L) ($p < 0.05$).

The effect of suppression by herb medicines was clearly seen using the TNF-α level of RAW264.7 cells (Fig. 4). TNF-α production and secretion in 50 mg/L samples increased by 5.8% compared to the control group. However, TNF-α in 100 mg/L of the samples were similar to that of the control group. TNF-α in 200 and 400 mg/L samples decreased by 3.1% and 4.3%, respectively. The amount of the TNF-α was 5.7% in 800 mg/L and 6.1% 1200 mg/L. Significant suppression was not observed in administered groups ($p>0.05$). The increase in proportion to the cell culture time was not significant.

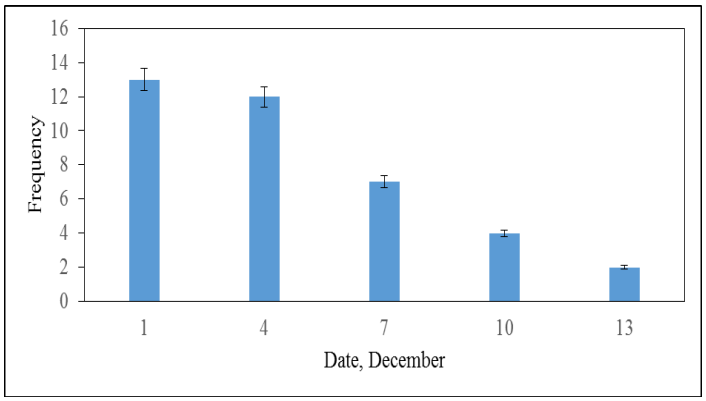

Figure 4: Relative concentrations of TNF-α released from RAW 264.7 by treatment with herbal medicines. RAW 264.7 (1×106 cells) was cultured in a 60 mm culture dish and treated with LPS (1 ng/ml) and different concentrations of herbal medicine extracts. After incubation for 24 hours, ELISA assays were performed with indicated specific antibodies coated on the commercial ELISA plates in materials and methods. All data are mean of triplicated independent reactions.

DISCUSSION

Tumor necrosis factor (TNF) inhibitors, sometimes called TNF-alpha or TNF-α inhibitors, are medications that help reduce the inflammatory process in the treatment of autoimmune and inflammatory conditions. TNF inhibitors work by blocking the activity of a protein called TNFα. This protein normally helps with important functions such as fat metabolism and blood clotting, and excess TNFa can contribute to chronic inflammation and joint damage.[18] Kim et al.[19] performed an anti-inflammatory experiment with oriental medicine (*Friltillariae thunbergii* Bulbus) using sputum, cough, and acute airway inflammation animal models. Raw cells decreased and significantly inhibited the increase of NO, TNF-α and IL-6 in the experimental groups at 30, 50, 100, 300, and 500 μg/ml concentrations. TNF-α secretion was suppressed according to the concentrations of nine herbal extracts including *Schisandra chienensis*.[20] As expected, TNF- α has a very low level of secretion from T cells, and secretion was further suppressed when herbal extracts were treated compared to the control group (Fig. 3).

NO is synthesized from L-arginine by a group of nitric oxide synths (NOS) enzymes. NOS plays an important role in the regulation of physiological synthesis in the human body, which exists in three forms: neural NOS (nNOS), inducible NOS (iNOS), and endothermic NOS

(eNOS). Among them, iNOS is one of the important enzymes that cause inflammatory control.[21] Gagam-Danguieumja (GDE) water extract including *Liriopis* tuber inhibited production of NO in a dose dependent manner and also decreased the expression of inducible nitric oxide synthase (iNOS).[22] In this study, nitric oxide (NO) radical scavenging activities were inhibited with enhancements in concentration of herbal medicines (Table 3). Kim et al.[23] reported that *L. platyphylla* is one of the well-known herb used in oriental fork medicine for treatment asthma and bronchial and lung inflammation since ancient times. In particular, it is effective for treating bronchitis, pharyngitis, and asthma accompanied by dry cough.[24-25] In this study, in the case of herbal medicine, long-term use was more effective in relieving cough than short-term use (Table 2, Figs 1 and 2). Taking it for at least a week was effective in relieving coughs.

Chronic cough can be defined as a cough lasting more than eight weeks. Neuropathy chronic cough is thought to be laryngeal neuropathy, and the seizure of coughs even with small stimuli is similar to the symptom manifestation of trigeminal neuralgia, so drugs used for trigeminal neuralgia are used a lot experimentally. Neuromodulating medics such as gabapentin, amitriptyline, pragabalin, and baclofen are used to treat chronic coughs for neuropathy.[26]

Harvard Medical School.[27] suggested many causes of coughing. Dozens of conditions can cause a recurrent, lingering cough, but the lion's share are caused by just five: postnasal drip, asthma, gastroesophageal reflux disease (GERD), chronic bronchitis, and treatment with ACE inhibitors, used for high blood pressure and heart failure. A dry cough means it's tickly and doesn't produce any phlegm (thick mucus). Because there isn't mucus blocking the lungs or airways, nothing comes out when human cough.

Several drugs are used to reduce sputum and help discharge, but the effect is weak and rarely proven accurately.[28] Although there are differences in the degree of administration of chronic coughing, symptoms of the mental nervous system, digestive system, and hypersensitivity reactions can usually occur. Side effects include drowsiness, dizziness, fatigue, and discomfort due to symptoms of the mental nervous system, loss of appetite, abdominal pain, stomach discomfort, heartburn, and vomiting due to symptoms of the digestive system, and rash may appear due to hypersensitivity.[28] Among antitussives, mucolytic agents and expectorants in clinical practice, the effect of the drug is not clear and the effect of long-term use has not been proven. Therefore, it is effective to use the least amount of drugs for a short period of time only when they are clinically adapted.[29]

Herbal medicine is also toxic, and *Pinellia rhizoma* is typically a cough suppressant, but it is toxic when used as a living plant. It is not easy to remove toxic substances from this plant. The results of this study are limited in that it is only the case of a patient with a dry cough among the many cough causes previously suggested by Harvard Medical School.

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