

A pilot study of the multiherb Kampo Medicine Bakumondoto for Cough in Patients
with Chronic Obstructive Pulmonary Disease

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Abstract:

OBJECTIVES: To evaluate the effect of bakumondoto, Kampo medicine, on cough in patients with chronic obstructive pulmonary disease (COPD). **DESIGN:** A 16-week, randomized, open-labeled, cross-over design. **SETTING:** Outpatient clinics at one university hospital and two general hospitals in Japan from May 2007 to March 2009.

PARTICIPANTS: Twenty-four elderly patients (14 men and 9 women aged over 65) with COPD. **INTERVENTION:** Treatment with or without bakumondoto for 8 weeks in a cross-over design. **MEASUREMENTS:** The primary outcome measurements were the frequency and intensity of cough assessed by a visual analogue scale (VAS) and a daily cough diary. Secondary outcome measurements were quality of life (QOL) assessed using St. George's Respiratory Questionnaire (SGRQ) and lung functions measured using spirometry. **RESULTS:** Treatment with bakumondoto significantly improved cough severity during the first treatment period (week 0 vs. week 8, $p=0.004$) and showed a trend to decrease during the second treatment period (week 8 vs. week16, $p=0.129$) assessed by the VAS. Neither QOL nor lung function was affected by the treatment with bakumondoto. **CONCLUSION:** Bakumondoto may be effective in suppressing cough in elderly patients with COPD. To further confirm the efficacy, a larger and placebo-controlled study with objective cough assessment is necessary.

Key Words: COPD; bakumondoto; Kampo; Cough

Introduction

Cough is a frequent symptom in patients with chronic obstructive pulmonary disease (COPD) and often impairs their quality of life (QOL) (Smith et al., 2006).

Bakumondoto has been used as an antitussive agent in China for centuries, and is prescribed in Japan for the treatment of bronchitis and pharyngitis accompanying severe dry cough (Miyata, 2003). Based on these experiences, the Japanese Respiratory Society guidelines suggest bakumondoto as a possible antitussive agent to use for patients with COPD. Previous studies have demonstrated that bakumondoto was effective for postinfectious cough (Fujimori et al., 1998), asthmatic cough (Watanabe et al., 2003), and cough caused by mycoplasma bronchitis (Watanabe et al., 2008); however, to our knowledge, no study has been undertaken to see the effects of bakumondoto on cough in COPD patients. Therefore, we conducted this study to evaluate whether bakumondoto would demonstrate a therapeutic efficacy on cough in elderly patients with COPD, in particular.

Materials and Methods

Subjects

Consecutive 24 elderly COPD outpatients who complained of chronic cough and met the criteria described below were recruited at Tadanoumi Hospital, Hiroshima University Hospital, and Higashi-Hiroshima Medical Center from May 2007 to March 2009. Inclusion criteria required a baseline forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) $\times 100$ (defined as $FEV_1\%$) $< 70\%$ and FEV_1 /predicted $FEV_1 \times 100$ (defined as $FEV_1\%pred$) $> 50\%$. Exclusion criteria were as follows: current smoker, patients who had respiratory diseases except COPD within the previous 4 weeks, and patients who received Kampo medicine within the previous 2 weeks.

The study protocol was approved by the ethics committee of Hiroshima University. All patients provided written informed consent, and this study was conducted in compliance with the ethical principles of the Helsinki Declaration.

Test Drug

Bakumondoto (Mai-men-dong-tang in Chinese) is a mixture of extracts from 6 crude herbs in fixed proportions (Ophiopogonis tuber: 37.0%, Pinelliae tuber: 18.5%, Zizyphi fructus: 11.1%, Glycyrrhizae radix: 7.85%, Ginseng radix: 7.85%, Oryzae

fructus: 18.5%). Each crude herb was decocted in a 10-fold weight of water for 60 min, filtered, and the filtrate was spray-dried to obtain an extract powder. For the analysis of components, 0.5 g of bakumondoto was ultrasonicated in 20 ml of methanol for 30 min. The solution was filtered through a 0.45 μ m membrane and then subjected to high-performance liquid chromatography (HPLC) analysis. The HPLC apparatus consisted of a Shimadzu LC 10A (analysis system software: CLASS-MIOA ver. 1.64, Tokyo, Japan) equipped with a multiple wavelength detector (UV 200-400 nm: Shimadzu SPD-M10AVP, diode array detector) and an auto injector (Shimadzu CT0-10AC). HPLC conditions were as follows: column, ODS (TSK-GEL 80TS, 250 x 4.6 mm i.d., TOSOH, Tokyo, Japan); solvent, (A) 0.05 M AcONH₄ (pH 3.6), (B) 100% CH₃CN; linear gradient, solvent A mixed with solvent B from 10% to 100% B in 60 min, retention time = 20 min); temperature, 40°C ; flow rate, 1.0 ml/min. The three dimensional HPLC profile of bakumondoto is shown in Fig. 1. The medical-grade extract powder of bakumondoto is commercially available in Japan and was obtained from Tsumura Co., Ltd. (Tokyo, Japan). Bakumondoto was administered at 3.0g of powder orally before each meal, three times daily (9.0g/day).

Fig.1

Study Design

This study was conducted using a cross-over method, with an 8-week treatment

period and an 8-week non-treatment period. This study became an open-labeled study because it was impossible to prepare a suitable placebo due to the unique flavor and odor of bakumondoto. Twenty-four patients were randomized into either group A (n=13) or group B (n=11) by means of sealed envelopes. Patients in group A took bakumondoto for the first 8 weeks, and discontinued the drugs for the following 8 weeks. In group B, the treatment was reversed in a cross-over manner. The regular medication for COPD in each patient was unchanged throughout the 16-week study period.

Outcome Measurements

The primary outcome measurement was change in severity of cough assessed by a visual analogue scale (VAS) and a daily cough diary. The patients subjectively evaluated their cough using the VAS, which consisted of a 10-cm horizontal line scoring between 0 (no cough) at the left end and 10 (extremely strong or frequent) at the right. They scored the VAS for cough frequency and for cough intensity separately. Therefore, the total VAS score ranged from 0 to 20 points at each evaluation. The VAS evaluation was performed at the start of the study and at every 4 weeks during the study period.

Using the daily cough diary, the patients were also asked to daily record the severity of

cough based on the four categories; 0 for no cough, 1 for mild cough, 2 for strong cough, and 3 for extremely strong cough, in each of three time periods; morning to afternoon (6:00a.m. to 2:00p.m.), afternoon to night (2:00p.m. to 10:00p.m.), and during sleep (10:00p.m. to 6:00a.m.) during the study period. Therefore, a daily total score of cough severity ranged from 0 to 9 points. In advance of the start of the study, we had decided to use the average of the daily cough scores in the last 3 weeks of each 8-week treatment or non-treatment period for the analysis. This is because it generally takes several weeks for Kampo to display its stable efficacy (Mizukami, 2009) and carry-over effect of bakumondoto in the non-treatment period should be excluded.

The secondary outcome measurements were quality of life (QOL) assessed at every 4 weeks using St. George's Respiratory Questionnaire (SGRQ), and lung function measured at every 8 weeks using a spirometer (Chestgraph HI-701; CHEST M.I. Inc, Tokyo, Japan).

Statistical Analysis

The data are expressed as the mean \pm SD. Comparison of the VAS scores between pre- and post-treatment with bakumondoto was analyzed by the Wilcoxon signed-rank test. The two groups' data were analyzed by the Wilcoxon rank-sum test comparing the changes of the average scores in the cough diaries from the first 8-week period to the

second. A p value of <0.05 was considered to be significant. Analyses were performed using SAS, version 9.13 (SAS Institute, Inc., Japan).

Safety

Throughout the 16-week study period, adverse events for which a causal relationship with bakumondoto could not be ruled out were noted in two patients. In these two patients, alkaline phosphatase levels slightly increased after eight weeks of the treatment with bakumondoto. No other adverse events were observed.

Results

Characteristics of the Study Subjects

One patient of the A group was excluded from the analysis because no data on cough severity was recorded. The characteristics of the remaining 23 patients who enrolled in this study are summarized in Table 1. There were no significant differences in age, sex ratio, VAS score, FEV₁%, and FEV₁%pred at baseline between the two groups. Two patients from each group refused to take bakumondoto in the middle of the treatment period due to difficulty of swallowing the medicine. The part of halfway data until these patients stopped taking bakumondoto was included in the analysis. The remaining 10 patients in group A and 9 patients in group B completed the 16-week study.

Table1

Outcomes

As shown in Fig. 2A, VAS scores in group A significantly decreased during the treatment period (week 0 vs. week 8, $p=0.005$). VAS scores in group B also showed a trend to decrease during the treatment, however this change did not reach statistical significance (week 8 vs. week16, $p=0.129$). Then, the VAS scores for cough intensity and frequency were analyzed separately. As shown in Fig.2B, the VAS scores for cough intensity in each of groups A and B during the treatment period tended to

improve, however these changes did not reach statistical significance (group A, week 0 vs. week 8, $p=0.055$; group B, week 8 vs. week 16, $p=0.387$). The VAS score for cough frequency during the treatment period significantly improved in group A (Fig. 2C; week 0 vs. week 4, $p=0.007$; week 0 vs. week 8, $p=0.001$). It also showed a trend to decrease during the treatment period in group B, however this change did not reach statistical significance (Fig.2C; week 8 vs. week 16, $p=0.055$).

Fig.2ABC

We next examined the changes in the average scores of cough severity recorded in the daily cough diary. The average score for cough severity in group A changed from 2.90 at the treatment period to 3.88 at the non-treatment period. Similarly, the average score for cough severity in group B changed from 3.83 at the non-treatment period to 3.12 at the treatment period. As shown in Fig. 3, the lines connecting the average scores during 6 to 8 weeks and 14 to 16 weeks of the study period in the two groups crossed and the changes from the former to the latter time points significantly differed between groups A and B (group A, 0.98 ± 1.08 vs. group B, -0.71 ± 1.04 ; $p=0.006$).

The SGRQ scores and FEV₁% did not significantly change before and after the treatment with bakumondoto in each group (data not shown). No serious adverse event was observed.

Fig.3

Discussion

Cough is one of the most frequent symptoms reported by patients with COPD (Rennard et al., 2002) and is known to impair QOL (Miravittles et al., 2007). Successful treatment of cough in COPD patients should have great clinical significance; however, effective therapy has not yet been identified (Smith et al., 2004). A recent randomized, placebo-controlled trial has shown that codeine, a common antitussive agent, was not effective in the management of cough in COPD patients (Smith et al., 2006). In this study, interestingly, codeine also failed to significantly improve subjective cough severity from the baseline. In another clinical trial, theophylline and long acting β -agonist did not show a statistically significant improvement in subjective measurements of cough from the baseline (Nishimura et al., 1995; Aalbers et al., 2002). To our best knowledge, there is no treatment that has improved subjective cough severity in patients with COPD. In the present study, bakumondoto was found to significantly improve cough severity subjectively assessed using daily cough diary and the VAS without any serious adverse events. However, this statistically significant improvement in cough severity assessed by VAS was observed only in group A but not in group B. We believe that this is caused by the lower average VAS scores in group B (7.9 ± 3.0) compared with those in group A (10.2 ± 4.5) at baseline. Another possible reason may be simply the too small sample size to detect

statistical significance.

There are a couple of studies that suggest the mechanisms of bakumondoto to serve as an antitussive agent. Using a guinea-pig model of long-term exposure to cigarette-smoke, Kamei et al. showed that bakumondoto had an effect to reduce cough sensitivity (Smith et al., 2005). They also found that bakumondoto decreased nitric oxide (NO) metabolites in bronchoalveolar lavage fluid, suggesting that the antitussive effect of bakumondoto might be mediated by the inhibition of synthesis or release of NO. In fact, a high level expression of inducible NO synthase (iNOS) in sputum macrophages, alveolar walls, small airway epithelium are observed in COPD patients (Ichinose et al., 2000; Paska et al., 2002) and a recent cross-sectional study has shown that there was a significant elevation in fraction of exhaled NO in patients with stable COPD (Beg et al., 2005). Other studies reported by Aizawa et al. (1999, 2003) demonstrated that bakumondoto inhibited airway hyperresponsiveness induced by ozone in guinea pigs through inhibiting the release of acetylcholine from vagal nerve terminals. Because the dysregulation of vagal nervous system leading to decreased cough threshold is suggested as a mechanism for cough in COPD patients (Undem et al., 2005), bakumondoto may have a beneficial effect on cough induced through this process.

Based on these suggested mechanisms for cough, bakumondoto can be regarded as

a peripherally acting antitussive drug. Centrally acting drugs, such as codeine and dextromethorphan, are currently most used antitussives, however, they are often associated with unpleasant or intolerable side effects, including sedation, nausea, and constipation. To avoid these side effects of centrally acting drugs, bakumondoto may be a more suitable antitussive drug for cough in elderly COPD patients. In addition, through animal or *in vitro* experiments, Miyata et al. reported that bakumondoto had various pharmacological actions, such as anti-inflammatory, anti-allergic, immunomodulatory, secretory-modulating, and metabolic regulatory effects (Miyata, 2004; Miyata et al., 2007). These wide-ranging effects of bakumondoto may be suitable for the treatment of patients with COPD, which is now recognized as a systemic disease.

Although it subjectively improved cough in COPD patients, bakumondoto did not affect QOL assessed by SGRQ. Because the questions regarding cough occupy only a small portion in SGRQ, this result indicates that respiratory symptoms, such as breathlessness or wheezing, other than cough did not change by the treatment with bakumondoto. If cough-specific health-related quality of life questionnaires (e.g. the Cough Quality of Life Questionnaire and the Leicester Cough Questionnaire) were used instead of SGRQ, the outcomes might be different.

Besides the small sample size, we are aware that there are a couple of limitations in

this study. Due to the unique flavor and odor of bakumondoto, placebo could not be prepared. The usage of other Kampo medicine as placebo was considered, however, we judged that this substitution would cause an ethical problem. Therefore, this study was conducted as an open-labeled one without placebo. In addition, the outcome measurements did not include objective assessment of cough such as measurement of cough reflex sensitivity. Further analysis to objectively assess the efficacy of bakumondoto as an antitussive agent is definitely needed.

In conclusion, this study demonstrates that the multiherb Kampo Medicine bakumondoto may be effective in subjectively suppressing cough in COPD patients without impairing their QOL or affecting lung function while general medical treatment for COPD was being undertaken. Bakumondoto did not cause any adverse events even in elderly patients. To our best knowledge, this is the first study that demonstrated the statistically significant improvement in cough severity assessed by subjective measurements. To further confirm the efficacy of bakumondoto as an antitussive agent in COPD, larger and placebo-controlled study with objective cough assessment would be necessary.

Acknowledgments

Author Contributions: Kenichi Mukaida was the investigator at Tadanoumi hospital, analyzed the data, and prepared the manuscript. Noboru Hattori was the investigator at Hiroshima University Hospital, interpreted the data, and prepared the manuscript. Isao Murakami was the investigator at Higashi Hiroshima Medical Center and analyzed the data. Akihito Yokoyama interpreted the data. Nobuoki Kohno supervised the study and interpreted the data.

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References

- Aalbers R., Ayres J., Backer V., Decramer M., Lier P.A., Magyar P., Malolepszy J., Ruffin R., Sybrecht G.W., 2002. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled, 3-month trial. *Eur. Respir. J.* 19, 936-943.
- Aizawa H., Shigyo M., Nakano H., Matsumoto K., Inoue H., Hara N., 1999. Effect of the Chinese herbal medicine, Bakumondo-to, on airway hyperresponsiveness induced by ozone exposure in guinea-pigs. *Respirology*. 4, 349-354.
- Aizawa H., Yoshida M., Inoue H., Hara N., 2003. Traditional oriental herbal medicine, Bakumondo-to, suppresses vagal neuro-effector transmission in guinea pig trachea. *J. Asthma*. 40, 497-503.
- Beg M.F., Alzoughaibi M.A., Abba A.A., Habib S.S., 2009. Exhaled nitric oxide in stable chronic obstructive pulmonary disease. *Ann. Thorac. Med.* 4, 65-70.
- Fujimori K., Shimatsu Y., Suzuki E., Arakawa M., 1998. A pilot phase II study of combination therapy with oxatomide, an antihistamine, plus dextromethorphan and Bakumondo-to, an herbal drug, in patients with postinfectious persistent cough. *Nihon Kokyuki Gakkai Zasshi*. 36, 338-341. (Abst. in English)
- Ichinose M., Sugiura H., Yamagata S., Koarai A., Shirato K., 2000. Increase in reactive nitrogen species production in chronic obstructive pulmonary disease airways. *Am. J.*

Respir. Crit. Care. Med. 162, 701-706.

Kamei J., Yoshikawa Y., Saitoh A., 2005. Antitussive effect of Bakumondoto (Mai-men-dong-tang) in guinea-pig exposed to cigarette smoke. J. Trad. Med. 22, 44-48.

Miravittles M., Molina J., Naberan K., Cots J.M., Ros F., Llor C., 2007. EVOCA study. Factors determining the quality of life of patients with COPD in primary care. Ther. Adv. Respir. Dis. 1, 85-92.

Miyata T., 2003. Novel Approach to Respiratory Pharmacology Pharmacological Basis of Cough, Sputum and Airway Clearance. YAKUGAKU ZASSHI. 123, 987-1006.

(Abst. in English)

Miyata T., 2004. Pharmacological characteristics of traditional medicine as curative 'Polypharmacy'. J. Trad. Med. 21, 155-165.

Miyata T., 2007. Pharmacological basis of traditional medicines and health supplements as curatives. J. Pharmacol. Sci. 103, 127-131.

Mizukami K., Asada T., Kinoshita T., Tanaka K., Sonohara K., Nakai R., Yamaguchi K., Hanyu H., Kanaya K., Takao T., Okada M., Kudo S., Kotoku H., Iwakiri M., Kurita H., Miyamura T., Kawasaki Y., Omori K., Shiozaki K., Odawara T., Suzuki T.,

Yamada S., Nakamura Y., Toba K., 2009. A randomized cross-Over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the

behavioural and psychological symptoms of dementia. *International Journal of Neuropsychopharmacology*. 12, 191-199.

Nishimura K., Koyama H., Ikeda A., Sugiura N., Kawakatsu K., Izumi T., 1995. The Additive Effect of Theophylline on a High-Dose Combination of Inhaled Salbutamol and Ipratropium Bromide in Stable COPD. *Chest*. 107, 718-723.

Paska C., Maestrelli P., Formichi B., 2002. Increased expression of inducible NOS in peripheral lung of severe COPD patients. *Eur. Respir. J.* 20, 95s.

Rennard S., Decramer M., Calverley P.M., Pride N.B., Soriano J.B., Vermeire P.A., Vestbo J., 2002. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur. Respir. J.* 20, 799-805.

Smith J., Owen E., Earis J., Woodcock A., 2006. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. *J. Allergy Clin. Immunol.* 17, 831-835.

Smith J., Woodcock A., 2006. Cough and its importance in COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* 1, 305-314.

Smith J.A., Calverley P.M., 2004. Cough in chronic obstructive pulmonary disease. *Pulm. Pharmacol. Ther.* 17, 393-398.

Undem B.J., Kollarik M., 2005. The role of vagal afferent nerves in chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* 2, 355-360.

Watanabe N., Cheng G., Fukuda T., 2003. Effects of Bakumondo-to (Mai-Men-Dong-Tang) on cough sensitivity to capsaicin in asthmatic patients with cough hypersensitivity. *Arerugi*. 52, 485-491. (Abst. in English)

Watanabe N., Nakagawa T., Miyazawa T., 2008. Examination of effective antitussive against cough caused by mycoplasma bronchitis. *Kampo and Immuno-allergy*. 22, 63-68. (Abst. in English)

Figure legends.

Fig. 1. The three-dimensional HPLC profile of bakumondoto.

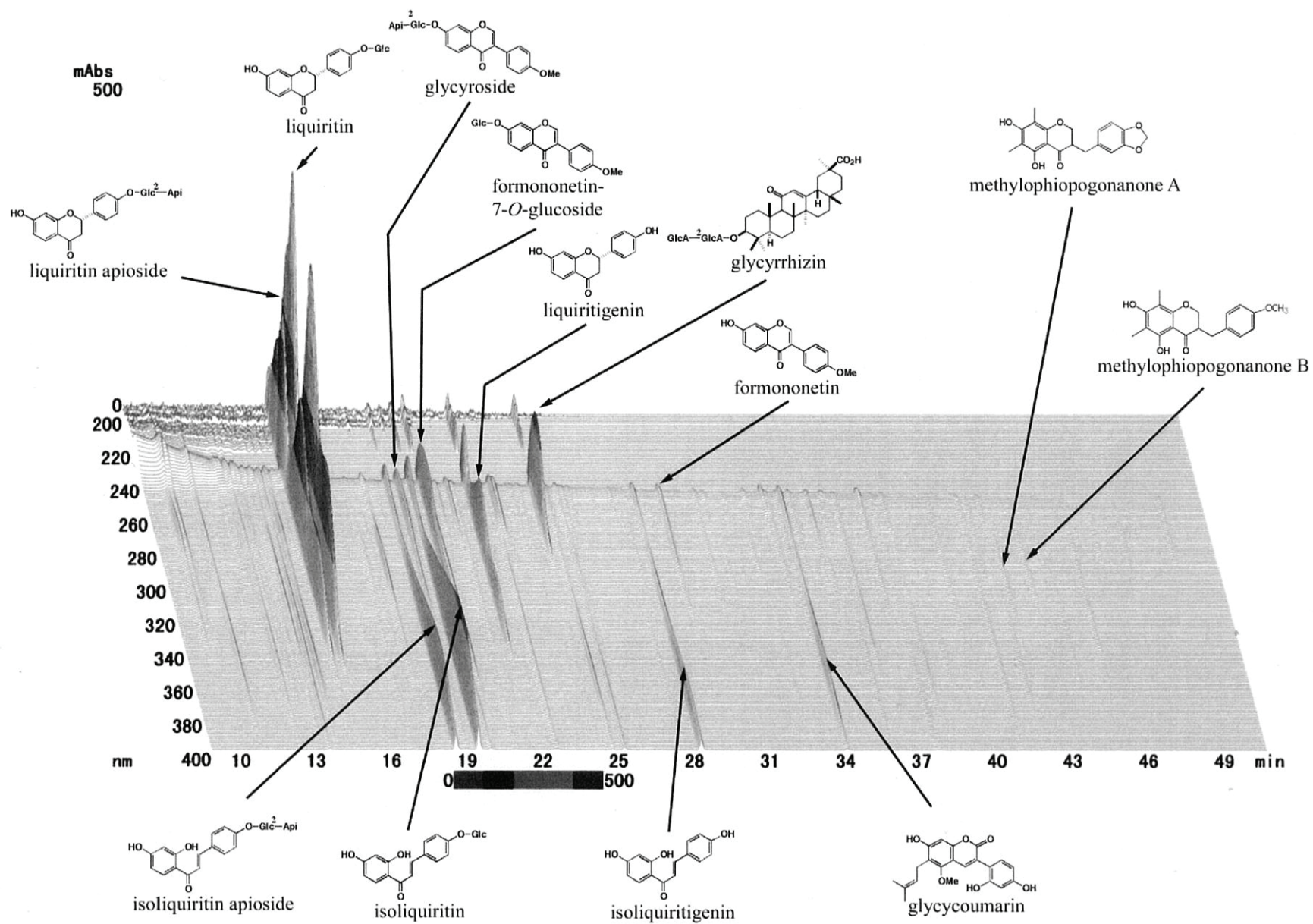
Fig. 2. Changes in scores of cough severity assessed by visual analog scale. Each value is presented as change from the baseline score, with the median +/- standard deviation (SD). Period of treatment with bakumondoto: Group A, 0 to 8 weeks; Group B, 8 to 16 weeks. (A) Summation of scores for cough intensity and frequency. Group A: 0 week vs. 8 week; **P=0.004. Group B: 8 week vs. 16 week; P=0.129. (B) Scores for cough intensity. Group A: 0 week vs. 8 week; P=0.055. Group B: 8 week vs. 16 week; P=0.387. (C) Scores for cough frequency. Group A: 0 week vs. 4 week; **P=0.007, 8 week; ***P=0.001. Group B: 8 week vs. 16 week; P=0.054.

Fig. 3. Changes in scores of cough severity assessed using daily cough diary. Each value is the average of the daily cough scores in the last 3 weeks of each 8-week treatment or non-treatment period, representing the mean +/- standard deviation (SD). Changes of cough diary score are 0.98+/-1.08 in Group A and -0.71+/-1.04 in Group B. Group A vs. Group B; **P=0.006.

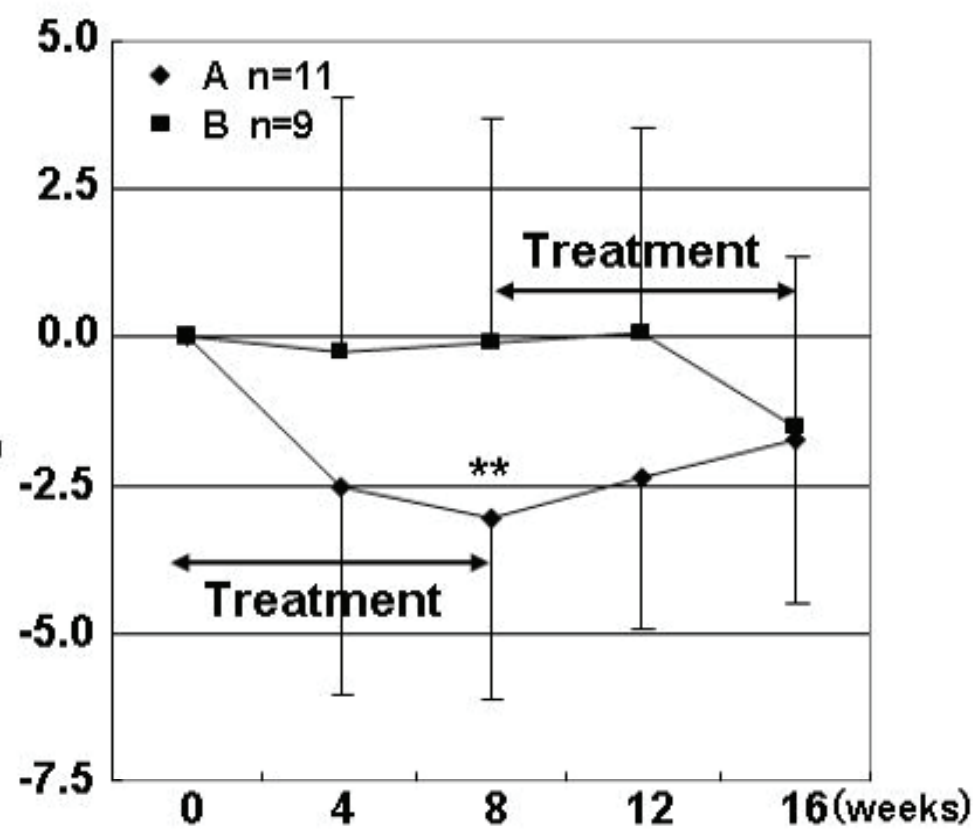
Table 1. Characteristics of the Studied Subjects.

Demographic data	Group A	Group B	Wilcoxon test
	(treatment	(treatment	
	week 0-8)	week 8-16)	
n	13	11	-
Gender (M/F)	9/4	6/5	-
Age (year), mean +/- S.D.	76.2+/-8.5	79.2+/-2.6	0.381
FEV1/ FVC (%)	61.9+/-9.3	66.8+/-8.5	0.202
FEV1%pred (%)	71.9+/-21.2	85.8+/-23.4	0.164
Total Cough VAS	10.8+/-4.8	7.9+/-3.0	0.164

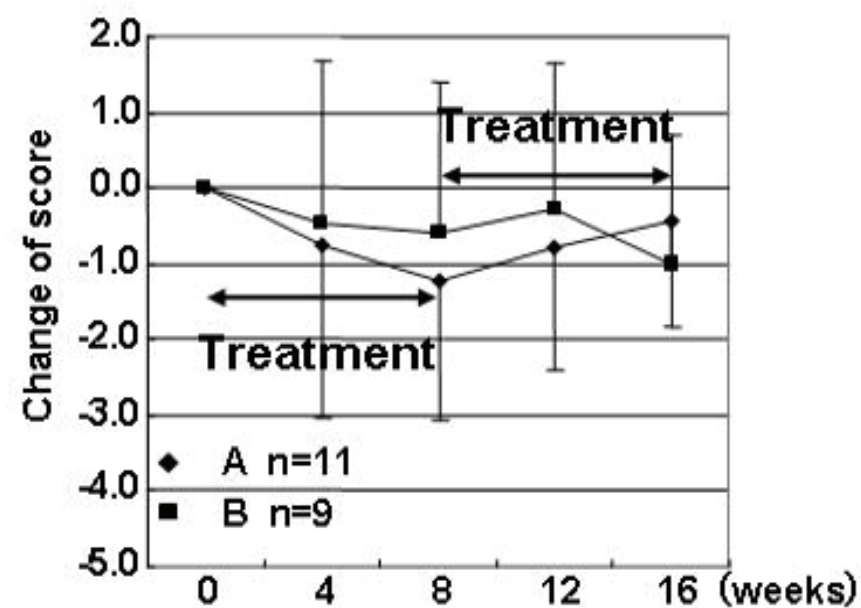
M = male; F = female; SD = standard deviation; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; VAS = visual analogue scale



A



B



C

