Non-superiority of Kakkonto, a Japanese Herbal Medicine, to a Representative Multiple Cold Medicine with Respect to Anti-aggravation Effects on the Common Cold: A Randomized Controlled Trial

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Abstract

Objective Kakkonto, a Japanese herbal medicine, is frequently used to treat the common cold not only with a physician's prescription, but also in self-medication situations. This study aimed to examine whether Kakkonto prevents the aggravation of cold symptoms if taken at an early stage of illness compared with a well-selected Western-style multiple cold medicine.

Methods This study was a multicenter, active drug-controlled, randomized trial. Adults 18 to 65 years of age who felt a touch of cold symptoms and visited 15 outpatient healthcare facilities within 48 hours of symptoms onset were enrolled. The participants were randomly assigned to two groups: one treated with Kakkonto (Kakkonto Extract-A, 6 g/day) (n=209) and one treated with a Western-style multiple cold medicine (Pabron Gold-A, 3.6 g/day) (n=198) for at most four days. The primary outcome of this study was the aggravation of cold, nasal, throat or bronchial symptoms, scored as moderate or severe and lasting for at least two days within five days after entry into the study.

Results Among the 410 enrollees, 340 (168 in the Kakkonto group and 172 in the Pabron group) were included in the analyses. The proportion of participants whose colds were aggravated was 22.6% in the Kakkonto group and 25.0% in the Pabron group (p=0.66). The overall severity of the cold symptoms was not significantly different between the groups. No harmful adverse events occurred in either group.

Conclusion Kakkonto did not significantly prevent the progression of cold symptoms, even when prescribed at an early stage of the disease.

Key words: Kakkonto, herbal medicine, common cold, randomized controlled trial, anti-aggravation, self-medication

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Introduction

Colds are the most common acute illness throughout the industrialized world. Since cold remedies and self-medication regimens have not yet been well established (1), a vast number of cold patients consult a doctor. Therefore, the limited medical resources in Japan are often pressed by cold epidemics. Colds also cast an enormous economic burden due to both loss of productivity and expenditures for
treatment (2).

Japanese herbal medicines originated in ancient China and modified during the long history of Japanese traditional medicine (3). Many Japanese physicians prescribe several kinds of herbal medicines with or without Western medicines, and many Japanese patients also favor herbal medicines as curatives. Even for infectious diseases, some herbal medicines are expected to be effective and have actually been verified using Western medicine. For example, Kaji et al. reported that Shosaikoto (TJ-9, Tsumura and Co., Tokyo, Japan) reduces the duration of the common cold in patients with a lapse of five days or more after symptom onset (4). Meanwhile, Homma et al. showed that Maobushisaishinoto (TJ-127, Tsumura and Co., Tokyo, Japan) is more effective in alleviating symptoms than a commonly used Western-style cold medicine (5).

Kakkonto, a Japanese herbal medicine, is available as an over-the-counter drug and frequently used to treat the common cold at the early stage in the self-medication setting. It is also often prescribed by physicians for primary medical care in Japan. This is because Kakkonto is empirically known to have anti-aggravating effects on colds, especially when used in the early stage of the disease. However, there is no evidence clinically proving the effectiveness of Kakkonto against common colds. Therefore, the aim of the present study was to examine whether Kakkonto prevents the aggravation of cold symptoms if taken at the early stages of illness. For comparison, a well-selected Western-style multiple cold medicine was used as a control.

Materials and Methods

Study design and ethics approval

This study was a multicenter, active drug-controlled, randomized trial. The study protocol was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000003610) and approved by the Medical Ethics Committee of the Kyoto University Graduate School of Medicine.

Setting and participants

This study was conducted at 15 outpatient healthcare facilities, including nine university health services, four private practices and two company medical offices. The facilities were located in Hokkaido, Fukushima, Gunma, Chiba, Tokyo, Nagano, Shizuoka, Kyoto, Osaka, Nara, Hiroshima, Shimane and Shanghai.

In order to enroll patients at the early stage of disease, we provided advance notice of the study using posters placed on billboards and news on the website of the participating medical facilities and respective clinical fields. We encouraged candidate participants to visit a healthcare facility immediately when they felt a touch of cold symptoms.

Based on this background, we included individuals 18 to 65 years of age with throat discomfort and some feeling of chills without sweating, as well as a history of colds during the preceding three years, who visited a participating facility within 48 hours after the beginning of cold symptoms. Patients who were moderately or severely afflicted, had a fever of 37.5°C or more, had already taken medicine for the cold or had a serious underlying disease were excluded before enrollment. Written informed consent was obtained from all participants.

Randomization

The participants were randomly assigned to either of the two treatment groups in a 1:1 ratio. Randomization was conducted by the trial coordinator based on computer-generated random digits. Random allocation was performed stratified by the location of the medical facility (cold districts, such as Hokkaido, Tohoku and Hokuriku, or the warmer districts, such as Kanto, Tokai, Kinki, Chugoku, Shikoku and Kyushu) due to concerns regarding differences in pathogens based on atmospheric temperature. The medications were sealed in uniform packets sequentially numbered according to the allocation table. The trial coordinator supplied the packets to the local administrators (physicians). The local administrators enrolled the participants and assigned them to interventions. The participants were instructed to open the packets after leaving the medical facility, and the group assignment was masked to the local administrators.

Interventions

The following two treatment groups were assessed: one group was to orally take Kakkonto (Kakkonto Extract-A; 2.0 g/pack, Kracie Pharma, Ltd., Tokyo, Japan) and the other group was to orally take multiple cold medicine (Pabron Gold-A; 1.2 g/pack, Taisho Pharmaceutical Co., Ltd., Tokyo, Japan). Both medicines can be purchased in a drug store without a doctor’s prescription.

The standard daily dose (6.0 g) of Kakkonto Extract-A used in this trial included 5.2 g of the essential components extracted from seven crude drugs: Japanese Pharmacopoeia (JP) Pueraia Root (Kakkon) 8.0 g, JP Ephedra Herb (Mao) 4.0 g, JP Jujube (Taiso) 4.0 g, JP Cinnamon Bark (Keihi) 3.0 g, JP Penoy Root (Syakuyaku) 3.0 g, JP Glycyrrhiza (Kanzo) 2.0 g, and JP Ginger (Shokyo) 1.0 g. Kakkonto Extract-A prepared with the amount specified above contains 12-36 mg of total alkaloids (ephedrine and pseudoephedrine), 21-84 mg of paconiflorin and 19-57 mg of glycyrrhizic acid. The details of each crude drug can be obtained on the website of the Japanese Pharmacopoeia (6). Kakkonto extracts have a characteristic odor and sweet, then hot and slightly bitter taste. Kakkonto extracts are generally taken three times a day before or between meals. Since Kakkonto Extract-A can be served in granules or tablets, we adopted a granular form in this trial.

The Western-type compound cold medicine, Pabron Gold-A, consisted of the following nine Western pharmacological agents in a standard daily dose of 3.6 g: dihydrocodeine phosphate 24 mg, dl-methyl ephedrine phosphate 60 mg,
guaiifenesin 125 mg, acetaminophen 900 mg, lysozyme hydrochloride 60 mg, carboxamine maleate 7.5 mg, absolute caffeine 75 mg, vitamin B1 derivative 24 mg and vitamin B2 12 mg. Pabron Gold-A is also available in granular form and is generally taken three times a day after meals.

As a rule of this trial, the participants took three packs of Kakkonto Extract-A or Pabron Gold-A (6 g and 3.6 g, respectively) a day for at most four days from entry. If their symptoms were alleviated before day 4, they were allowed to decrease the dose or discontinue the medication. On the other hand, if their symptoms worsened, they were allowed to consult a doctor and take other specific medications.

**Follow-up**

All participants were requested to complete a prescribed form (Cold Diary) every day from the onset of illness through day 7. This form included 14 cold complaints, such as nasal symptoms (rhinorrhea, nasal congestion and sneezing), pharyngeal symptoms (soreness and scratchiness), bronchial symptoms (cough and sputum) and other symptoms (fever, chills, headache, hoarseness, stiff shoulders, arthralgia or myalgia and general fatigue). Each symptom was classified into four grades, i.e., “none,” “mild,” “moderate” or “severe,” according to the Jackson method (7). “Mild” was defined as a symptom of which the participant was unaware while busy; “moderate” was defined as a symptom that always provoked discomfort; and “severe” was defined as a symptom causing difficulties in daily life. The participants also recorded body temperature, restriction of daily activities and their general physical condition every day. The restriction of daily activities had four grades: “none,” “partly restricted,” “considerably restricted” or “absent from duty.” The general physical condition was rated on a zero-to-10 scale: from zero (extremely bad) to 10 (extremely good). Each participant recorded the daily number of packs taken for the first four days.

The participants were required to revisit the medical facility one week later or after recovery to return the Cold Diary and unused drugs. If a participant did not make a second visit, then we telephoned him/her as a reminder.

**Outcomes**

The primary outcome of this study was the aggravation of cold symptoms within five days after entry into the study. We considered that the participants attained the primary endpoint when one of their nasal (runny or congested nose), throat (sore throat) or bronchial (cough or sputum) symptoms became moderate or severe for two consecutive days or more during the first five days after study entry. When a symptom was recorded on the first day as moderate in the Cold Diary, aggravation to a severe grade was considered to reach the primary endpoint. The secondary outcomes included aggravation of cold symptoms within seven days after study entry and the severity of the main cold symptoms during the first five and seven days. The severity of the main cold symptoms was assessed according to the sum of the nasal (runny or congested nose), throat (sore throat) and bronchial (cough or sputum) scores. Here, we replaced each symptom grade with numerical scores, i.e., “none” as 0, “mild” as 1, “moderate” as 2 and “severe” as 3.

**Statistical analysis**

We assumed that the occurrence of the primary outcome would be 54.5% in the Kakkonto group and 69.5% in the Pabron group based on a previous study (8). A power calculation indicated that a sample of 161 persons per group was required to detect intergroup differences, where the power was set at 0.90 and the α-error was set at 0.05.

We compared the baseline characteristics between the two groups using Student’s t-test or the Wilcoxon rank-sum test for continuous variables and Pearson’s chi-square test or Fisher’s exact test for categorical variables. The proportions of participants who colds were aggravated during the initial five and seven days in the two groups were evaluated using an analysis of Pearson’s chi-square test and multivariable logistic regression models. The sum of the main cold symptoms scores during the first five days and seven days was assessed using the Wilcoxon rank-sum test and multiple linear regression models. Multivariable analyses were constructed to control for potential confounding factors affecting the association between patient allocation and outcomes. The variables included in the multivariable model were age, gender, season (December 1 through March 31 or the remaining portion of the year), immediateness of the visit (within 24 hours or later), presence of herbal medicine-specific symptoms (stiff shoulders and chills) at baseline, the participant’s preference of study drugs (herbal medicine, Western medicine or no preference) and the severity of one of the initial nasal, throat or bronchial symptoms (mild or more). We also carried out a sensitivity analysis excluding participants who were eventually diagnosed with other diseases and stratified the analyses according to the existence of stiff shoulders and the preference of medicines using Fisher’s exact test and multivariable logistic regression models.

All analyses were performed on an intention-to-treat basis, in which we used all data including the primary outcome under the condition that the group assignment was masked to both the local administrators and data processors. We used the STATA 12.0 (STATA Corporation, College Station, USA) to perform the statistical analyses. All tests of significance were two-tailed, and p values of <0.05 were considered to be statistically significant.

**Results**

This study began on October 1, 2010 and ended on June 30, 2011 when a sufficient number of participants had been enrolled. Figure shows the participant flow of the study. A total of 410 candidates were recruited for this study. Excluding one participant who registered a second time and two participants who applied the randomization twice, 407 par-
participants were randomly assigned to receive *Kakkonto Extract-A* (the Kakkonto group, n=209) or *Pabron Gold-A* (the Pabron group, n=198). Of the 407 participants, 15 (11 in the Kakkonto group and four in the Pabron group) did not submit a Cold Diary. Fifty-two participants (30 in the Kakkonto group and 22 in the Pabron group) were excluded from the analysis because they documented in the diary that they had at least one severe local symptom at the first visit even though they reported that their overall illness was trifling at enrollment. Therefore, the remaining 340 participants (168 in the Kakkonto group and 172 in the Pabron group) were eligible for the analyses. The 52 participants who had submitted a diary but were excluded from the analysis were similar to the included participants in characteristics, e.g., age (26.9±8.53 years vs. 28.7±10.9 years, respectively \( p=0.25 \)) and drug preference (herbal medicine, Western medicine or none; 24.0%, 38.0% and 38.0% vs. 32.8%, 32.2% and 34.9%, respectively \( p=0.44 \)).

**Baseline characteristics**

Table 1 shows the baseline characteristics of the eligible participants. The mean age was 28 years, men were predominant in number and two-thirds of the participants were registered within 24 hours of indisposition in both the Kakkonto and Pabron groups. The selection of a drug preference between herbal and Western medicines was almost even, irrespective of the group assignment. The two groups were also similar with respect to the season of entry, timing of the office visit and prevalence of symptoms, except for stiff shoulders.

After the treatment of the cold in the early stage, no significant differences were found between the two groups in the doses of the study drugs taken during the first four days (8.12 packs in the Kakkonto group vs. 8.41 packs in the Pabron group, \( p=0.31 \)) or the proportion of participants who took other drugs (26.8% vs. 26.2%, \( p=0.90 \)) and those who were diagnosed with other diseases (2.4% vs. 1.7%, \( p=0.72 \)).

**Anti-aggravation outcomes**

Table 2 presents the main results of the current study. The proportion of participants whose colds were aggravated during the initial five days after entry was 22.6% in the Kakkonto group and 25.0% in the Pabron group, indicating no statistically significant differences (multivariable \( p=0.66 \)). These results were robust even when the same analysis was
Table 1. Baseline Characteristics of Participants in the Kakkonto and the Pabron Groups

<table>
<thead>
<tr>
<th></th>
<th>Kakkonto group n=168</th>
<th>Pabron group n=172</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>28.6 ± 10.6</td>
<td>28.8 ± 11.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Males</td>
<td>101 (60.1)</td>
<td>90 (52.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Entry from December through March</td>
<td>56 (33.7)</td>
<td>68 (39.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Visit within 24 hours</td>
<td>118 (71.5)</td>
<td>109 (63.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>Drug preference</td>
<td></td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>Herbal medicines</td>
<td>54 (32.8)</td>
<td>56 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Western medicines</td>
<td>48 (29.3)</td>
<td>60 (35.1)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>62 (37.8)</td>
<td>55 (32.2)</td>
<td></td>
</tr>
<tr>
<td>Influenza vaccination within one year</td>
<td>46 (27.5)</td>
<td>49 (28.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Influenza infection within one year</td>
<td>11 (6.6)</td>
<td>14 (8.1)</td>
<td>0.68</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11 (6.6)</td>
<td>7 (4.1)</td>
<td>0.34</td>
</tr>
<tr>
<td>Prevalence of symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>50 (30.1)</td>
<td>47 (27.8)</td>
<td>0.72</td>
</tr>
<tr>
<td>Stiff shoulders</td>
<td>71 (43.0)</td>
<td>54 (31.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Muscle or joint pain</td>
<td>33 (20.0)</td>
<td>25 (14.7)</td>
<td>0.25</td>
</tr>
<tr>
<td>Runny nose</td>
<td>114 (67.9)</td>
<td>114 (66.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>84 (50.0)</td>
<td>90 (52.3)</td>
<td>0.75</td>
</tr>
<tr>
<td>Sneezing</td>
<td>73 (44.0)</td>
<td>73 (43.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Sore throat</td>
<td>134 (79.8)</td>
<td>144 (83.7)</td>
<td>0.40</td>
</tr>
<tr>
<td>Scratchiness of throat</td>
<td>135 (81.3)</td>
<td>129 (75.9)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>57 (34.6)</td>
<td>73 (43.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Cough</td>
<td>75 (44.6)</td>
<td>79 (45.9)</td>
<td>0.83</td>
</tr>
<tr>
<td>Sputum</td>
<td>56 (33.3)</td>
<td>61 (35.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>Chills</td>
<td>92 (55.4)</td>
<td>98 (58.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Feverishness</td>
<td>63 (38.0)</td>
<td>63 (37.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>General malaise</td>
<td>88 (53.0)</td>
<td>84 (49.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Moderate grade in main symptoms severity*</td>
<td>64 (38.1)</td>
<td>52 (30.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Restriction of daily activities</td>
<td>49 (30.3)</td>
<td>45 (27.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>General physical condition, scored 0-10</td>
<td>6.44±2.05</td>
<td>6.45±2.16</td>
<td>0.83</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>36.6±0.40</td>
<td>36.6±0.38</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Values are expressed as number (percentage) or mean (± standard deviation). Percentage was calculated excluding missing data.

* The main cold symptoms consisted of nasal (running or congestion), throat (soreness) and bronchial (cough or sputum) symptoms.

Table 2. Aggravation and Severity of the Cold and Adverse Events according to Medications

<table>
<thead>
<tr>
<th></th>
<th>Kakkonto group n=168</th>
<th>Pabron group n=172</th>
<th>p value</th>
<th>Univariable analysis</th>
<th>Multivariable analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggravation of cold symptoms within 5 days†</td>
<td>38 (22.6)</td>
<td>43 (25.0)</td>
<td>0.61</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Aggravation of cold symptoms within 7 days†</td>
<td>41 (24.4)</td>
<td>52 (30.2)</td>
<td>0.23</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Sum of the main symptom scores during 5 days‡</td>
<td>9.9 ± 6.2</td>
<td>10.2 ± 6.1</td>
<td>0.69</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Sum of the main symptom scores during 7 days‡</td>
<td>12.1 ± 8.3</td>
<td>12.4 ± 8.0</td>
<td>0.63</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Adverse reactions§</td>
<td>7 (4.2)</td>
<td>12 (7.0)</td>
<td>0.35</td>
<td>0.42</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as number (percentage) or mean (± standard deviation).

*Adjusted for age, gender, immediateness of office visit, existence of stiff shoulders and chills at first visit, season of entry, drug preference, and severity of main symptoms (nasal, throat or bronchial discomfort) at first visit.

†Aggravation of cold was judged when one of the nasal (running or congestion), throat (soreness) or bronchial (cough or sputum) symptoms became moderate or severe on two consecutive days during the first 5 or 7 days. When a baseline symptom was recorded as moderate, aggravation to severe was regarded as the endpoint.

‡The main cold symptoms consisted of nasal (running or congestion), throat (soreness) and bronchial (cough or sputum) symptoms.

§Adverse reactions included dry mouth, gastrointestinal trouble, drowsiness or polyuria.
performed after excluding the participants who were eventually diagnosed with other diseases (21.3% and 24.9% in the Kakkonto and Pabron groups, respectively [multivariable \( p=0.43 \)). The proportion of participants whose colds were aggravated during the seven days after the entry was 24.4% in the Kakkonto group and 30.2% in the Pabron group (multivariable \( p=0.30 \)). The sum of the main cold symptom scores during the first five days and seven days also exhibited no significant differences between the groups (9.9 vs. 10.2 [multivariable \( p=0.52 \)) and 12.1 vs. 12.4 [multivariable \( p=0.57 \)), respectively.

None of the above analyses produced any statistically significant differences when the participants were stratified according to the existence of stiff shoulders or chills at the first visit. When limiting the analysis to those who visited a care facility within 24 hours of symptom onset, no statistically significant differences in the frequency of symptom aggravation were found between the groups. Moreover, even among those who prefer herbal medicines and those who prefer Western medicines, the study findings were unaltered (data not shown).

**Adverse reactions**

No harmful adverse events occurred in either group. The proportion of participants with adverse reactions, such as drowsiness or gastrointestinal troubles, was somewhat lower in the Kakkonto group, although the difference was statistically insignificant (4.2% vs. 7.0%, multivariable \( p=0.42 \)).

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**Discussion**

To the best of our knowledge, this randomized controlled trial is the first clinical study that attempted to prove the effectiveness of Kakkonto in treating the common cold. Our results indicate that Kakkonto did not surpass a representative Western-style multiple cold medicine with respect to cold suppression, even when taken in the early stage of disease. Considering the pharmacological actions of the control cold medicine, Kakkonto hardly prevented aggravation of the common cold.

The term “common cold” refers to virus-induced, relatively mild upper respiratory tract illnesses. Pathologically, they are catarrhal diseases without tissue destruction. Rhinoviruses are the most common pathogens, collectively causing 30-50% of colds. Coronavirus are the second most common pathogens, accounting for 10-15% of colds. Influenza viruses are estimated to cause 5-15% of cases, while unknown pathogens account for 20-30% (9).

Although there is no clinical evidence regarding whether Kakkonto compound or its seven ingredients are effective against colds, the antiviral and anti-inflammatory effects of both the entire Kakkonto compound and its ingredients have been repeatedly shown in animal and isolated cell experiments. Kurokawa et al. showed that Kakkonto suppresses the interleukin-1\( \beta \) produced by influenza virus infection in mice (10). Tanabe et al. reported that genistein, the principal ingredient of JP Pueraria Root (Kakkon) in Kakkonto, suppresses the leucocyte-derived neutrophil chemotactic factor-1 and -2 in an air pouch-type allergic inflammation model in rats (11). Ephedra Herb (Mao) is known to have an inhibitory effect against the growth of influenza A/PR/8/34 (H1N1) virus in Madin-Darby canine kidney cells (12). Glycyrrhiza species, an active component of Kanzo, has also been shown to exhibit antiviral effects in several animal studies. These components suppress the viral activity of herpes simplex virus-induced encephalitis and influenza A virus-induced pneumonia, yielding a subsequent reduction in mortality (13, 14). The antiviral activities of these components against HIV-1, several acute respiratory syndrome (SARS)-related coronavirus, respiratory syncytial virus, arboviruses, vaccinia virus and vesicular stomatitis virus have been demonstrated in in vitro studies (15). A polysaccharide fraction of Zizyphi fructus, Taiso, has also been proven to augment the activity of natural killer cells that recognize and attack virus-infected cells and tumor cells (16). In light of this evidence, Kakkonto is expected to reduce the cold virus activity and prevent cold symptom aggravation.

On the other hand, no pharmaceutical agent in Pabron Gold-A has either antiviral or anti-inflammatory effects, but rather simply alleviates cold symptoms. Dihydrocodeine phosphate is used for its antiinflammatory and sedative effects. Meanwhile, pseudoephedrine provides a decongestant effect (17). Two trials comparing guaifenesin with placebo have been conducted; one showed a reduction in coughing with guaifenesin, while the other did not (18). Acetaminophen reduces pharyngeal soreness and headaches (19, 20). Carboxinoxamine maleate exhibits an anti-histaminic effect against nasal symptoms (21). Absolute caffeine has also been reported to ease headaches more effectively than a placebo (22). To our knowledge, lyszyme hydrochloride, a vitamin B1 derivative, and vitamin B2 exert no remarkable alleviating effects on colds. Therefore, we deemed Pabron Gold-A to be a neutral agent for disease progression.

The most plausible explanation for the ineffectiveness of Kakkonto is its shortness of pharmacological actions in humans due to the low concentration of active components in herbs, different from that observed in industrially synthesized chemical components. In a study in mice, which revealed the effectiveness of Kakkonto against the early stage of influenza virus infection, Kakkonto was administered at more than eight times per body weight compared with the dose used in this study of humans (23). Indeed, a daily dose of 6.0-7.5 g of herbal medicines, which is twice or thrice as much as that used in Western medicines, is prescribed in clinical practice. Further studies using larger doses of herbs are needed to ensure their effectiveness.

Another possible reason why we failed to find differences in effects between Kakkonto and Pabron is that the respective drugs suppress cold symptoms in different ways. That is, Kakkonto exhibited antiviral and anti-inflammatory effects followed by the presentation of reduced cold symp-
toms, while Pabron directly suppressed cold symptoms. Anti-inflammatory actions may result in a delay in the recovery of the disease in exchange for the alleviation of severe symptoms, as suggested in our previous study (8). This phenomenon would override the anti-aggravation effects. Therefore, when taking a medicine at the early stage of a cold, the potential adverse effects (4.2% vs. 7.0%) and expense (210 yen/day vs. 120 yen/day, for Kakkonto and Pabron, respectively) rather than the overall effectiveness of these medicines should be considered.

The present study has some admitted limitations. First, we did not adopt a placebo-controlled design. It was quite difficult to prepare a placebo of Kakkonto with a similar appearance, smell and taste. Encapsulating a granule form of Kakkonto is inappropriate because herbal medicines can achieve outstanding effects through their distinctive pungent smells and tastes. Second, we evaluated only subjective outcomes. The common cold is originally a disease entity based on an individual’s subjective symptoms, and evidence of subjective symptoms is useful in the self-medication setting. Microbiological measurements are impractical to obtain in daily clinical routine practice. Nevertheless, we performed objective data processing by replacing the severity of cold symptoms with algebraic numerals and masking the group allocation to the analysts in this study. Third, we did not consider the herbal medicine-specific physical nature, “sho,” in Japanese. The only condition we considered at participant inclusion was the existence of sweating and chills, which is one of the most important signs of applicability when prescribing Kakkonto. Because this trial aimed to contribute to self-medication against colds among people in general, the use of close medical examinations was not warranted. However, if herbal medicine specialists had prescribed Kakkonto based on the strict herbal medicine-specific patient nature, the study results would have been different. In spite of the several limitations listed above, the findings of the current study provide interesting insight into self-medication against colds.

In conclusion, Kakkonto, one of the most popular Japanese herbal medicines, did not significantly prevent the progression of cold symptoms compared with a well-selected multiple cold medicine, even when prescribed at an early stage of the disease.

The authors state that they have no Conflict of Interest (COI).

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