Regular Article

Comparison of the Benefit Feeling Rate Based on the Sho of OTC Kakkonto, Cold Remedy and Cold Remedy with Kakkonto Combination Product

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Kakkonto (KK), a traditional Japanese Kampo formulation for cold and flu, is generally sold as an OTC pharmaceuticals used for self-medication. Kampo formulations should be used according to the Sho-symptoms of Kampo medicine. These symptoms refer to the subjective symptoms themselves. Although with OTC pharmaceuticals, this is often not the case. We surveyed the relationship of agreement of Sho with the benefit feeling rate (BFR) of patients who took KK (*n*=555), cold remedies with KK (CK, *n*=315), and general cold remedies (GC, *n*=539) using internet research. BFR of a faster recovery was greater in participants who took the medication early and who had confidence in their physical strength in all treatment groups. BFR was significantly higher in the GC group than in the KK group for patients with headache, runny nose, blocked nose, sneezing, and cough. BFR was also significantly higher in the GC group than in the CK group for headache (males) and cough (females). BFR was the highest in the KK group for stiff shoulders. All cold remedies were more effective when taken early, and the larger the number of Sho that a patient had, the greater the BFR increased. Therefore, a cold remedy is expected to be most effective when there are many cold symptoms and when it is taken at an early stage of the common cold.

Key words kakkonto; benefit feeling rate; internet survey; Sho; OTC pharmaceutical; cold remedy

Kakkonto is a traditional Japanese formulation mainly used for treating the common cold, which is available as prescription and OTC pharmaceuticals. Traditionally, kakkonto use in the early stages of the common cold is considered to be highly effective at preventing the condition from worsening. This effect was investigated by Okabayashi *et al.* in a multicentre, randomized controlled trial using the OTC general cold remedy, Pabron Gold-A®, as the control.[1)] The objective of the study was to investigate whether kakkonto is highly effective, subsequently resulting in self-medication by hospital patients and decreased burden on the hospital. Kakkonto was not found to be more effective than Pabron Gold-A®. In that study, however, "Sho" of kakkonto, was not considered in the subject selection criteria. Okabayashi *et al.* described their observations about a trial that involved select patients who were matched with the criteria of Sho, which would demonstrate that kakkonto is more effective than conventional remedies. In the package insert of ethical kakkonto, the indications and usage section states that it should be used by "persons who are comparatively physically fit, who have headache, fever, chills, and stiff shoulders, without spontaneous sweating." This constitution/symptom of a patient is known as Sho. The term Sho refers to a particular pathological status of a patient evaluated based on the Kampo diagnosis, and is patterned according to the patient's constitution, symptoms, among others.[2)] Terasawa defined Sho as follows: "Sho is described as being a diagnosis reached by recognizing the current symptoms of the patient through fundamental concepts such as qi, blood and fluid; yin and yang; deficiency and excess; cold and heat; exterior and interior; the five viscera; and six stage pattern, and then comprehensively diagnosis of symptoms that express the specific nature of the disease."[3)] Based on the concept of Sho, kakkonto is used for patients with yang pattern (headache, fever, chills, stiff shoulders) and excess pattern (comparatively physically fit).[4)]

Goda conducted a utilization survey of OTC Kampo formulations, and the results suggested that kakkonto may be highly effective in the early stages of the common cold.[5)] Goda's study was based on the evaluation by pharmacists and purchasers of medication on the effect of Kampo formulation sold by pharmacists in pharmacies. Goda expected to discover a correlation between conformance of the patient profile to Sho, and the medication effect. However, the pharmacists would only sell kakkonto to patients who were matched with Sho, so the study was reported as having limitations as a method for evaluating the relationship between Sho and efficacy.

On the other hand, many clinical studies have reported that other Kampo formulations are effective even when used without being overly concerned about Sho.[6–11)] For example, Fujiuchi *et al.* demonstrated that the effect of goshajinkigan on prostatic hyperplasia in patients who presented with a deficiency pattern, was not related to deficiency and excess.[6)]

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Ishii *et al.* noted that, when keishikashakuyakuto was used for deficiency patterns, it still had an adequate effect when prescribed for treating irritable bowel syndrome, without being concerned about Sho or the disease pattern.[7)]

Kakkonto is available as an OTC pharmaceutical for self-medication. There is also a combination product, which contains kakkonto and normal cold remedy components (*i.e.*, cold remedy with kakkonto, CK). However, no usage target has been described in the package insert of the CK corresponding to Sho, and the indications and usage simply states, "eases cold symptoms." Conversely, the indications and usage for OTC kakkonto are described as "the following various symptoms in people who have moderate or better physical strength: in the early stage of the common cold (with no sweating), head cold, rhinitis, headache, stiff shoulders, muscle pain, hand and/or shoulder pain," and these are considered to be the conditions for use. Sho is the collection or summation of each of these symptoms.[3)] When a patient has many of these symptoms, we consider the patient's status as that of Sho. We hypothesize that, as the number of symptoms that agree with Sho increases, an even higher efficacy will be achieved. We decided to investigate whether the effect of kakkonto, CK, and general cold remedy differed based on physical strength, the presence or absence of sweating, and the presence or absence of symptoms such as headache, fever, chills, and stiff shoulders. We conducted our study using internet research.

METHOD

Abbreviations Kakkonto is abbreviated as KK, cold remedy with kakkonto is abbreviated as CK, and general cold remedy is abbreviated as GC. However, the GC in this study was a product excluding CK, of the OTC pharmaceuticals that match the product classification, small classification "cold remedy (internal use)." Because CK is not classified as Kampo formulation for OTC classification in Ministry of Health, Labour and Welfare of Japan.[12,13)] In addition, all cold remedies, including KK, CK, and GC, were collectively abbreviated as CR.

Questionnaire Creation The question and response options are shown in Table 1.

The information gathered was as follows: Question 1: The respondent's confidence in his/her physical strength immediately before contracting the cold, Question 2: When the respondent began the medication, Question 3: Symptoms felt immediately prior to taking the medication, Question 4: Whether the respondent felt the cold was cured faster due to the medication, and Question 5: Which symptoms were eased by the medication? Questions 1 to 3 were questions relating to Sho, while questions 4 and 5 provided information on the respondents' subjective views of the medication's efficacy.

When answering question 3, respondents were given a list of items from the indications and usage in the package insert of a typical product, selected from several prescription KK, which are generally regarded as Sho.[14)] When answering question 5, respondents were given a list of symptoms taken from the indications list in a general OTC cold remedy package insert, plus the response of "stiff shoulders."

Questionnaire Survey We implemented the survey through internet research (Rakuten Research Inc., Company, Shinagawa, Tokyo, Japan). Respondents were registered monitors of Rakuten Research.

The respondents were men and women aged between 20 and 69 living in Japan. The survey was conducted from 22 October 2016 to 25 October 2016.

The survey results were formatted in a manner that did not enable identification of respondents. Additionally, we have previously conducted research using the same type of internet research.[15–19)]

Survey Responses and Data Analysis

The work flow from administration of the survey to analysis of the data is shown in Fig. 1.

First, we selected people who had taken KK, CK, or GC in the past year to treat a cold. Next, we prepared a list of 133 brand name CR products. The brand names were searched using the JAPIC Prescription/OTC Product Compendium Installation (July 2016 version), and the products were classified according to their components and content. We asked the respondents to select the product they took from a list of 86 KK product brand names and 47 CK product brand names, and the respondents were placed in the KK or CK groups, accordingly. Respondents who chose "none of the above" were placed in the GC group.

When the respondent's recollection of the KK brand name was vague, they were regarded as having taken KK if the brand name contained the term "kakkonto extract," written in Chinese, Katakana, or Hiragana characters. When the respondent's recollection of the CK brand name was vague, they were directed to answer the CK survey if they were confident they had received instructions for CK use from a pharmacist or registered sales clerk at the time of purchase. Respondents who had not taken KK or CK were directed to answer the GC survey.

Prior to implementing this survey, we thought it would be difficult to secure a sufficient number of people who had taken CK, so the response screen flow was constructed so that respondents who had taken both KK and CK products were directed to answer the CK survey. In the case that more than 300 respondents had taken only CK, we would extract the respondents who had taken CK only, and analyse the results.

Data Cleaning

In order to enhance the veracity of the data, we attempted to filter out any fake responses. Therefore, when the same response numbers were repeated in an unnatural sequence, such as "1, 2, 1, 2," they were visually examined by one of the researchers and excluded from analysis. Respondents who selected three or more KK or CK brand names were also excluded from analysis.

Statistical Analysis

Comparison of the Respondents' Gender and Age between the Three Types of CR

The proportion test of males and females in each CR group was conducted using the population proportion test. An analysis of variance was used for comparison of intergroup ages, and the Tukey method was used for multiple comparisons.

Medication Use Based on Sho

The chi-square test of independence was used to compare whether there was a difference in the response rate distribution on the selected option between the three groups, in the questions related to Sho, (Questions 1 to 3). If this test revealed a significant difference, a multiple comparison test was conducted with the Ryan method, and a multiple com-

Table 1. Questionnaire Items

	Kakkonto	Cold remedy with kakkonto	Cold remedy
Q1	Immediately before catching a cold did you feel confident about your physical strength?	Immediately before catching a cold did you feel confident about your physical strength?	Immediately before catching a cold did you feel confident about your physical strength?
	1 I felt confident about my physical strength†	1 I felt confident about my physical strength†	1 I felt confident about my physical strength†
	2 I felt slightly confident about my physical strength†	2 I felt slightly confident about my physical strength†	2 I felt slightly confident about my physical strength†
	3 Could not say either way	3 Could not say either way	3 Could not say either way
	4 I did not feel very confident about my physical strength	4 I did not feel very confident about my physical strength	4 I did not feel very confident about my physical strength
	5 I had no confidence in my physical strength	5 I had no confidence in my physical strength	5 I had no confidence in my physical strength
Q2	When did you start taking kakkonto?	When did you start taking the cold remedy with kakkonto?	When did you start taking the cold remedy?
	1 As soon as the symptoms appeared (first stage of the cold)†	1 As soon as the symptoms appeared (first stage of the cold)†	1 As soon as the symptoms appeared (first stage of the cold)†
	2 Once the symptoms were quite strong (middle stage of the cold)	2 Once the symptoms were quite strong (middle stage of the cold)	2 Once the symptoms were quite strong (middle stage of the cold)
	3 Once the symptoms started to ease and the cold was starting to clear (end stage of the cold)	3 Once the symptoms started to ease and the cold was starting to clear (end stage of the cold)	3 Once the symptoms started to ease and the cold was starting to clear (end stage of the cold)
Q3	Did you have any of the following symptoms immediately before starting kakkonto?	Did you have any of the following symptoms immediately before starting cold remedy with kakkonto?	Did you have any of the following symptoms immediately before starting the cold remedy?
	Please choose all applicable answers.	Please choose all applicable answers.	Please choose all applicable answers.
	1 Sweating	1 Sweating	1 Sweating
	2 Fever	2 Fever	2 Fever
	3 Headache	3 Headache	3 Headache
	4 Feeling cold	4 Feeling cold	4 Feeling cold
	5 Stiff shoulders	5 Stiff shoulders	5 Stiff shoulders
	6 None of the above	6 None of the above	6 None of the above
Q4	This question is regarding whether you think taking kakkonto cured your cold faster.	This question is regarding whether you think taking cold remedy with kakkonto cured your cold faster.	This question is regarding whether you think taking the cold remedy cured your cold faster.
	Please imagine if you had not taken kakkonto.	Please imagine if you had not taken cold remedy with kakkonto.	Please imagine if you had not taken cold remedy.
	Do you think that your cold was cured faster by taking kakkonto?	Do you think that your cold was cured faster by taking the cold remedy with kakkonto?	Do you think that your cold was cured faster by taking the cold remedy?
	1 It was cured much faster†	1 It was cured much faster†	1 It was cured much faster†
	2 It was cured faster†	2 It was cured faster†	2 It was cured faster†
	3 The kakkonto made no difference	3 The cold remedy with kakkonto made no difference	3 The cold remedy made no difference
	4 It was cured slower	4 It was cured slower	4 It was cured slower
	5 It was cured much slower	5 It was cured much slower	5 It was cured much slower
Q5	Which of the following cold symptoms do you feel were eased due to kakkonto?	Which of the following cold symptoms do you feel were eased due to the cold remedy with kakkonto?	Which of the following cold symptoms do you feel were eased due to the cold remedy?
	1 Fever	1 Fever	1 Fever
	2 Headache	2 Headache	2 Headache
	3 Chills	3 Chills	3 Chills
	4 Stiff shoulders	4 Stiff shoulders	4 Stiff shoulders
	5 Runny nose	5 Runny nose	5 Runny nose
	6 Blocked nose	6 Blocked nose	6 Blocked nose
	7 Sneezing	7 Sneezing	7 Sneezing
	8 Sore throat	8 Sore throat	8 Sore throat
	9 Cough	9 Cough	9 Cough
	10 Sputum	10 Sputum	10 Sputum
	11 Muscle pain	11 Muscle pain	11 Muscle pain
	12 Joint pain	12 Joint pain	12 Joint pain
	1 Very effective. † 2 Effective.† 3 Slightly effective.† 4 Not effective. 5 Worsened. 6 Did not have any of these symptoms.	1 Very effective. † 2 Effective.† 3 Slightly effective.† 4 Not effective. 5 Worsened. 6 Did not have any of these symptoms.	1 Very effective. † 2 Effective.† 3 Slightly effective.† 4 Not effective. 5 Worsened. 6 Did not have any of these symptoms.

†Items used for ratio tests.

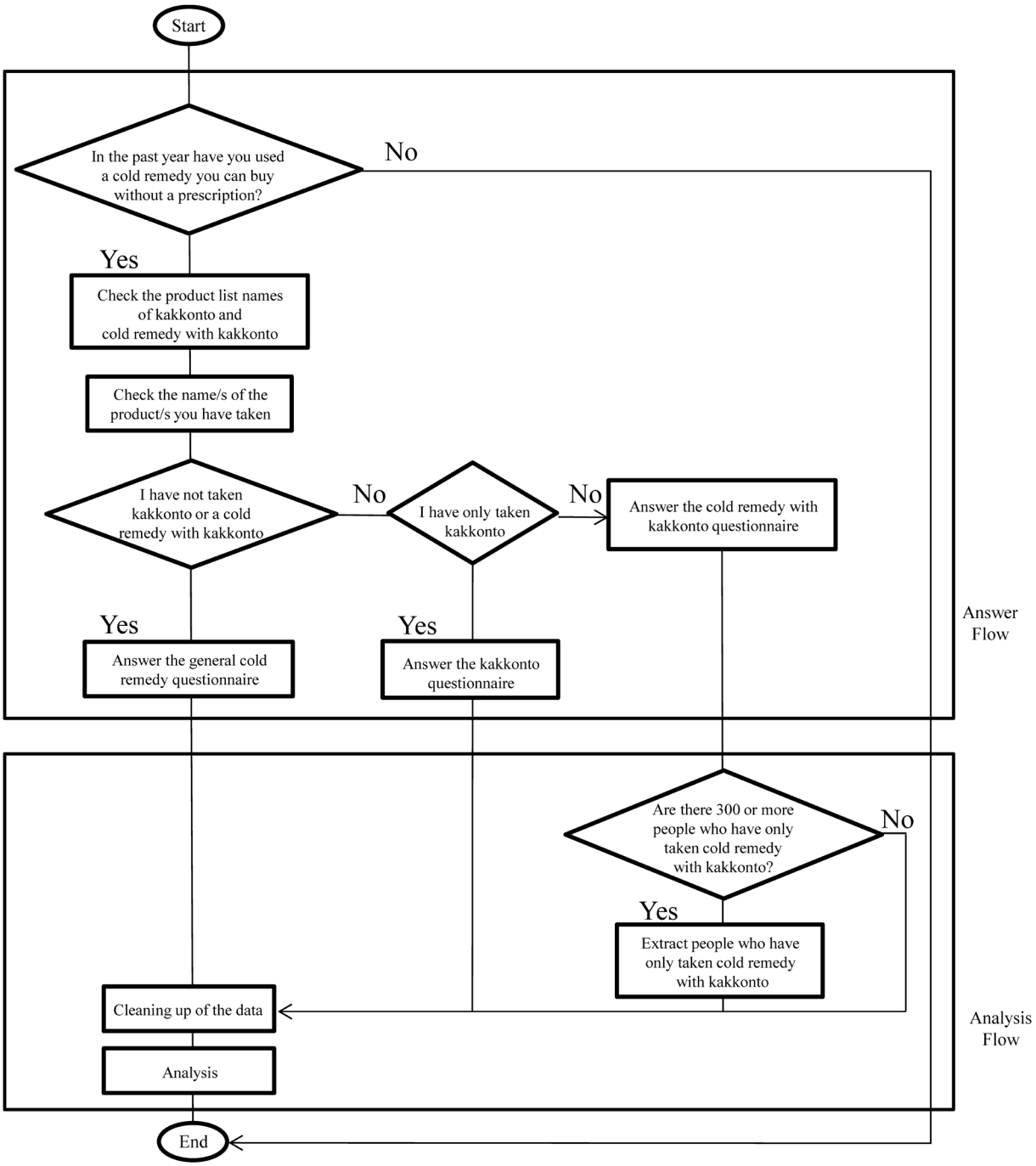

Fig. 1. Schematic Describing the Process from Survey to Analysis

parison was conducted for the proportion difference test with the Holm method, using the total response rate for items marked with "†" in Table 1. In other words, we conducted a multiple comparison test among the three groups, looking at the proportion of respondents with confidence in their physical strength (Question 1, options 1 and 2), and the proportion of people who took the medication at an early stage of the cold (Question 2, option 1). For Question 3 we used the chi-square test of independence for the presence or absence of each symptom (listed in options 1–6) and conducted multiple comparisons applying the Ryan and Holm methods. However, with regard to "sweating" in Question 3, the Sho for kakkonto is "no sweating," so the proportion of respondents who included "sweating" in their response were deducted from 1 to give the proportion who experienced "no sweating." The analysis was conducted using the "no sweating" ratio.

Comparing the Benefit Feeling Rate (BFR) of the Three Types of CR

The total response rate for items in Question 4 and Question 5 marked with "†" is the efficacy rate as felt by the patients, named the "benefit feeling rate (BFR)." To compare the BFR of the three types of CR we conducted a chi-square test of independence in the same manner as described above, and applied the Ryan and Holm methods to conduct multiple comparisons of BFR.

Comparing the BFR of the Three Types of CR Based on Respondent's Confidence of Physical Strength

To compare BFR, based on physical strength before con-

tracting the cold in the three groups, with the efficacy of hastening recovery (Question 4), the persons with confidence in their physical strength and persons without confidence in their physical strength obtained from Question 1 were ranked on an ordinal scale of 1–5, or BFR decimal places were rounded up and ranked on a 100-scale ordinal scale, and then the rank correlation coefficient and regression formula were calculated.

Comparing the BFR Based on the Timing of Taking the Three Types of CR and the Presence or Absence of Sho

To investigate the efficacy of when the medication was administered in each CR group, we compared the timing of the medication in Question 2 with the BFR in Question 4. However, few respondents had taken medication in the late stages of the cold; therefore, the proportional difference was determined based on whether the respondent took the medication at an early or middle stage. We also determined the proportional difference of BFR based on the presence or absence of each Sho listed in Question 3.

Sho That Tends to Respond to the Three Types of CR

A partition analysis was conducted to extract the Sho of patients who felt a stronger efficacy of KK, CK, and GC. When doing so, physical strength (1–5) and timing of taking medication (1–3) were put on an ordinal scale, while each of the symptoms immediately before taking the medication in Question 3 were put on the nominal scale; these were set as the explanatory variables. Selection options 1 and 2 of Question 4 were summarised and set as 1, and all others were set as 2; these were set as the objective variables. JMP®5.1.2 (SAS Institute Japan) was used for partition analysis.

A p value of less than 0.05 was deemed to be significant. When there was a significant difference in both the Ryan and Holm methods or in the Holm method alone, the Holm method was adopted. An asterisk was placed next to a p value when the significant difference was seen only with the Ryan method.

Other than partition analysis, all analyses were computed using the R Project for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We received responses from 1976 people, of whom 700 took KK, 676 took CK, and 600 took GC. After eliminating ineligible surveys, there remained 555 respondents (males: 335, females: 220) in the KK group, 573 in the CK group, and 539 (males: 330, females: 209) in the GC group. Three-hundred and fifteen of the CK respondents had taken only CK, and as this figure exceeded 300, we did not use the responses of people who had used both KK and CK, leaving 315 respondents (males: 219, females: 96) in the CK group, while the other groups remained the same.

The proportion of male respondents was higher for all three types of CR, and the proportion of male respondents for CK was significantly higher than that of KK or GC (CK>KK: $p=0.026$, CK>GC: $p=0.036$, data not shown). There was no significant difference among the three groups in age distribution ($p=0.6346$, data not shown). There was also no significant difference between male and female respondents in terms of age distribution (males: $p=0.53$, females: $p=0.69$, data not shown). Given that there was a significant difference in the proportion of male and female respondents for the three types of CR. In epidemiological studies, differences in age and sex can easily cause bias in the results of the efficacy of a drug. Therefore, in order to eliminate bias when evaluating BFR of Kakkonto data from male and female respondents were analysed separately. A summary of the response data is shown in Table S1 (males) and Table S2 (females).

Taking Medication Based on Sho To investigate whether KK and CK were taken due to Sho, we compared the response rate distribution on the selected option among the three types of CR for the questions relating to Sho (Questions 1 to 3). The Sho that showed a significant difference among the groups are shown in Table 2.

The percentage of people who felt confident in their physical strength immediately before contracting the cold in Question 1 was significantly higher for male respondents who took CK and KK compared to that reported for GC.

Female respondents tended to take KK at an earlier stage than they took CK ($p=0.003$) or GC ($p=0.001$) in Question 2, regarding the timing of taking medication. However, this tendency was not seen with male respondents.

A higher percentage of female respondents who did not sweat but took GC rather than KK ($p=0.008$) or CK ($p=0.001$) was observed in Question 3 regarding Sho. There was a higher percentage of female respondents who had fever and took CK ($p=0.024$) or GC ($p=0.024$) rather than KK. There was a higher percentage of both male and female respondents with stiff shoulders who took KK rather than GC ($p=0.008$ males; $p=0.004$ females), and more female respondents took CK than GC ($p=0.046$). There was a higher percentage of male respondents who selected, "Nothing Applicable," who had taken CK and GC rather than KK ($p=0.019$,

Table 2. Comparison of Prevalence of Sho among Cold Remedies (CRs, Only Sho with Significant Differences Are Shown)

	Question No./item		Multiple comparison (p value)		
			KK *vs.* CK	KK *vs.* GC	CK *vs.* GC
1	Percentage of people who felt physically strong	Male	N.S.	KK>GC (0.023)	CK>GC (0.001)
2	Percentage of people who took the medication at an early stage	Female	KK>CK (0.003)	KK>GC (0.001)	N.S.
3	Percentage of people without sweating	Male	N.S.	GC>KK (0.008)	GC>CK (0.001)
3	Percentage of people with fever	Female	CK>KK (0.024)	GC>KK (0.024)	N.S.
3	Percentage of people with stiff shoulders	Male	N.S.	KK>GC (0.008)	N.S.
		Female	N.S.	KK>GC (0.004)	CK>GC (0.046)
3	Percentage of people who selected "None of the above"	Male	CK>KK (0.019*)	GC>KK (p>0.001)	N.S.
		Female	N.S.	GC>KK (0.024)	GC>CK (0.006)

KK: kakkonto, CK: cold remedy with kakkonto, GC: general cold remedy. * The significant difference was seen only with the Ryan method.

p=0.01, respectively), while with these female respondents, there was a higher percentage who had taken GC rather than KK or CK (p=0.024, p=0.006, respectively).

There were no significant differences among the three types of CR in terms of the percentage of people with headache and chills who had taken them.

Comparison of BFR Due to the Three Types of CR There was no significant difference in BFR among the three types of CR in the length of time it took to recover (Question 4). The items in Question 5 (GC indications and usage and stiff shoulders) where there was a significant difference in BFR are shown in Table 3. There were significant differences in the improvement of the following symptoms. Headache (males): GC>KK, GC>CK; headache (females):

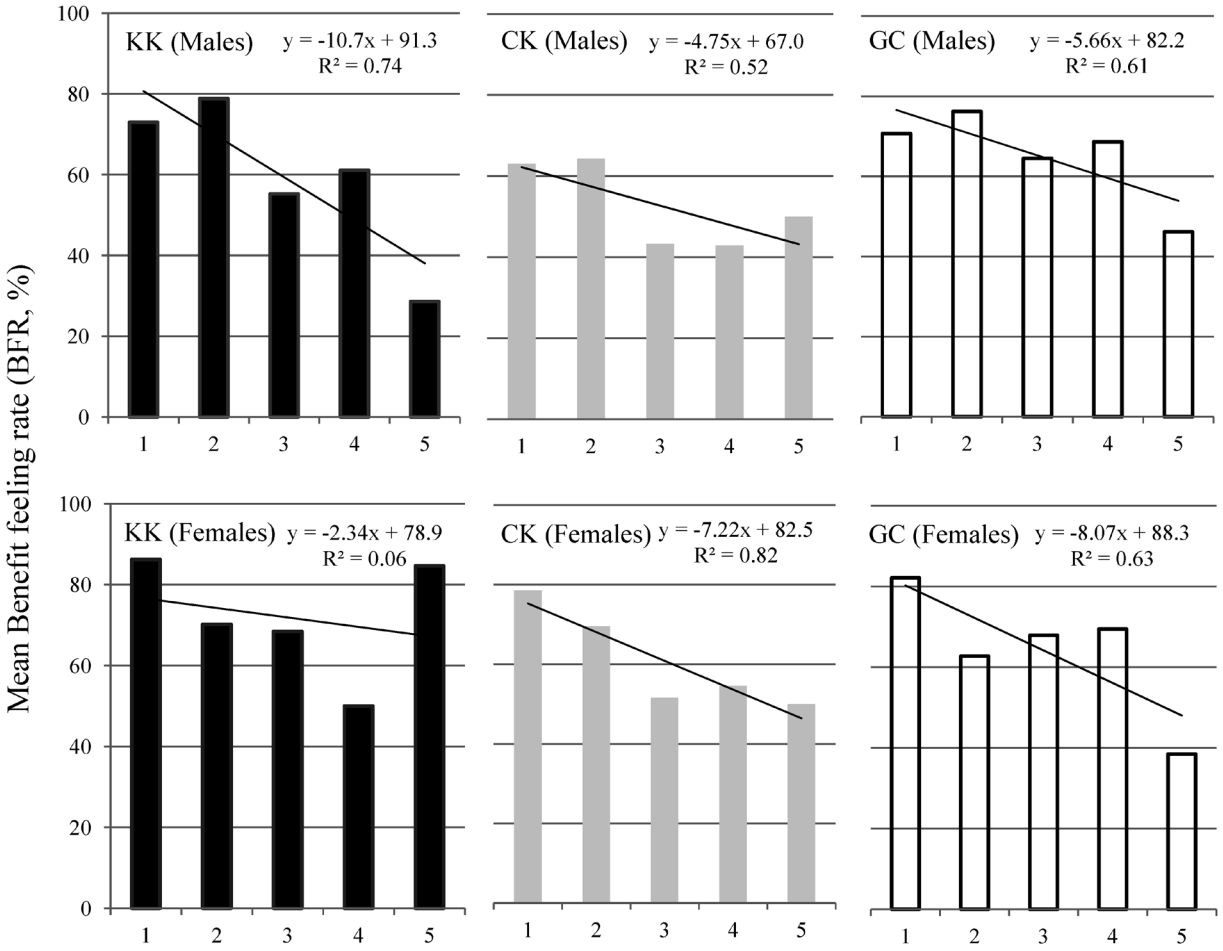

Fig. 2. Speed of Cold Recovery (Benefit Feeling, BFR) and Correlation with Physical Strength

1 I felt confident about my physical strength. 2 I felt slightly confident about my physical strength. 3 Could not say either way. 4 I did not feel very confident about my physical strength. 5 I had no confidence in my physical strength. KK: kakkonto, CK: cold remedy with kakkonto, GC: general cold remedy.

Table 3. Patient Feeling about Cold Remedy (CR) Efficacy (Question 5)

Question		Multiple comparison (p value)		
		KK *vs.* CK	KK *vs.* GC	CK *vs.* GC
Percentage of people who found it effective for headache	Male	N.S.	GC>KK (0.015)	GC>CK (0.017)
	Female	N.S.	GC>KK (0.031)	N.S.
Percentage of people who found it effective for stiff shoulders	Female	KK>CK (0.017*)	KK>GC (0.001)	N.S.
Percentage of people who found it effective for runny nose	Male	N.S.	GC>KK (p>0.001)	N.S.
	Female	N.S.	GC>KK (0.004)	N.S.
Percentage of people who found it effective for blocked nose	Male	N.S.	GC>KK (0.032)	N.S.
	Female	N.S.	GC>KK (0.002)	N.S.
Percentage of people who found it effective for sneezing	Male	N.S.	GC>KK (0.004)	N.S.
	Female	N.S.	GC>KK (0.013*)	N.S.
Percentage of people who found it effective for cough	Male	N.S.	GC>KK (0.001)	GC>CK (0.025)
	Female	N.S.	GC>KK (0.007)	N.S.
Percentage of people who found it effective for sputum	Female	CK>KK (0.033*)	GC>KK (0.004)	N.S.

KK: kakkonto, CK: cold remedy with kakkonto, GC: general cold remedy. *The significant difference was seen only with the Ryan method.

GC>KK; stiff shoulders (females): KK>CK, KK>GC; runny nose (males and females): GC>KK; blocked nose (males and females): GC>KK; sneezing (males and females): GC>KK; cough (males): GC>KK, GC>CK; cough (females): GC>KK; and sputum (females): CK>KK, GC>KK. There was no significant difference among the treatment groups in both male and female respondents for fever, sore throat, chills, muscle pain, and joint pain.

Comparing the BFR of Three Types of CR Based on Physical Strength before Contracting the Cold Figure 2 shows the speed of cold recovery based on physical strength. Cold recovery tended to be faster in all treatment groups when the medication was taken at an early stage and when the person had higher levels of confidence in their physical strength. Particularly, in male respondents who took KK, the absolute value of the rank correlation coefficient was large, which suggests that the influence of physical strength on BFR is significant.

Comparing the BFR of Three Types of CR Based on the Timing of Taking Medication and the Presence or Absence of Sho BFR was higher for all CR in both male and female respondents when the medication was taken at an early stage rather than at the middle stage (Table 4). However, there was a significant difference for male respondents who took KK and GC, while the BFR of GC in female respondents tended to be higher when taken at an early stage.

To investigate whether the presence or absence of Sho affected the speed of cold recovery, we compared BFR for speed of cold recovery based on the presence or absence of Sho (Table 5). BFR was significantly higher in respondents who selected "No" for "nothing applicable" in Question 3 for KK (males), CK (males), and GC (females), so it is thought that the possession of at least one Sho increases BFR. In terms of individual Sho, the BFR was much greater with KK (females) for chills and no headache, with CK (males) for fever, and with GC (males) for chills.

Sho Elicited Efficacy with the Three Types of CR The results of partition analysis are shown in Table 6. In males taking KK, suitable conditions for increasing BFR were feeling confident in their physical strength before contracting the

Table 4. Effect of Timing of Starting Medication on Speed of Recovery (Benefit Feeling Rate, BFR)

	KK			CK			GC		
	Early stage	Middle stage	*p* Value	Early stage	Middle stage	*p* Value	Early stage	Middle stage	*p* Value
Male	0.707	0.560	0.012	0.572	0.538	0.629	0.743	0.553	0.001
Female	0.679	0.611	0.427	0.641	0.531	0.302	0.711	0.582	0.064

KK: kakkonto, CK: cold remedy with kakkonto, GC: general cold remedy.

Table 5. Influence of Presence or Absence of Sho on Benefit Feeling Rate (BFR, Only Sho with Significantly Different Results Are Shown)

KK male		KK female		CK male		GC male		GC female	
Nothing applicable $p<0.001$		Headache $p=0.011$		Fever $p=0.014$		Feeling cold $p=0.03$		Nothing applicable $p<0.001$	
Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
0.345 ($n=29$)	0.686 ($n=306$)	0.580 ($n=88$)	0.727 ($n=132$)	0.635 ($n=104$)	0.487 ($n=115$)	0.758 ($n=157$)	0.619 ($n=173$)	0.071 ($n=56$)	0.686 ($n=153$)
		Feeling cold $p=0.020$		Nothing applicable $p=0.008$					
		Yes	No	Yes	No				
		0.727 ($n=121$)	0.596 ($n=99$)	0.364 ($n=33$)	0.591 ($n=186$)				

KK: kakkonto, CK: cold remedy with kakkonto, GC: general cold remedy.

Table 6. Sho Conditions That Increased Benefit Feeling Rate (BFR)

KK male			CK male			GC male		
Conditions	*n*	BFR	Conditions	*n*	BFR	Conditions	*n*	BFR
None	335	0.666	None	219	0.557	None	330	0.685
Q1=1, 2	178	0.764	Q1=1, 2	130	0.639	Q2=1, 3	227	0.745
Q3 (6)=0	165	0.794	Q3 (6)=0	113	0.681	Q1=1, 2	95	0.832
KK female			CK female			GC female		
Conditions	*n*	BFR	Conditions	*n*	BFR	Conditions	*n*	BFR
None	220	0.669	None	96	0.604	None	209	0.670
Q1=1, 2, 3, 5	156	0.737	Q1=1, 2	37	0.730	Q1=1, 2, 3, 4	196	0.689
Q3 (4)=1	85	0.824	Q3 (3)=1	16	0.938	Q2=1	134	0.731

KK: kakkonto, CK: cold remedy with kakkonto, GC: general cold remedy.

cold (Q1=1, 2), and adding the expression at least one of Sho listed in Q3 to the condition. There were 178 respondents who felt physically strong immediately before contracting the cold, and the BFR for these respondents was 0.764, while males who had added any of the Sho listed in Question 3 to the condition, had their BFR increased even more to 0.794. The 335 men, who took KK, had an average BFR of 0.666.

An increase in BFR based on similar conditions was also seen in males taking CK, but the BFR value was lower than that of the KK group. In females taking KK, BFR was high in respondents with chills (Q3 (4)=1), while with CK (females), respondents with physical strength who added headache to the condition had high BFR (0.938), although there were only a few respondents with these conditions (n=16). With GC both males and females demonstrated high BFR when the medication was taken at an early stage of the cold (Q2=1). Conversely, there were no factors that increased the BFR among the symptoms corresponding to Sho in Q3.

DISCUSSION

The items that produced a significant difference in KK compared to that of GC in male or female respondents, who had at least one Sho when they took the medication (Table 2), were as follows: having confidence in their physical strength (males), taking the medication at an early stage of the common cold (females), and having stiff shoulders (males and females). Based on this information, people should be aware that these three Sho are targeted when using kakkonto. However, the percentage of people with no sweating, fever, headache, or chills who took KK was not higher than of those who took CK or GC, so these Sho are not targets when selecting KK. Similarly, with CK there was a significant difference in two Sho, namely having physical strength (males) and having stiff shoulders (females) compared to GC, but we think that there was less consideration of Sho for CK compared to KK.

In a simple comparison of the BFR of recovery speed (Q4) with the three types of CR, there were no significant differences. However the BFR for symptoms recovery in GC, which was significantly higher than KK (Table 3), were as follows: headache (males and females), runny nose (males and females), blocked nose (males and females), sneezing (males and females), cough (males and females), and sputum (females). Only the BFR for stiff shoulder (females) in KK was significantly higher than GC and CK. This result may be due to the direct effect of active ingredients contained in GCs (*i.e.*, analgesics, antihistamines, nasal vasoconstrictors, antitussives, and expectorants). It is unlikely that KK could exceed BFR of GC when KK has none of these components added. On the other hand, while CK was inferior to GC for headache (males) and cough (females), there were no significant differences with the BFR for other symptoms. This result may be due to CK containing some active ingredients that provide symptomatic treatment, although in smaller quantities than GC.[11] CK is a combination of GC and KK, but compared to the maximum amount of components normally contained in GC, the amount of the same components that could be contained in CK must be subtracted by the amount of KK components contained in the medication, which may mean that these components have a similar but weaker effect than that of GC.[11]

Generally, KK is thought to have a stronger effect in people with higher levels of physical strength, and the results of this study are consistent with that assumption (Fig. 2, Table 5 (KK male)). However, Fig. 2 demonstrates that the greater a person's physical strength when they take the medication, the greater the BFR of CR in general, not just KK. In addition, it may not necessarily be the case that the BFR on people with physical strength is high with KK, rather it may be that the BFR of KK is low for people with no physical strength. Thus, it is essential to consider a person's physical strength when recommending KK use. Furthermore, while there was a greater BFR when KK was taken at an early stage, taking GC at an early stage also had a greater BFR (Table 4), so taking the medication at an early stage may be a common principle for cold remedies. While the possession of at least one Sho was a factor in increasing the efficacy of CR, the higher the number of Sho matches the more the BFR tended to increase (Table 7). Therefore, the more cold symptoms that are present, the greater the efficacy that is felt.

In this study, we evaluated the efficacy of the three types of CR on the BFR, which is the subjective view of the user. In addition, the evaluation of KK based on Sho was expanded to CK and GC. We adopted this method since the effect of Kampo formulations is considered to be based on the patient's subjective symptoms,[20] and we wanted to evaluate whether the efficacy of KK truly increased based on Sho, using CK and GC as the controls. Recently, there has been permeation of the concept of patient-focused medical care, and the im-

Table 7. Correlation between the Number of Sho Matches and the Benefit Feeling Rate (BFR)

Number of Sho matches		1	2	3	4	5	6	7	8
KK male	Total	18	93	124	78	19	2	1	0
	BFR	0.222	0.581	0.702	0.782	0.842	0.500	0	—
KK female	Total	4	81	87	40	6	2	0	0
	BFR	0.250	0.600	0.700	0.730	1	0.500	—	—
CK male	Total	13	70	76	44	14	2	0	0
	BFR	0.231	0.457	0.618	0.727	0.571	0	—	—
CK female	Total	6	32	39	10	6	3	0	0
	BFR	0.333	0.563	0.590	0.800	0.667	1	—	—
GC male	Total	19	117	136	48	8	2	0	0
	BFR	0.579	0.615	0.713	0.750	1	1	—	—
GC female	Total	17	84	76	20	12	0	0	0
	BFR	0.647	0.571	0.737	0.750	0.833	—	—	—

KK: kakkonto, CK: cold remedy with kakkonto, GC: general cold remedy.

portance of Patient Reported Outcomes has been indicated.[21] Thus, when evaluating OTC pharmaceuticals typified by Kampo formulations, we felt that use of internet research would be effective due to the ability to collect subjective data about the experiences of a large number of unique individuals in a short time.

CONCLUSION

We investigated the subjective efficacy on people who took KK, CK, and GC, using internet research. We found that GC got beneficial patient feeling more than KK for treating the cold symptoms of headache, runny nose, blocked nose, sneezing, cough, and sputum, and CK did not get beneficial patient feeling more than GC for treating those of headache and cough. With all CR, there was greater BFR in people who took the medication during the early stage of the cold and in people with physical strength. With all CR, the BFR increased as the number of matched Sho increased.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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