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【 ORIGINAL ARTICLE 】

Outpatient Prescriptions of Kampo Formulations in Japan

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Abstract:

Objective Kampo is a traditional Japanese medicine using formulae of natural agents. Although Kampo is widely practiced, information regarding the current prescriptions of Kampo formulations is lacking. The aim of the study was to describe the outpatient use of Kampo formulations in the current Japanese health insurance system.

Methods From the JMDC Claims Database, we identified subscribers with outpatient prescriptions of Kampo extract formulations between April 2017 and March 2018. Prescription records were summarized at the individual level to describe the pattern of each formula's use, such as the frequency of prescription and the number of days within a year that were covered by the prescriptions. We also examined whether or not Kampo formulations were prescribed in combination with other drugs.

Results Of the 4.5 million subscribers, 13.5% received prescriptions of Kampo extracts within 1 year, and 54% of Kampo users were women. The most commonly prescribed Kampo formulae included kakkonto, shoseiryuto, and maoto, which were used for the short term covering a median of 5 to 7 days. There were also several formulae that were prescribed for longer periods. The median numbers of days covered by kamishoyosan and keishibukuryogan were 60 and 56, respectively. Kampo formulations were used in combination with Western drugs in 85% of prescriptions.

Conclusion Kampo formulations are commonly prescribed under the Japanese insurance system and are frequently used in combination with Western drugs. The pattern of prescriptions varied across different formulae.

Key words: Kampo, traditional medicine, outpatient, database

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Introduction

Kampo is a traditional Japanese medicine characterized by a diagnosis based on a pattern of symptoms and treatment with a formula of natural agents (1-3). Following the introduction of Chinese medicine in the 6th century, Kampo medicine developed independently in Japan. With Westernization led by the government in the late 19th century, disciplines of Western medicine prevailed. However, Kampo medicine later reemerged and was integrated into the Japanese healthcare system. In 1967, Kampo products were first approved for coverage by national health insurance (3). The current health insurance system covers Kampo products for prescription, available as both herbs for decoction and extract formulations.

Clinical studies have shown the efficacy of Kampo formulae in treating different conditions (2, 4). Among the reported evidence are daikenchuto for constipation and ileus (5, 6), yokukansan for behavioral and psychological symptoms of dementia (7), hangeshasinto for chemotherapy-induced diarrhea (8), and saibokuto for bronchial asthma (9). The majority of randomized controlled trials were small and based on a diagnosis by Western medicine (2). In addition to the clinical trials, large-scale observational studies using administrative databases have been conducted recently and provided real-world evidence of the effects of Kampo formulae (10-14).

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According to survey studies in Japan, more than 80% of physicians use Kampo products in daily practice (15, 16). However, despite their efficacy and widespread use, the basic details regarding the current prescription patterns of Kampo formulae have rarely been investigated. A study using sampled claims data reported that Kampo products accounted for 1.3% of the total number of prescriptions, and shakuyakukanzoto was the most frequently prescribed formula (17). However, further information, such as the frequency with which different Kampo formulae are used, the number of days covered by prescriptions, and the status of co-administration with Western drugs, is lacking.

Therefore, using a large-scale database of health insurance claims, we conducted a study to investigate the outpatient prescriptions of Kampo formulations in the current Japanese insurance system.

Materials and Methods

Data source

For this study, we used the JMDC Claims Database (JMDC, Tokyo, Japan), a database of health insurance claims and health examination results in Japan. The database stores anonymous data provided by employer health insurance groups. Subscriber information included sex, year and month of birth, and the period over which the data were obtained. All monthly medical claims data of outpatient, inpatient and pharmacy services that are covered by health insurance are recorded in the database. This includes diagnoses, consultations, drugs, and procedures. Diagnoses are recorded based on the International Classification of Diseases 10th Revision (ICD-10) codes and the Japanese standardized diagnosis codes. Information on whether or not the diagnosis was considered the main diagnosis and whether the diagnosis was suspected or confirmed is also recorded. Drugs are classified according to the Anatomical Therapeutic Chemical Classification System (ATC) and the Japanese code for reimbursement.

Participants

Using the data from the JMDC Claims Database, we first identified subscribers who were under observation for the entire 12-month period from April 2017 to March 2018. We then identified patients with outpatient prescriptions of Kampo extract formulations (148 in total). Patients who received herbs for decoction during the 12-month period were excluded. We also excluded patients with missing data on the day of prescription of Kampo formulations and patients who received multiple prescriptions of the same formulation in a single day.

Patient-level analyses

Sex, age as of April 2017, and diagnoses were identified for each patient. Age was categorized into <20, 20-39, 40-59, and ≥60 years old. Diagnoses were extracted from those recorded between April 2017 and March 2018 as a confirmed main diagnosis. Based on the ICD-10 classification, the diagnoses were categorized into infectious and parasitic (A00-B99), neoplasms (C00-D48), blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89), endocrine, nutritional and metabolic (E00-E90), mental and behavioral (F00-F99), nervous system (G00-G99), eye and adnexa (H00-H59), ear and mastoid process (H60-H95), circulatory system (I00-I99), respiratory system (J00-J99), digestive system (K00-K93), skin and subcutaneous tissue (L00-L99), musculoskeletal system and connective tissue (M00-M99), and genitourinary system (N00-N99). We summarized the sex, age, and diagnoses of patients receiving each Kampo formula. Patient characteristics were compared with the entire group of subscribers who were under observation from April 2017 to March 2018 in the database.

Prescription records were summarized at an individual level to calculate the frequency of prescription, the average number of days covered by one prescription, and the number days within one year that were covered. We also calculated the proportion of days covered between the day of the first prescription and March 31, 2018. Summary statistics were presented as medians and interquartile ranges.

Prescription-level analyses

We obtained data on the outpatient prescription provided to each patient on the same day that the Kampo extract formulations were prescribed. For each day of prescription containing Kampo formulations, we identified whether Kampo formulations were prescribed alone or in combination with other drugs (Kampo or Western). Finally, for each formula, we identified the first- and second-most frequently co-administered Western drugs.

Results

A flowchart of patient selection is presented in Figure. We identified 4,525,519 subscribers who were under observation for the 12-month period. There were 611,451 subscribers (13.5%) who received at least 1 prescription of Kampo extract formulation. Analyses were conducted on 592,241 individuals who met the inclusion criteria.

The 20 Kampo formulae with the largest number of prescribed patients are presented in Table 1. Kakkonto was the formula prescribed to the largest number of patients, followed by shoseiryuto and maoto. The characteristics of patients who received each type of Kampo formula compared with the 592,241 included subscribers and all observed subscribers are also presented in Table 1. In general, the proportion of women was larger among patients receiving Kampo formulations than in the general population. The results for the other Kampo formulae are presented in Supplementary material 1.

Prescription patterns for the 20 formulae are presented in Table 2. The median frequencies of prescription were one or

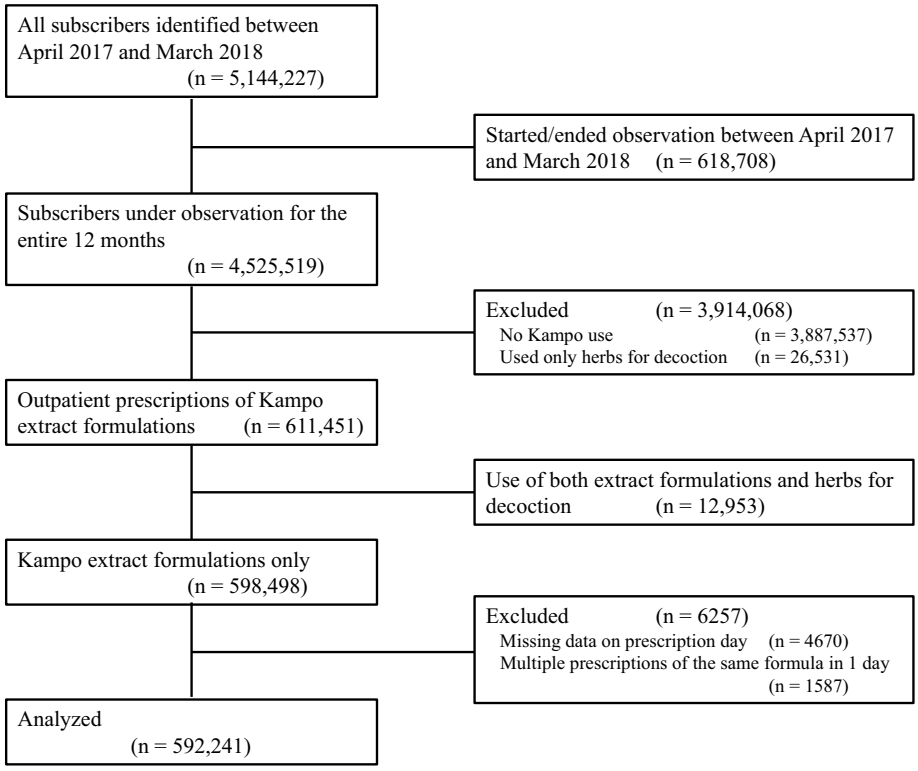

Figure. **Flowchart of patient selection for inclusion in this study.**

two times per year for all 20 types. Several formulae, such as kakkonto and maoto, were prescribed for short periods with a median coverage of 5 to 7 days. There were also several formulae that were prescribed for longer periods. The median numbers of days covered by kamishoyosan and keishibukuryogan were 60 and 56, respectively. Kamishoyosan had the greatest number of total days of prescription (1.8 million days among 17,136 patients) followed by tokishakuyakusan (1.7 million days among 19,413 patients). The results for the other Kampo formulae are presented in Supplementary material 2.

A total of 1,520,251 prescriptions of Kampo formulations were provided for 592,241 individuals. This included 171,119 (11.3%) with no co-administration of other Kampo formulations or Western drugs, 1,145,288 (75.3%) with co-administration of Western drugs, 51,062 (3.4%) with co-administration of other Kampo formulations, and 152,782 (10.0%) with co-administration of both other Kampo formulations and Western drugs. The co-administration patterns of 20 of the most frequently prescribed Kampo extract formulae are presented in Table 3. As expected, the formulae with the largest number of prescribed patients in the patient-level analysis, such as kakkonto and shoseiryuto, were also prescribed frequently in the prescription-level analysis. In addition, formulae that were frequently prescribed to a single patient, such as tokishakuyakusan and kamishoyosan, also had a large number of prescriptions. Kampo formulations were used in combination with Western drugs in more than half of cases for all 20 formulae. However, the patterns of co-administration differed across the Kampo formulae. The rates of co-administration with Western drugs for kakkonto and maoto were over 90%. Acetaminophen was the most frequently used Western drug in combination with both of these formulae. The proportion of prescriptions without other drugs was highest for tokishakuyakusan (27%). The results for the other Kampo formulae are presented in Supplementary material 3.

Discussion

The present study summarizes the results from an investigation of the outpatient prescriptions of Kampo extract formulations using a large-scale claims database in Japan. Of the 4.5 million subscribers, 13.5% received prescriptions for Kampo extracts within a 1-year period. Overall, Kampo formulations were used in combination with Western drugs in 85% of prescriptions. The prescription pattern differed widely according to the type of Kampo formula.

The characteristics of subscribers who received prescriptions of Kampo extract formulations differed from that of the general population; the proportion of women was larger, the proportion of the young age group was smaller, and the prevalence of each category of disease was higher. These results were similar to those of a previous study that also used health insurance claims data (17). A survey of patients attending a general outpatient clinic also showed that women and patients with more medical conditions were more likely to use complementary and alternative medicine (18). Dysmenorrhea and menopausal syndromes are indications for several Kampo formulae, including tokishakuyakusan,

Table 1. Number and Characteristics of Subscribers Receiving Kampo Extract Formulations.

Kampo formula	N	Female, %	Age		Age, %				Diagnosis[a], %													
			Mean	SD	0–19	20–39	40–59	≥60	A00-B99	C00-D48	D50-D89	E00-E90	F00-F99	G00-G99	H00-H59	H60-H95	I00-I99	J00-J99	K00-K93	L00-L99	M00-M99	N00-N99
Kakkonto	92,699	53	39	15	13	38	40	8	11	6	2	11	7	5	17	4	10	51	16	17	15	10
Shoseiryuto	71,333	55	37	16	18	38	37	8	11	5	2	10	6	4	18	4	8	57	14	19	12	9
Maoto	66,789	41	31	18	30	33	33	4	12	4	1	7	5	3	16	5	6	60	11	18	10	6
Bakumondoto	61,571	57	40	15	10	37	44	9	11	6	1	11	6	4	18	4	9	61	15	17	13	9
Goreisan	41,277	54	31	19	32	32	31	5	28	5	1	9	8	6	19	10	8	46	19	21	13	9
Maobushisaishinto	33,628	50	37	16	18	34	41	8	10	5	1	9	6	4	18	4	8	55	14	17	13	8
Kikyoto	28,691	53	37	15	14	41	39	6	11	5	1	10	6	4	19	4	8	60	16	19	13	9
Shakuyakukanzoto	25,714	51	49	15	6	17	51	26	10	9	1	20	8	8	18	4	22	30	22	16	33	14
Kakkontokasenkyushin'i	24,975	51	33	18	25	35	34	6	13	5	1	9	6	4	19	6	7	64	14	21	12	8
Hochuekkito	19,856	51	41	15	11	32	47	10	12	8	2	14	19	7	19	5	11	43	21	21	16	16
Tokishakuyakusan	19,413	96	38	12	6	49	43	3	11	12	4	17	12	6	20	5	7	37	20	21	14	32
Kamishoyosan	17,136	97	44	11	3	24	69	4	10	15	2	17	23	9	21	6	11	35	22	22	19	30
Hangekobokuto	17,057	66	41	14	8	34	49	8	10	9	2	13	32	7	19	6	11	47	28	19	17	14
Shosaikotokakikyosekko	14,660	49	37	14	12	44	39	5	12	5	1	10	6	4	18	4	8	62	17	18	13	9
Rikkunshito	14,323	65	42	15	9	31	47	13	14	11	2	14	17	7	20	5	12	38	49	20	18	15
Keishibukuryogan	13,904	84	43	12	6	24	64	6	10	17	2	16	12	7	20	5	12	33	20	23	20	29
Jumihaidokuto	12,582	62	27	13	37	45	16	2	10	4	1	5	5	3	21	3	3	35	10	59	9	8
Daikenchuto	11,518	59	44	17	11	22	50	17	14	20	2	15	12	7	19	5	14	34	47	19	18	15
Saikokeishito	10,552	50	34	17	24	33	37	6	14	5	1	9	8	4	18	5	7	55	18	19	12	8
Saireito	10,059	59	37	15	12	45	36	7	21	7	2	11	7	5	19	18	8	39	18	22	13	13
All included subscribers	592,241	54	37	17	18	34	40	8	12	6	1	11	9	5	18	5	9	48	17	20	14	11
All observed subscribers	4,525,519	44	34	18	28	29	36	7	9	4	1	7	4	2	14	4	6	32	8	15	9	5

The 20 Kampo formulae with the largest number of patients are presented.

[a]Diagnoses are based on International Classification of Diseases 10th Revision codes.

kamishoyosan, and keishibukuryogan (19-21). In the present study, over 80% of patients using these formulae were women, and the tokishakuyakusan, kamishoyosan, and keishibukuryogan formulae were 11th, 12th, and 16th in the number of subscribers receiving the formula, respectively. Therefore, these Kampo formulae influenced the statistics on the characteristics of patients receiving Kampo formulations. In addition, women receiving Kampo accounted for over 50% of patients taking most of the formulae. This suggests a potential preference for Kampo drugs by women compared with men.

The characteristics of patients, as expressed by Western diagnoses, reflected the conditions of patients receiving each Kampo formula. Some examples of the prescribed Kampo formulae and the diseases the patients had been diagnosed with are daikenchuto or rikkunshito for diseases of the digestive system, jumihaidokuto for diseases of the skin and subcutaneous tissue, hangekobokuto for mental and behavioral diseases, and tokishakuyakusan for diseases of the musculoskeletal system and connective tissue. In addition, postoperative constipation may explain the high proportion of patients with neoplasms among those receiving daikenchuto. However, there were also patients without typical diagnoses for each formula. For example, approximately half of the patients receiving daikenchuto did not have a diagnosis in the "digestive system" category. A traditional Kampo diagnosis based on a pattern of symptoms may have been implemented in addition to the Western diagnosis.

The three Kampo formulae with the largest number of prescribed patients were kakkonto, shoseiryuto, and maoto. Kakkonto is used for the common cold, shoseiryuto is used for asthma and rhinitis, and maoto is used for influenza. These common conditions resulted in a large number of patients receiving these formulae. However, for these formulae, the frequency of prescription within 1 year for a subscriber (mostly once), average number of days covered by one prescription (median 4 to 7 days), and the number of days covered within 1 year (median 4 to 7 days) were low. A typical case of receiving kakkonto for 5 days at the beginning of January would lead to a proportion of days covered (between the day of the first prescription and end of the study period) of approximately 5%. Therefore, these formulae were used for a short period of time in most cases.

Among the 20 Kampo formulae with the largest number of prescribed patients, the largest numbers of total days covered were observed for kamishoyosan (median 60 days), keishibukuryogan (median 56 days), and tokishakuyakusan (median 42 days). For these formulae, the median frequency of prescription was two times a year, and one prescription covered four weeks on average. For kamishoyosan, the 75th percentile point of days covered and proportion of days covered were 161 days and 82%, respectively. In contrast to the short-term use of Kampo formulations, this pattern of prescription may reflect the medium- to long-term use aimed at altering the overall constitution of patients. Kampo is often perceived to be safe (16). However, some formulations do

Table 2. Prescription Patterns of Kampo Extract Formulations.

Kampo formula	N	Total prescription days	Frequency of prescription[a], median [IQR]	Average number of days covered by one prescription, median [IQR]	Number of days covered[a], median [IQR]	Proportion of days covered[b](%), median [IQR]
Kakkonto	92,699	1,248,442	1 [1, 1]	5 [4, 7]	5 [4, 8]	5 [2, 10]
Shoseiryuto	71,333	1,257,078	1 [1, 1]	7 [5, 11]	7 [5, 14]	6 [3, 19]
Maoto	66,789	362,592	1 [1, 1]	4 [3, 5]	4 [3, 5]	5 [3, 9]
Bakumondoto	61,571	743,906	1 [1, 1]	7 [5, 7]	7 [5, 12]	5 [3, 11]
Goreisan	41,277	870,358	1 [1, 1]	5 [3, 7]	5 [3, 14]	4 [2, 11]
Maobushisaishinto	33,628	316,108	1 [1, 1]	5 [4, 6]	5 [4, 7]	5 [3, 9]
Kikyoto	28,691	203,685	1 [1, 1]	5 [4, 5]	5 [4, 7]	3 [2, 7]
Shakuyakukanzoto	25,714	1,073,747	1 [1, 2]	11 [5, 20]	14 [7, 35]	9 [3, 27]
Kakkonto-kasenkyushin'i	24,975	443,274	1 [1, 2]	7 [5, 7]	7 [5, 14]	6 [3, 14]
Hochuekkito	19,856	1,123,567	1 [1, 3]	14 [7, 28]	20 [7, 60]	13 [5, 43]
Tokishakuyakusan	19,413	1,685,254	2 [1, 4]	27 [14, 30]	42 [21, 119]	30 [11, 73]
Kamishoyosan	17,136	1,822,352	2 [1, 5]	28 [15, 30]	60 [28, 161]	37 [14, 82]
Hangekobokuto	17,057	1,021,716	1 [1, 3]	14 [7, 25]	21 [10, 60]	14 [5, 48]
Shosaikoto-kakikyosekko	14,660	113,750	1 [1, 1]	5 [4, 7]	5 [4, 7]	4 [2, 7]
Rikkunshito	14,323	889,373	1 [1, 3]	14 [9, 28]	28 [14, 63]	16 [6, 50]
Keishibukuryogan	13,904	1,396,507	2 [1, 4]	28 [14, 30]	56 [21, 150]	33 [12, 80]
Jumihaidokuto	12,582	831,784	2 [1, 3]	21 [14, 28]	35 [14, 84]	24 [10, 58]
Daikenchuto	11,518	1,108,965	2 [1, 4]	20 [10, 30]	30 [14, 150]	26 [7, 83]
Saikokeishito	10,552	143,337	1 [1, 1]	5 [4, 7]	5 [4, 7]	4 [2, 9]
Saireito	10,059	338,565	1 [1, 2]	7 [5, 14]	10 [5, 28]	7 [3, 23]

The 20 Kampo formulae with the largest number of patients are presented.

[a]Observed between April 2017 and March 2018.

[b]Days covered by prescription divided by the number of days from first prescription to March 31, 2018.

IQR: interquartile range

contain glycyrrhizin from licorice root, which may cause pseudoaldosteronism, while others contain ephedrine from ephedra herb. In addition, liver injury and interstitial pneumonitis have been reported (22, 23). Patients should be carefully monitored when using Kampo formulations, especially when treated for the long term.

In the prescription-level analysis, approximately 85% of all Kampo extract prescriptions were accompanied by Western drugs. A previous study showed similar concurrent use with biomedical drugs; 92% of patients who were prescribed Kampo extracts were co-administered biomedical drugs (17). We further categorized Kampo prescriptions by formulae and evaluated the pattern of concurrent use. Kampo formulae used for a short term, including kakkonto and maoto, were co-administered with Western drugs over 90% of the time. Antipyretics and mucolytics were frequently used in these cases. Other typical patterns of co-administration included anxiolytic-hypnotics (etizolam, brotizolam, or zolpidem) in addition to formulae for psychological symptoms (yokukansan or hangekobokuto) and a combination of Kampo and Western drugs for gastrointestinal symptoms (mosapride, magnesium oxide, or esomeprazole in addition to rikkunshito or daikenchuto). These co-administration patterns showed that Kampo and Western drugs with similar indications were frequently used in combination.

The proportion of using Kampo alone was relatively high in formulae used for dysmenorrhea and menopausal syndromes (tokishakuyakusan, kamishoyosan, and keishibukuryogan). This may be attributed to the subjective nature of symptoms found in these conditions that causes difficulty in treating with Western medicine. A previous survey of physicians also showed that 44% of obstetrics/gynecology specialists and 18% of internal medicine physicians used Kampo alone for treatment (15). In the same survey, 77% of obstetrics/gynecology specialists replied that they would provide Kampo as the first-line treatment for certain conditions (15). Kampo medicine may be especially important in this field.

The results from this study showed that Kampo formulations are commonly prescribed under the Japanese insurance system and frequently used in combination with Western drugs. We described one aspect of how Kampo is "integrated" in a real-world setting. One challenge in Kampo medicine is how to build evidence of its clinical effectiveness. In a review article concerning research strategies, Watanabe et al. suggested that clinical trials could be conducted with individualized treatment according to the Kampo diagnosis, as Kampo medicine is a complex and individualized treatment system (2). Considering the current real-world practice of Kampo medicine as shown in the present study, we additionally suggest that the complex combinations of Kampo and Western drugs be considered as a

Table 3. Co-administration Patterns of Kampo Extract Formulations.

Kampo formula	Number of prescriptions	Combination, %				Frequently co-administered Western drugs			
		None	Kampo	Western	Kampo and Western	First most frequently used type	%[a]	Second most frequently used type	%[a]
Kakkonto	133,461	7	3	78	12	Acetaminophen	29	Carbocisteine	18
Shoseiryuto	107,734	6	2	81	11	Carbocisteine	29	Acetaminophen	15
Bakumondoto	87,333	4	2	84	10	Carbocisteine	38	Dextromethorphan	17
Maoto	79,738	5	1	88	6	Acetaminophen	59	Carbocisteine	31
Goreisan	66,710	9	6	68	17	Domperidone	17	Acetaminophen	16
Kamishoyosan	62,493	20	9	51	20	Etizolam	10	Loxoprofen	10
Shakuyakukanzoto	61,088	8	2	78	13	Loxoprofen	24	Rebamipide	14
Tokishakuyakusan	59,417	27	8	51	14	Ritodrine	9	Loxoprofen	8
Hochuekkito	51,288	14	9	53	23	Loxoprofen	8	Carbocisteine	7
Hangekobokuto	49,690	13	7	61	19	Etizolam	9	Alprazolam	8
Keishibukuryogan	47,656	19	11	47	22	Loxoprofen	11	Heparinoid	7
Maobushisaishinto	44,642	4	3	81	12	Acetaminophen	31	Carbocisteine	28
Kakkonto-kasenkyushin'i	42,460	3	3	83	11	Carbocisteine	48	Betamethasone	23
Bofutsushosan	38,932	11	4	66	19	Loxoprofen	12	Amlodipine	11
Rikkunshito	38,214	8	6	68	18	Mosapride	14	Esomeprazole	12
Yokukansan	38,033	14	7	60	19	Aripiprazole	10	Brotizolam	10
Daikenchuto	36,848	8	3	73	15	Magnesium oxide	35	Mosapride	12
Kikyoto	36,119	3	3	77	17	Tranexamic acid	38	Carbocisteine	30
Jumihaidokuto	35,913	5	2	79	13	Heparinoid	29	Pyridoxal	20
Yokukansan-kachinpihange	21,317	13	11	50	26	Zolpidem tartrate	9	Etizolam	9

The 20 most frequently prescribed Kampo formulae are presented.

[a]Proportion among prescriptions made in combination with Western drugs.

topic for future research.

Several limitations of the study must be acknowledged. First, the study was conducted using a claims database, and the detailed conditions of each patient could not be determined. The diagnoses that we compiled represented the overall conditions during the one-year period. In addition, the prescriptions received on the same day as the Kampo formulations may have been used for different diseases. Second, data on Kampo products purchased outside health insurance could not be obtained. Some Kampo formulations may have been purchased as over-the-counter drugs. Therefore, the use of Kampo formulations is likely more frequent than summarized herein. Furthermore, subscribers who joined or withdrew from the insurance during the one-year period were excluded from the analysis. Finally, the database lacked information on older individuals because they are enrolled in a different insurance scheme after retirement. Prescription patterns may be different in these groups of people.

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

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