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Research Article

Safety of herbal medicine for elderly patients with chronic disease in the Republic of Korea

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ABSTRACT

Introduction: Elderly patients with chronic diseases may experience unintended adverse events (AEs) related to medication. This study investigated the detection of drug safety signals associated with herbal medicine by analyzing spontaneous AE reports in this patient group to generate new safety information.

Methods: The "Korea Institute of Drug Safety and Risk Management Korea Adverse Event Reporting System database (KIDS-KD)" was used to investigate patients over 65 years old with chronic disease from 2013 to 2016. The target of analysis is seven herbal medicines such as ginkgo leaf extracts, ivy leaf extracts, herbal cough suppressants and expectorants. AEs associated with herbal medicine were considered a signal if they accounted for greater than 0 of the 95% lower confidence interval of the Information Component (IC_{025}). The relevance of unexpected Adverse Drug Reactions (ADRs) was determined based on a review of the KIDS-KD and then derived as safety information.

Results: Among 113 types of herbal medicine-AE combinations, 56 drug-event combinations (DECs) in elderly patients with chronic disease were detected as signals. Of those, 12 types of DECs were investigated as unexpected ADR and finally 9 types were assessed as necessitating reporting of safety information: ginkgo leaf extracts (depression, thrombocytopenia), ivy leaf extracts (bullous eruption, muscle weakness, nocturia, lip ulceration, neuropathy peripheral, anxiety, malaise).

Conclusions: The elderly have a high prevalence of chronic diseases, resulting in polypharmacy, and potentially creating a high risk of ADRs. Establishing a pharmacovigilance system for herbal medicine is of great importance.

1. Introduction

Chronic diseases are non-infectious or degenerative with morbid states that persist for at least three months. In addition, chronic diseases improve and are aggravated repeatedly, gradually progressing in a worse direction [1]. Although they increase with age and develop because of various and complex risk factors, they have rarely been identified clearly [2,3]. The third Korea National Health and Nutrition Examination Survey (KNHANES) in 2005 revealed that 38.5% of patients with chronic diseases aged ≥19 years had utilized Korean Medicine (KM) services [4]. Additionally, a survey of whether Complementary and Alternative Medicine (CAM) had been concurrently implemented in 423 patients hospitalized in three long-term hospitals due to chronic diseases revealed that 334 (79.0%) were receiving CAM in parallel with their regular treatment [5]. Moreover, patients with chronic diseases were found to be more likely to be administered multiple drugs for treatment and management of such diseases and therefore experience unintended adverse events (AEs) of the drugs.

A total of 198 applications for medical disputes related to treatment with KM were reported to the Korea Consumer Agency in 1999, and

Abbreviations: ADRs, adverse drug reactions; AEs, adverse events; ATC, anatomical therapeutic chemical; BCPNN, Bayesian Confidence Propagation Neural Network; DEC, drug-AE combination; DECs, drug-event combinations; IC, information component; IC_{025}, 95% lower confidence interval of the Information Component; ICD, International Statistical Classification of Diseases and Related Health Problems; KIDS, Korea Institute of Drug Safety and Risk Management; KIDS-KD, KIDS korea adverse event peporting system Database; KNHANES, Korea National Health and Nutrition Examination Survey; OTC, over-the-counter; PMDA, Pharmaceuticals and Medical Devices Agency; PV, pharmacovigilance; SAEs, serious adverse events; TCM, Traditional Chinese medicine; UMC, Uppsala Monitoring Center; WHO-ART, WHO Adverse Reaction Terminology

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Table 1
Charlson Comorbidity Index.
Source: Quan H. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data. *Med Care*. 2005;43:1130-9

Charlson Weight	Condition	Classification of Disease Codes
1	Myocardial infarction	I21-I22, I252
	Congestive heart failure	I099, I110, I130, I132, I255, I420, I425-I429, I43, I50, P290
	Peripheral vascular disease	I70, I71, I731, I738-I739, I771, I790, I792, K551, K558-K559, Z958-Z959
	Cerebrovascular disease	G45-G46, I60-I69, H340
	Dementia	F00-F03, G30, F051, G311
	Chronic pulmonary disease	J40-J47, J60-J67, I278-I279, J684, J701, J703
	Connective tissue disease	M05-M06, M315, M32-M34, M351, M353, M360
	Ulcer disease	K25-K28
	Mild Liver disease	B18, K700-703, K709, K713-K715, K717, K73-K74, K760, K762-K764, K768-K769, Z944
	Diabetes	E100-E101, E106, E108-E111, E116, E118-E121, E126, E128-E131, E136, E138-E141, E146, E148-E149
2	Diabetes with complications	E102-E105, E107, E112-E115, E117, E122-E125, E127, E132-E137, E142-E145, E147
	Hemiplegia	G041, G114, G801-G802, G81-G82, G830-G834, G839
	Moderate to severe renal disease	N032-N037, N052-N057, N18, N19, N250, I120, I131, Z490-Z492, Z940, Z992
	Any tumor including leukemia and lymphoma	C00-C26, C30-C34, C37-C76, C81-C85, C88, C90-C97
3	Moderate or severe Liver disease	K704, K711, K721, K729, K765-K767, I850, I859, I864, I982
	Metabolic solid tumor	C77-C80
6	AIDS	B20-B22, B24

these have increased every year, reaching 859 cases in 2010. Additionally, the number of the settled medical disputes related to KM treatment increased from six in 1999 to twenty in 2010 [6]. In addition, 101 adverse drug reactions (ADR) associated with herbal formulas from 97 patients were reported to the spontaneous ADR reporting system in the electronic medical records of one hospital from 2012 to 2014, with most reported ADR being gastro-intestinal system disorders (41.5%), followed by skin-related disorders (25.8%) and diarrhea (17.8%) [7]. In a systemic review of randomized controlled trials of herbal medicine, 480 AEs were reported in 15,441 subjects included in 244 studies, with the most frequently reported being symptoms involving the digestive system (44.3%), followed by those involving the nervous system (17.3%) and anorexia (16.3%) [8].

Pharmacovigilance (PV) is defined as scientific activities relating to the detection, assessment, understanding, and prevention of AEs or any other drug-related problems [9]. Spontaneous AE reporting is a primary method of evaluating the safety of a drug after a drug has been released onto the market. ADRs not discovered during the clinical trial phase of a drug are more likely to be developed and newly discovered after the drug's release onto the market [10].

Therefore, it is necessary to monitor the safety of herbal medicines being administered for treatment and management of chronic diseases. Safety grading and clinical evaluation of the potential toxicities of herbal medicine are studied and patient cases relevant to its safety should be collected and analyzed [11]. Spontaneous AEs reporting is considered a good source to identify post-marketing adverse drug reactions (ADRs) [12]. This study was conducted to detect drug safety signals of herbal medicine by analyzing the spontaneous AE reports in elderly patients with chronic diseases and generate new safety information.

2. Methods

2.1. Source of data

The Korea Institute of Drug Safety & Risk Management (KIDS) provides the AE reporting database (KIDS-KD) through deliberation on the research plan and it is utilized in analyses of the safety information of drugs [13]. The KIDS-KD is composed of eight distributed tables including patient information and information regarding the administered drug, AEs, seriousness of the report, reporter, causality assessment of the drug-AE combination (DEC), patient's medical history, and sequence of reporting such as initial and follow-up report. The information provided that sex and age of the patient, ingredients and dose of the administered drug, duration of administration, name and onset date of AE, duration of AE, progress of recovery, seriousness of the AE (resulting in death, life-threatening, etc.), type of reporter (medical institute, pharmaceutical manufacturer, etc.), causality assessment outcome and patient's medical history or history of allergies.

KIDS-KD has anonymized all the information according to research ethics, thus no identifiable information such as the name of the patient or reporting institute, product name or manufacturer's name of the drug, or detailed descriptive information pertaining to the report are provided. The Anatomical Therapeutic Chemical (ATC) Classification System developed by the Collaborating Centre for Drug Statistics Methodology, which affiliated with the World Health Organization (WHOCC), has used the drug information. AEs are also used by the WHO Adverse Reaction Terminology (WHO-ART) [14].

2.2. Study subjects

The target population of this study was defined as patients who reported AEs after taking herbal medicines among patients over 65 years old with chronic disease whose medical histories and drug indications in the KIDS-KD from 2013 to 2016. The categories of chronic diseases are very diverse according to WHO, CDC and so on [15]. In this study, chronic diseases were considered diseases applicable to the Charlson comorbidities, which are comorbidities with a weighted value given among those affecting death that have been mapped onto diagnosis codes such as the International Statistical Classification of Diseases and Related Health Problems (ICD) through clinical review [16] (Table 1).

The KIDS-KD provides the drug name as an ATC name, and seven kinds of herbal medicines were defined by comparing the drugs for which the upper level of the ATC name was available but the lower level was not due to characteristics of the herbal medicine in the master file of the KIDS. For example, if the list of the drugs for which the upper level of the ATC name is applicable to other analgesics and antipyretics, but not to its lower levels such as rimazolium, glafenine, floctafenine, etc., making further ATC classification of them unavailable (e.g., *galgeun-tang, sogyeonghwalhyul-tang,* and *paedok-san*), they were defined as herbal medicine. The defined herbal medicines were named artemisia extract, psylla seeds extract, herbal antiobesity drugs, herbal analgesics and antipyretics, ginkgo leaf extract, ivy leaf extract, and herbal cough suppressants and expectorants (Table 2).

2.3. Signal detection and safety information generation

Data mining using spontaneous reports on AEs is one of research methodology of pharmacoepidemiology (PE). Data mining provides

Table 2
Herbal Medicine in KIDS-KD.

ATC code	ATC Name	Drugs Included
A02X	Other drugs for acid related disorders	artemisia extract
A06AC01	Ispaghula (psylla seeds)	psylla seeds extract
A08AX	Other antiobesity drugs	herbal antiobesity drugs
N02BG	Other analgesics and antipyretics	herbal analgesics and antipyretics
N06DX02	Ginkgo folium	ginkgo leaf extract
R05CA	Expectorants	ivy leaf extract
R05F	Cough suppressants and expectorants, combinations	herbal cough suppressants and expectorants

useful information to identify the causalities of AEs with drugs and makes signals of the potential causality or the relevance associated with the risks of drugs detectable [17].

In this study, the Information Component (IC) of the Bayesian Confidence Propagation Neural Network (BCPNN) was utilized as a data mining index as in the signal detection by the Uppsala Monitoring Center (UMC). This is a way to relate observed and expected values to find drug–adverse event combinations that have been reported more often than one would expect. IC_{025} is a lower limit of the 95% confidence interval. A positive IC_{025} value is the traditional threshold used in statistical signal detection. If IC_{025} was > 0, it was determined to be a signal [18]. The reporter determines the causality of a DEC as certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable based on the causality assessment system developed by the UMC [19]. The DECs from which the causality assessment had been determined to be certain, probable/likely, or possible by the reporter were selected as ADRs and those that are not included in the product label of the drug were considered unexpected ADRs. The unexpected ADRs were generated as safety information through a review of the KIDS-KD data (Fig. 1). Comparisons of the safety evaluations of herbal medicines were made between those administered to elderly patients and adult patients aged 19–64 years old with chronic diseases.

SAS Windows version 9.4 (SAS Institute Inc., Cary, NC, USA) was utilized to establish a research database and to calculate a data mining index.

3. Results

The number of AEs reported from 2013 to 2016 was 793,790, of which 637,291 were reported in patients aged ≥19 years. The number of the AEs reported for patients whose information regarding medical history included any disease applicable to chronic diseases or who were administered any drug indicated for chronic diseases was 215,956, giving a total of 1,091,868 DECs. Here, reports on quasi drugs and the in the reports for which active ingredients or names of AEs had been omitted were excluded and cases in which multiple initial and follow-up reports were calculated as one report by applying their initial reports only. The drugs reported as simply co-administered that were not suspected drugs or interacting were also excluded. There were 205,976 reports applicable to the subjects of this study and 421,147 DECs. There were 456 reports (642 DECs) applicable to herbal medicine and 207 reports (270 DECs) reported for elderly (Fig. 2).

The number of reports from elderly patients has increased: 19 reports in 2013, 43 reports in 2014, 68 reports in 2015, 77 reports in 2016. By classification of chronic disease, 10 reports in cardiovascular disease, 33 reports in cerebrovascular disease, 14 reports in dementia, 66 reports in chronic pulmonary disease, 1 report in connective tissue disease, 22 reports in ulcer disease, 2 reports in liver disease, 11 reports in diabetes, 2 reports in renal disease and 46 reports in cancer.

When calculating the data mining index, 56 types of DECs were detected as signals and 28 types were ADRs that were determined to be certain, probable, and possible upon assessment of causality by the reporters (Table 3).

The ADRs determined as unexpected through retrieval of the approved labels in Republic of Korea for the 12 types of DECs were skin discoloration and conjunctivitis for artemisia extract, as well as depression, purpura, and thrombocytopenia associated with ginkgo leaf extract, and bullous eruption, muscle weakness, neuropathy peripheral, anxiety, lip ulceration, nocturia, and malaise in response to ivy leaf extract, although these have not been reflected in their approved labels to date [20].

Data describing the 12 types of DECs selected as unexpected ADRs were reviewed and skin discoloration and conjunctivitis of artemisia

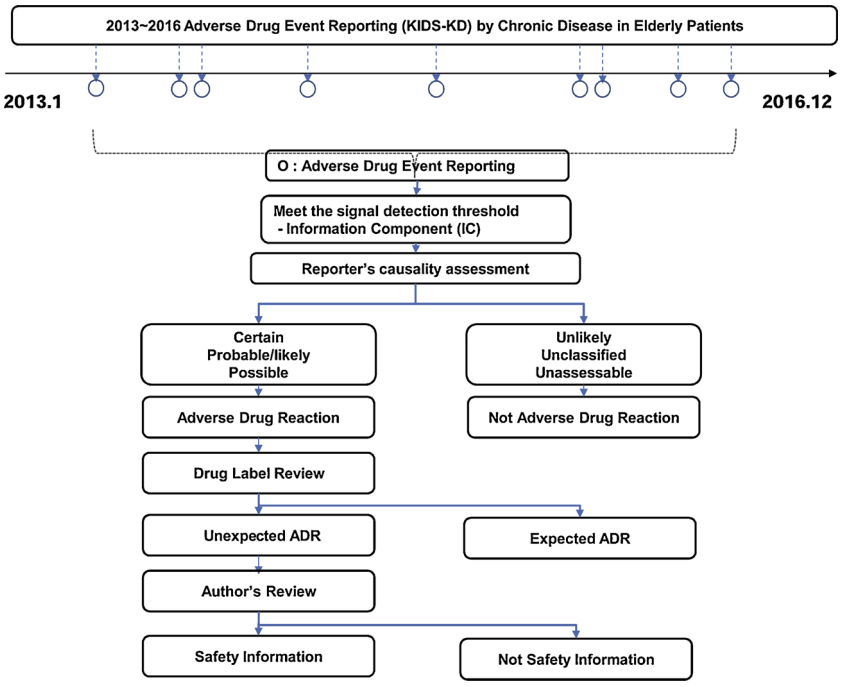

Fig. 1. Analysis and evaluation of KIDS-KD.

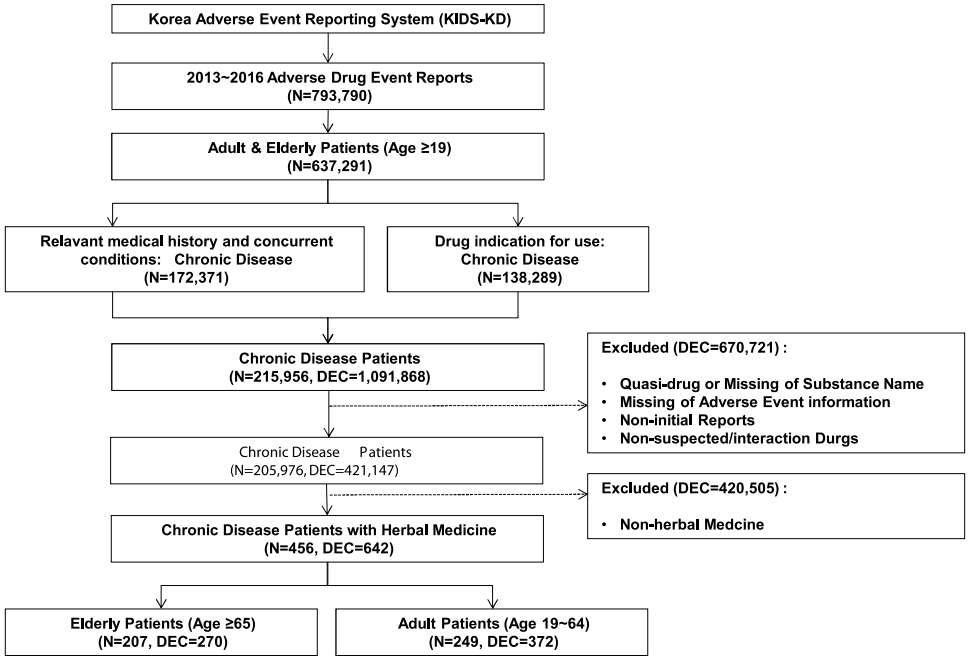

Fig. 2. Selection of subjects from KIDS-KD.

Table 3
Signal Detection of Herbal Medicines.

Herbal Medicine	Adverse Event	IC_{025}	
		Elderly Patients	Adult Patients
artemisia extract	skin discoloration	1.197	–
	conjunctivitis	0.934	–
	hepatocellular damage	0.082	–
	palpitation	0.281	–
	epistaxis	0.600	–
	gingival bleeding	0.600	–
psylla seeds extract	allergy	1.393	–
herbal analgesics and antipyretics	edema generalized	6.656	–
ginkgo leaf extract	urticaria	1.342	0.563
	myalgia	2.211	–
	depression	1.004	–
	palpitation	1.490	–
	tachycardia	2.215	–
	dyspnea	1.310	0.102
	purpura	0.872	–
	thrombocytopenia	2.215	–
	edema	1.004	–
	edema generalized	1.004	–
ivy leaf extract	bullous eruption	0.495	–
	muscle weakness	0.161	–
	neuropathy peripheral	0.161	0.496
	anxiety	0.495	–
	diarrhea	0.726	0.760
	lip ulceration	0.495	–
	glucose tolerance abnormal	0.495	–
	nocturia	0.161	–
	edema generalized	0.161	–
	malaise	0.006	0.094

extract and purpura of ginkgo leaf extract were excluded from the safety information. Skin discoloration associated with artemisia extract was reported in a 72-year-old male patient with cancer who was concomitantly administered multiple drugs including nebivolol, pseudoephedrine, magnesium oxide, atorvastatin, bicalutamide, propiverine, aspirin, and ambroxol. The level of contribution of the other drugs was more highly rated considering that they had been administered in closer proximity to the onset date of skin discoloration than the artemisia extract. Conjunctivitis of artemisia extract was reported in a 78-year-old female patient with cancer who was concomitantly administered multiple drugs including rosuvastatin, edoxaban, and choline alfoscerate. The level of contribution of the other drugs was more highly rated because they had been administered in closer proximity to the onset date of conjunctivitis than the artemisia extract.

Purpura associated with ginkgo leaf extract was reported in a 73-year-old patient with cardiovascular disease who was concomitantly administered aspirin. The contribution of the aspirin was more highly rated because the pharmacological action of aspirin inhibits platelet activity. The remaining nine DECs were finally generated as safety information because their causality could not be ruled out. Among them, seven DECs excluding malaise and neuropathy peripheral to ivy leaf extract were not generated as safety information in adult patients with chronic diseases, while they were generated as safety information in elderly patients (Table 4) (Fig. 3).

4. Discussion

4.1. Pharmacovigilance of herbal medicine

In China, the total number of AEs reported to the China Food and Drug Administration (CFDA) from 1999 to 2016 amounted to almost

Table 4
Safety Information for Herbal Medicines.

Herbal Medicine	Adverse Event	Safety Information	
		Elderly Patients	Adult Patients
ginkgo leaf extract	depression	Y	N
	thrombocytopenia	Y	N
ivy leaf extract	bullous eruption	Y	N
	muscle weakness	Y	N
	neuropathy peripheral	Y	Y
	anxiety	Y	N
	lip ulceration	Y	N
	nocturia	Y	N
	malaise	Y	Y

	Step 1	Step 2	Step 3	Step 4	Step 5
artemisia extract	52	27	6	2	0
psylla seeds extract	6	2	1	0	0
herbal antiobesity drugs	1	0	0	0	0
herbal analgesics and antipyretics	1	1	1	0	0
ginkgo leaf extract	24	14	10	3	2
ivy leaf extract	28	11	10	7	7
herbal cough suppressants and expectorants	1	1	0	0	0
	113	56	28	12	9

- Unit: Types of Herbal medicine-Event Combination (DEC)
- Step 1: All types of Adverse Event (AE) reported
- Step 2: Signal Detection
- Step 3: Adverse Drug Reaction (ADR)
- Step 4: Unexpected ADR
- Step 5: Safety Information

Fig. 3. Flow of generation of safety information.

10.75 million reports, while there were more than 1.43 million reports in 2016 alone. Among them, around 420,000 reports (29%) were unknown serious adverse events (SAEs) of drugs. In the classification of drugs by drug type reported during 2016, chemical medicine, biological medicine, and Traditional Chinese medicine (TCM) accounted for 81.5%, 1.6%, and 16.9% of the total, respectively [21]. Therefore, the number of AEs reported from TCM was 240,000, including 23,000 SAEs. In Japan, the number of AEs reported from over-the-counter (OTC) Kampo medicine by the Ministry of Health, Labour, and Welfare (MHLW) was 367 for 2005 through 2014 consisting of 151 reports of abnormal liver function, 55 reports of rash and hypersensitivity reaction, and 51 reports of liver injury. Summary of the AEs by preparation revealed that the majority of AEs reported were from *Bofutsushosan* (110), followed by *kakkonto, hachimijiogan,* and *daisaikoto*, from which 45, 15, and 14 were reported, respectively [22]. The CFDA generated safety information based on 443 reports of AEs from *Zhenju Jiangya Tablets* used for hypertension, which were mainly composed of *Chrysanthemum indicum* L. and *Pinctada martensii Dunker* [23]. In 2014, the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan distributed a safety alert on an OTC drug extracted from *Inchinkoto* regarding its potential to cause mesenteric venous thrombosis [24]. However, Republic of Korea still does not have official statistics on the AEs associated with herbal medicine.

4.2. Safety information derived from this study

This study generated nine types of safety information from herbal medicine administered to elderly patients with chronic diseases in Republic of Korea by utilizing the KIDS-KD of 2013–2016; 1) ginkgo leaf extract-depression, 2) ginkgo leaf extract-thrombocytopenia, 3) ivy leaf extract- bullous eruption, 4) ivy leaf extract-muscle weakness, 5) ivy leaf extract-nocturia, 6) ivy leaf extract-lip ulceration, 7) ivy leaf extract-neuropathy peripheral, 8) ivy leaf extract-anxiety, 9) ivy leaf extract-malaise.

1) Depression associated with ginkgo leaf extract was reported by a 78-year-old female patient with dementia, and this was caused by single administration of ginkgo leaf extract. The influence of her underlying disease could not be ruled out because it was dementia; however, the contribution of ginkgo leaf extract was determined to be meaningful since no other drugs were concomitantly administered. In a review of other literature, a study showed that ginkgo leaf extract improves psychoneuropathy, including depression [25], and coherence with the existing knowledge was absent however, this ADR was determined to be the safety information on which monitoring of additional reports is required since it was a spontaneous report on the ADR in Republic of Korea.

2) Thrombocytopenia associated with ginkgo leaf extract was reported in an 82-year-old male patient with diabetes mellitus following a single administration of the medicine. The contribution of ginkgo leaf extract was determined to be meaningful because no other drugs or diseases that might explain the ADR existed and no other drugs were administered concomitantly. A review of other literature revealed a study that showed that ginkgo leaf extract preparation inhibits platelet aggregation [26] and coherence with the existing knowledge was absent however, this ADR was determined to be the safety information on which monitoring of additional reports is required since it was a spontaneous report on the ADR in Republic of Korea.

3) Bullous eruption associated with ivy leaf extract was reported in a 71-year-old female patient to whom famotidine and doxofyline were concomitantly administered.

Additionally, 4) muscle weakness and 5) nocturia associated with ivy leaf extract were reported in a 69-year-old male patient to whom codeine was concomitantly administered and a 66-year-old female patient to whom fexofenadine and erdosteine were concomitantly administered, respectively.

6) Lip ulceration in response to ivy leaf extract was reported in a 66-year-old female patient to whom moxifloxacin was concomitantly administered. All of these patients had chronic respiratory diseases and the reporters did not rule out other drugs as the cause of AEs and instead rated their level of contribution as equivalent since no specific causative drug could be identified. A review of other domestic and foreign literature revealed no studies investigating AEs associated with ivy leaf extract.

Both 7) peripheral neuropathy and 8) anxiety in response to ivy leaf extract were reported in 70-year-old male patients, while a 77-year-old male patient reported 9) malaise. All of these patients had chronic respiratory diseases. The contribution of ivy leaf extract to the AEs was determined to be meaningful because no other drugs or diseases that might explain these ADRs existed and no other drugs were administered concomitantly. A review of other domestic and foreign literature

revealed no studies investigating the relationship between these conditions and ivy leaf extract.

The ADRs generated as the safety information on ivy leaf extract were determined to require monitoring of additional reports on them since they were the ADRs spontaneously reported in Republic of Korea. Moreover, the peripheral neuropathy of ivy leaf extract was reported for a 53-year-old male patient, while malaise was reported for a 49- and 37-year-old female patient, as well as a 64-year-old male patient. The reporter determined that ivy leaf extract may have been the cause of these effects.

The spontaneous reports on AEs allowed sub-group analyses or stratified analyses based on covariates such as age, sex, and nationality [27]. When comparing the safety information pertaining to herbal medicine administered to elderly patients with chronic diseases with that for adult patients with chronic diseases, seven of the nine total types of safety information (depression and thrombocytopenia associated with ginkgo leaf extract and bullous eruption, muscle weakness, anxiety, lip ulceration, and nocturia in response to ivy leaf extract, were generated as the safety information for elderly patients with chronic diseases.

Studies of the characteristics of ADRs in the elderly aged ≥60 years based on reports of AEs from a single institute in 2010–2013 revealed that the elderly had a significantly greater tendency to develop psychiatric, cardiovascular and urinary diseases than other age groups [28]. Depression and anxiety, thrombocytopenia, and nocturia are psychiatric disorders, a cardiovascular disorder, and a urinary disorder were similar to previous research results. Thus, more attention should be paid to AEs such as these when drugs are administered to elderly patients.

4.3. Advantages and limitations

This study is significant being the first study to research herbal medicine AE signals using KIDS-KD. In particular, safety information for nine types of herbal medicine, which were not previously known in elderly patients, have been identified. However, It should be noted that this study has several limitations. First, the KIDS-KD cannot calculate or estimate the incidence of AEs because there is no denominator information for patients actually taking or administering the drug. Second, since all the safety information from elderly patients in this study was generated based one report each, more data is needed before concluding that age is a risk factor for the pertinent safety information. Thus, more reports on the AEs of herbal medicine need to be accumulated and greater AEs reporting is needed.

4.4. Necessity for research on herbal medicine safety information for elderly patients

Although herbal medicine is considered to be safer because it is not synthetic, this may result in the safety monitoring being overlooked. Herbal medicine is being used increasingly around the world; however, information regarding its safety for patient populations that may have different genomes and metabolic and biological activities is insufficient [29]. The elderly have a high prevalence of chronic diseases, resulting in polypharmacy, and potentially creating a high risk of ADRs due to drug-drug and drug-herb interactions. Therefore, PV aims to ensure that drugs are used in a reasonable and safe manner, and effective PV needs to establish useful safety information pertaining to herbal medicine.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Dongguk University, Gyeongju (DRG IRB 20170016). Patient consent was exempted because of the total anonymity of all research data used in this study.

Authors' contributions

Yeonju Woo and Min Kyung Hyun planned the study and wrote the manuscript.

Availability of data and materials

The datasets analyzed during the current study are available from a public database of the KIDS-KD upon reasonable request (https://open.drugsafe.or.kr/). The KIDS-KD for this study was obtained through the deliberation of the KIDS (research plan number: 1711A0062).

Declaration of Competing Interest

The authors have no conflicts of interest to declare with respect to the authorship and/or publication of this article.

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