

Development of Hazardous Materials Management Standard for Decoction Type of Personalized Herbal Medicine

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Key Words

hazardous materials management standard, personalized herbal medicine, decoction, Korean herbal medicine

Abbreviations

FDA: Food and drug administration, GMP: Good manufacture practice, MHMs: Manufactured herbal medicines HMs: Herbal medicines, PHMs: Personalized herbal medicines, MFDS: Ministry of food and drug safety, TM: Traditional medicine, WHO: World health organization

Abstract

Objectives: This study was conducted to development of hazardous materials management standards for the decoction type of personalized herbal medicines (PHMs).

Methods: This study was conducted in two stages. We searched documents about criteria to use words such as 'Herb', 'Herbal medicine', and 'Botanical Drug' and summarized the results. We organized the committee consisted of seven experts, and held two meetings to reach an agreement on hazardous management stand-

ards of the decoction type of PHMs.

Results: The seven documents were presented in the literature review and six items related to hazardous management standards of decoction were identified. The second expert meeting brought that a total of six items, including heavy metal, pesticide residues, sulfur dioxide, benzopyrene, mycotoxin, and micro-organism limits, were selected for safety management of decoction type of PHMs. Also, the criteria and test methods for each standard were suggested for monitoring the decoction type of PHMs.

Conclusion: The study suggested hazardous material management standards and criteria for the decoction types of PHMs. In the future, it would be necessary to conduct a pilot test to ensure the validity and credibility of the safety management standard and criteria. Furthermore, the government level safety management system should be introduced to verify the safety of decoction medicines.

1. Introduction

Herbal medicines (HMs) are defined as herbal preparations prepared by mixing two or more herbs extracted from animals, plants, or minerals [1, 2]. HMs have been in use for thousands of years across the world and recognized as to be safe to use [3]. While the HMs are considered to be safer compared

Received: Jun 09, 2020 Reviewed: Jun 09, 2020 Accepted: Jun 11, 2020

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to conventional medicine products, there have been cases of drug-induced liver injuries (DILI) and other adverse events with HMs [4]. As a result, the issue of safety of HMs is gaining more and more attention [5]. While some noted that the quality of the preceding studies on the safety issues of HMs is not of a satisfactory level and that the methods of the study had significant issues [6], now there is a wide-spread consensus that it is necessary to ensure the safety of HMs beyond a certain level, since they are now acknowledged as a type of medicine products.

The manufactured herbal medicines (MHMs) that are recognized as medicine products are generally regulated by the Food and Drug Administration (FDA) [7]. These products are now required to be approved by the authorities and must be prepared in GMP-certified facilities [7]. In the case of the United States (US), new medicines are approved after going through a rigorous process of clinical trials in three stages by the FDA [8]. In the case of South Korea, the products which are mentioned in traditional texts of HMs are exempt from clinical trials and the requirement to submit toxicology test reports [7]. However, they are still required to prepare good manufacture practice (GMP)-certified facilities that are approved by the Korea Ministry of Food and Drug Safety (MFDS) [7].

In some countries where traditional medicine (TM) is being practiced (such as South Korea, China, and Taiwan, etc.), the patients are prescribed with personalized herbal medicines (PHMs) which are prepared and concocted at the TM clinics themselves [9]. A PHM is a personalized preparation that is prescribed based on the patient diagnosis at TM clinics, unlike the MHMs that are manufactured by a pharmaceutical company [9, 10]. Of the PHMs in use in South Korea, decoction formulations account for 54.8%, making them the most frequently used of all formulations in the country [11]. Also, the herbs to be used in a PHM must be of medical grades that conform with the hazardous material standards (e.g., heavy metals, pesticides, aflatoxins, sulfur dioxide, and benzopyrene) as designated by the Korea MFDS [12]. However, there can be safety concerns in the management and preparation of the PHMs, while non-medicinal herbs can also be used in preparing decoctions. As a result, there are difficulties in ensuring the safety of the final PHMs [13].

As for the previous studies, there have not been any studies on the safety management standards that could be applied to decoction type of PHMs in general except for some cases [14, 15] where the safety and efficacy were studied in individual prescriptions of decoction medicines. Traditionally, HMs have been used safely. Therefore, the safety issue of this type of medicine has not received much attention. However, the level of social demand for the safety of foods and medicines by the general public is increasing. It is now time to verify the safety of decoction medicines that are most frequently administered among HMs, which is a type of TMs.

In this study, the researchers conducted literature reviews and interviews with experts, to establish the safety management standard for the hazardous materials test items, test criteria, and test methods for decoction type of PHMs. The purpose of this study is to establish such a safety management standard for decoctions and generate

the basic data that could be used to monitor hazardous materials in decoctions.

2. Method

To secure the safety of HMs, we conducted this study in the following order to develop the hazardous materials management standard. Firstly, we gathered the certified study reports that are related to herbs, HMs, HM products, botanical drugs, and botanical medicine extracts and summarized their results. This was followed by two meetings with experts based on the findings in the previous stage to develop the management standard.

2.1. Literature Search and Classification

In other to survey the official management standards related to HMs in South Korea and other countries, we searched the related documents on the safety standards of “herbs,” “herbal medicines,” “herbal medicinal products,” “botanical medicines,” and “botanical medicinal products, etc.” using the official government website of the MFDS under the Ministry of Health of South Korea.

For gathering information from overseas sources, we also searched the websites of WHO, CODEX, and other official websites of the United States, Japan, China, and EU using keywords such as “herb,” “herbal medicine,” “botanical drug,” “food,” and “natural product,” etc.

The terminology for natural-derived medicine is divided into four categories in the WHO guideline [16, 17]; (1) Herbs (crude plant material), (2) Herbal materials (whole plants or parts of medicinal plants), (3) Herbal preparations (the basis for finished herbal products), (4) Finished herbal products or herbal medicinal products. The results of the literature search were classified and organized according to the material type (herb and herbal material) and final product type (herbal preparation and finished herbal product).

2.2. Consists of the Expert Committee

To select the experts who will provide their opinions on the safety management standards for HMs, we contacted the experts who were working for the government agencies related to food or medicines, the professors who were participating in research projects related to foods or medicines at universities, or the experts in the private sectors providing consulting or working in the related private sectors concerning safety management standards.

As for the government agencies, one expert from Korea Institute for Health and Social Affairs (KIHS) and another from National Development Institute for Korean Medicine (NIKOM) participated in the meeting, while one faculty member of the school of Food Science and Biotechnology of Kyungpook National University joined the meeting to represent the academic sector. Lastly, as for the private sector, one representative expert from each of Daegu University Hazard Analysis and Critical Control Point (HACCP) Education Center, Korea Pharmaceutical

Test & Research Institute, Food Hygiene Safety Institute, and KnA Consulting participated in the meeting.

2.3. The 1st Expert Meeting

The participants thoroughly reviewed the management items related to the safety of the decoction type of PHMs in South Korea and other countries before the meeting. The meeting was held as the participants were allowed to present any opinion they thought to be relevant. The meeting went on for two hours, and all of the participants were allowed to present their opinions.

Afterward, the test items that are deemed to be essential for securing the safety of decoction medicines were identified based on the items presented by the experts. As a principle, the conclusion of the meeting was to be drawn with an unanimous agreement. For any items with disagreement, the discussions were to continue until an agreement was finally reached.

With this, the items that are deemed essential for the decoction type of PHMs were identified among the items that were presented by the experts.

2.4. The 2nd Expert Meeting

Concerning the items identified during the first meeting, the researchers summarized and presented the criteria and test methods suggested by the participating experts. All of the experts were advised to review the criteria and test methods thoroughly before the meeting. During the

two-hour meeting, all of the participating experts were liberally allowed to give any opinion they deemed relevant regarding the criteria and test methods. Afterward, a step of finalizing the consensus on the criteria and test methods was taken. For any disagreements on the criteria or test methods, the participants continued discussing until an agreement was reached. With this, the criteria and test methods for each item for securing the safety of the decoction type of PHMs were decided.

3. Result

3.1. Literature Review

The three documents that were identified through the search of South Korean databases were Korean pharmacopeia [1], the Korean herbal pharmacopeia [18], and the 'quality control guideline for herbal or botanical medicine extracts' [19].

The five documents identified through the search of overseas databases were the 'guidelines for the regulation of herbal medicines in the South-East Asia region of world health organization (WHO)' [16, 17], pharmacopoeia of the people's Republic of China [20], Japanese pharmacopoeia [21], Japanese standards for non-pharmacopoeial crude drugs [22], European pharmacopoeia [23], and the US botanical drugs development guidance for industry [24].

The literature review of the safety management standards related to the decoction type of PHMs resulted in the identification of six items, which included heavy metal,

Table 1 The Result of the Literature Review of the Safety Management Standards for Decoctions Type of Personalized Herbal Medicine.

Classifications		WHO	South Korea	China	Japan	Europe	US
Heavy metals	H and HM	○	○	△	○	○	×
	HP and HMP	○	○	△	○	△	△
Pesticides	H and HM	○	○	△	○	○	○
	HP and HMP	○	○	△	○	△	△
Sulfur dioxide	H and HM	×	○	△	×	×	×
	HP and HMP	×	×	×	×	×	×
Benzopyrene	H and HM	×	△	×	×	△	×
	HP and HMP	×	○	×	×	△	×
Mycotoxins	H and HM	△	△	△	×	△	△
	HP and HMP	○	×	△	△	○	△
Microorganism or Microbial limit	H and HM	○	×	×	×	△	△
	HP and HMP	○	○	×	×	○	○

○: Be applicable, ×: Not applicable, △: Determined according to the detailed requirements.

* H: herb, HM: Herbal Material, HMP: herbal medicinal products, HP: herb preparations, US: United State

pesticide residue, sulfur dioxide, benzopyrene, mycotoxin, micro-organism limits (Table 1).

3.2. Selection of Safety Management Standard: Result of the 1st Expert Meeting

Based on the two suggestions below, it has been agreed to prepare standards for the management of hazardous substances based on 'the quality control guideline for herbal or botanical medicine extracts.' (1) The formula that was the most similar to decoctions was the herbal or botanical medicine extracts. Therefore, the 'quality control guideline for herbal or botanical medicine extracts,' which is the only standard with a guideline on herbal extracts, shall serve as the basis. (2) Since the purpose of this study is to suggest the management standard for the decoctions to be used in South Korea, the medical product management standard by Korean MFDS will be followed.

As a result, five items of heavy metal, pesticide residues, sulfur dioxide, benzopyrene, micro-organism limits, and pH were identified. According to the WHO guideline [16, 17] and the European pharmacopoeia [23], mycotoxin was added to the list, as well. As a result of the 1st expert meeting, a total of six hazardous material management standard items were identified. The items of test and their rationale were as shown in Table 2.

3.3. Selection of Test Criteria and Test

Method: Result of the 2nd Expert Meeting

During the 2nd expert meeting, the test criteria and test methods for the pre-selected six standards identified during the 1st meeting were decided upon (Table 3.) As for the six items of heavy metal, pesticide residues, sulfur dioxide, benzopyrene, mycotoxin, and micro-organism limit, the standard for a formulation in Korean pharmacopoeia that was similar to decoctions (e.g. herbal or botanical medicine extracts) were used as the reference. Since the WHO guideline [16, 17] and the 'quality control guideline for herbal or botanical medicine extracts' [19] were not legally binding, it was agreed that the test criteria and test methods were to be developed based on the legally binding standards of Korea pharmacopoeia [1] and the Korean herbal pharmacopoeia [18].

4. Discussion

HMs have been prescribed based on thousands of years of experience and the original pharmacological theories in TM. The decoction type of PHM, which is a type of extract prepared through the mixing and dispensing processes of herbs, has been most widely used throughout history and is still the most preferred formulations in China, South Ko-

Table 2 The Safety Management Standard for Decoctions Type of Personalized Herbal Medicine.

Number	Safety Management Standard	Rationale of Application
1	Heavy metals (lead, arsenic, mercury, cadmium)	- The guideline for herbal or botanical medicine extracts - Korean pharmacopoeia
2	Pesticide residues (five organic chlorine types) (Total DDT, total BHC, aldrin, endrin, and dieldrin)	- The guideline for herbal or botanical medicine extracts - Korean pharmacopoeia
3	Sulfur dioxide	- The guideline for herbal or botanical medicine extracts - Korean pharmacopoeia
4	Benzopyrene	- The guideline for herbal or botanical medicine extracts
5	Mycotoxin (total aflatoxin, aflatoxin B1)	- The WHO guideline
6	Micro-organism limits (total aerobic bacteria, total fungi, E. coli, salmonella, pseudomonas aeruginosa, staphylococcus aureus)	- The guideline for herbal or botanical medicine extracts - Korean pharmacopoeia

* BHC: benzene hexachloride, DDT: dichloro diphenyl trichloroethane.

rea, and Japan today [9]. While decoctions have been used for many years with a proven record of safety, the demand for the criteria for the efficacy and safety of decoctions and their regulations is increasing within the society [25, 26].

The TKM clinics of South Korea are required to use the medicinal herbs that conform to the hazardous material test criteria set by Korea MFDS in preparing decoctions. However, it is possible to use herbs that are not tested if these herbs are not included in the list of 601 registered herbs in Korean pharmacopoeia and the Korean herbal pharmacopoeia [1, 18]. Also, of these 601 medicinal herbs, there are only two items that have the criteria on benzo-pyrene, while 20 are regulated by the criteria for mycotoxin [1, 18]. As the test items for these medicinal herbs vary widely, the safety of the final decoction products has been questioned for years. For this purpose, the researchers conducted this study to secure the safety of the decoction type of PHMs, through the literature review and a process of consensus among experts.

As for the criteria for hazardous materials for the medicinal herbs used in South Korea, Korean pharmacopoeia and the Korean herbal pharmacopoeia requires tests on heavy metal, pesticide residues, sulfur dioxide, mycotoxin, and benzopyrene, depending on the characteristics of each item [1, 18]. And, as for extracts, the 'quality control guideline for herbal or botanical medicine extracts' has been used as the basis of regulating the quality of extracts that are used as the raw material for herbal or botanical medicines [19]. As for the extract of raw materials, the required test items are, respectively, heavy metal, pesticide residues, sulfur dioxide, mycotoxin, and other remaining contaminants, while the extracts are to be tested for heavy metal, pesticide residues, solvent residue, and other remaining contaminants [19]. According to the Pharmaceutical Act of South Korea, different purity test requirements apply as outlined in the Korean pharmacopoeia and the

Korean herbal pharmacopoeia [1, 18]. The micro-organism limit tests, in the meantime, cover the total aerobic bacteria, total fungal count, and specific micro-organisms (*E. coli*, salmonella, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*), for the herbal or botanical medicine extracts [19].

As for heavy metals, Korean pharmacopoeia requires that the total heavy metal is tested or that lead, mercury, arsenic, and cadmium are tested individually [1]. International pharmacopoeia or guidelines were also regulating chromium and copper. The heavy metals that were being regulated varied depending on the country. However, all countries were regulating arsenic and lead, while only China had the standard for the total heavy metal [20]. The heavy metal standards were in place in all countries for finished herbal products. And, only China and South Korea had heavy metal standards for herbal materials. Only South Korea had the standard for heavy metal in herbal or botanical medicine extracts.

The literature review on domestic and overseas documents showed that the standards for pesticide residues covered dichloro diphenyl trichloroethane (DDT), benzene hexachloride (BHC), aldrin, dieldrin, and endrin. Europe and the US were regulating aldrin, dieldrin, and endrin, while Japan was regulating two pesticide residues. South Korea was regulating all five pesticide residues.

As for sulfur dioxide, only South Korea had the standard to regulate chemicals as hazardous materials. HM materials are highly subject to the influence of the weather during the drying process. For this reason, it is a common practice to dry such materials indoors using coal as the fuel, instead of drying them outdoors under the sun. While this indoor drying process may be cheaper, it has been known to compromise health [27]. Therefore, it is necessary to set the testing criteria for monitoring sulfur dioxide.

Table 3 The Test Criteria and Test Methods for each Safety Management Item for Decoctions Type of Personalized Herbal Medicine.

Safety Management Standard		Test Criteria	Test Method	Rationale of Application
Heavy metal	Lead, arsenic, cadmium	Lead 5 ppm or less Arsenic 3 ppm or less Cadmium 0.3 ppm or less	Preparation of the test solution) Add 20 mL of nitric acid to 10.0 g(mL) of the sample. Then, stand for a certain amount of time within a hood to remove the emitted gas. Then, the substance was separated using an automatic wet heat separation device. Filter the separated liquid and dilute to 50 mL with distilled water to prepare the test solution. Then, manipulate 20 mL of nitric acid in the same manner with that of the test solution to prepare the blank for correction. Analysis instrument) Inductive coupling plasma spectrophotometer	Reference: KP, botanical medicine Test method: the general test method in KP Botanical medicine test method for lead, arsenic, and cadmium
	Mercury	0.2 ppm or less	Preparation of the test solution) Take precisely 50 mg (50 μ L) of the sample to be analyzed by adding into a mercury analysis vessel in an order of M reagent -> sample -> M reagent -> B reagent -> M reagent. Analysis instrument) Mercury analyzer	Reference: KP, botanical medicine Test method: the general test method of KP, botanical medicine test method, mercury
Pesticide residues (five organic chlorine types)		Total DDT 0.1 ppm or less Total BHC 0.2 ppm or less Aldrin 0.01 ppm or less Endrin 0.01 ppm or less Dieldrin 0.01 ppm or less	Preparation of the test solution) Mix 25 ml of the sample with 15 ml water and 90 ml acetone. Mix evenly for five minutes and depressurization-filter in a depressurization flask. Remove the remaining liquid to the aliquoting funnel. Add 50 ml saturated sodium chloride solution, 100 ml water, and 70 ml dichloromethane, and aliquot to collect the dichloromethane layer. Then, add 70 ml dichloromethane one more time to extract, before adding the dichloromethane layer and dehydration-filtering. The remaining liquid is depressurization-condensed in a 40°C water bath. Put this liquid into a Florisil cartridge that is activated by 6 ml of hexane and 6 ml hexane/acetone (8:2) solution after melting in 4 ml hexane in advance. Then, extract with 5 ml hexane/dichloromethane/acetone solution (50:48.5:1.5), and nitrogen-condensate the extracted liquid. Finally, this mixture was melted in 8:2 hexane/acetone solution 2 ml to prepare the test solution. Analysis instrument) gas chromatography	Standard: KP for herbal medicines (botanical drug) Test method: The standard test method of KP Botanical drug test method for pesticide residues

Safety Management Standard	Test Criteria	Test Method	Rationale of Application
Sulfur dioxide	30 ppm or less	Test solution preparation) Add 50ml of the sample to a distillation flask. Then, add 400 ml water, 4 ml/L hydrochloric acid 90 ml, and 100 ml of 5% ethanol. Heat the mixture to 100 °C, and pass nitrogen gas at a rate of 0.21 L/minute. Add 3% hydrogen peroxide solution 30 ml to the collection tube. Then, once the solution is boiled for 1 hour and 45 minutes, remove the collection tube and wash the top of the gas guide pipe with a small amount of 3% hydrogen peroxide solution and add it to the calculation. Then, use a micro burette to titrate with 0.01 mol/L hydrogen peroxide solution. The endpoint of the titration was when yellow color appeared and persisted for at least 20 seconds. The blank test was conducted in the same way. Analysis instrument) Automatic Potentiometric Titrator	Reference: KP, botanical medicine Test method: The general test method of KP, botanical drug test method for sulfur dioxide
Benzopyrene	5.0 ppb or less	Preparation) Add 80 ml water to a 25 mL sample. Ultrasound-extract for 90 minutes and add 100 ml hexane and 1 ml internal standard solution. Mix evenly for five minutes using a homogenizer, and perform ultrasound extraction for the following 30 minutes. Transfer the hexane layer to an aliquoting funnel. Add 50 ml hexane to the water layer and repeat the process twice. Extract and put the hexane layer into an aliquoting funnel. Add 50 ml water to the hexane layer to wash it and dehydrate it with sodium sulfate anhydrous. Activate a florisil cartridge and add the extraction solution. Then, eluate with hexane/dichloromethane (3:1) solution 20 mL. Blow away the effluent under nitrogen gas in a water bath of 35°C or lower. Then, melt the residue in 1 mL acetonitrile and filter with a membrane filter of 0.45 µm. Analysis instrument) HPLC/FLD	Reference: KP, botanical medicine Test method: KP general test method, botanical medicine, benzopyrene
Mycotoxin (total aflatoxin, aflatoxin B1)	Total aflatoxin (the sum of aflatoxin B ₁ , B ₂ , G ₁ , and G ₂) no more than 15.0 ppb (provided that aflatoxin B ₁ is no more than 10.0 ppb)	Preparation of the sample solution) Mix 5 ml sample with 10 ml of a solution of water and methanol (3:7). Conduct ultrasound extraction for 30 minutes and add 25 ml phosphoric acid buffer containing 2% tween 20 and filter it with a textile filter. The residual solution was passed through an immunoaffinity column (Aflatest, Vicam) for aflatoxin, before being washed with 10 ml phosphoric acid buffer containing 2% tween20 and 10 ml water. Then, after passing air for 10 seconds using a syringe, the immunoaffinity column for aflatoxin was dried. Add 0.5 ml to the immunoaffinity column for aflatoxin and eluate with gravity. Repeat this process three times, and put the effluent together. Then, add deionized water to a total volume of 2 ml and filter with a 0.45 µm syringe filter to prepare the test solution. Analysis instrument) HPLC/FLD	Reference: KP, botanical medicine Test method: the general test method of KP for botanical medicine, mycotoxin
Micro-organism limits	Total aerobic bacteria count	1×10 ⁵ or less (CFU/g, mL)	Standard: KP for herbal medicines (botanical drug) Test method: the general test method in KP for micro-organism limits.
	Total fungi count	1×10 ² or less (CFU/g, mL)	
	E. coli	None	
	Salmonella	None	
	pseudomonas aeruginosa	None	
Staphylococcus aureus	None	Take 10 ml of the sample and dilute it with pH 7.2 phosphoric acid buffer solution to prepare the test solution. Take 10 ml of the test solution and inoculate it on soybean casein digestion fluid medium and mix it. Culture at 32°C for 24 hours. Transfer the culture solution to the Cetrimide agar medium. Culture at 32°C for 72 hours and count the colonies of pseudomonas aeruginosa.	

* BHC: benzene hexachloride, DDT: dichloro diphenyl trichloroethane, KP: Korean pharmacopeia

According to Korea pharmacopeia [1], only *Rehmanniae Radix Preparata* (熟地黄) and *Rehmanniae Radix* (地黄) had the standards for testing benzopyrene. A decoction type of PHMs is a type of extraction prepared by mixing and processing herbal materials. However, in TM, the herbal materials go through additional processes, such as frying or burning, to maximize the efficacy in treatment [28]. During this additional processing, benzopyrene may be generated. Therefore, it is necessary to regulate this substance by setting a standard for it.

The standards on mycotoxin are based on aflatoxin, which is known to be of the highest toxicity. When compared based on the requirements on total aflatoxin, South Korea, Europe, and Japan had a stricter standard compared to the US. However, the detailed items of these standards varied among countries. As for South Korea, the requirement for all botanical medicines was total aflatoxin in 15 ppb or less and aflatoxin B1 10 ppb or less. For other countries, the standards varied depending on the types of products. The range of total aflatoxin was between 10 and 20 ppb.

In South Korea, the herbal or botanical medicine extracts were being regulated for the contamination by micro-organisms that were not regulated for herbal materials using micro-organism limit tests. The standards covered the total aerobic bacteria, total fungi, and specific micro-organisms (*E. coli*, salmonella, pseudomonas aeruginosa, and staphylococcus aureus). China had the standards for herbal extracts covering total aerobic bacteria and total fungi. The specific bacteria were not being regulated. The WHO guideline contains somewhat relaxed criteria for the hot water extracts of botanical drugs covering total aerobic bacteria and total fungi compared to the requirements in effect in South Korea. However, the WHO was recommending the regulation of clostridium and shigella, which were not being regulated in South Korea. The United States and Europe had the standard for total aerobic bacteria and total fungi in raw materials and finished products that were plant-based. Europe also had an additional set of criteria for specific micro-organisms (*E. coli* and salmonella).

A total of seven documents were identified through the search of international search. The result of the literature review showed that only South Korea had quality management standards for herbal or botanical medicine extracts as a medicine product. The expert meeting brought that a total of six items, which were, respectively, heavy metal, pesticide residues, sulfur dioxide, benzopyrene, mycotoxin, and micro-organism limits, were identified as the hazardous materials in a decoction type of PHMs. However, while the said guideline also contained the management criteria for the solvent for extracting, these were dismissed as deemed irrelevant to decoction medicines, which are extracted using hot water. Finally, the six items below are finalized as the hazardous material management standard for decoctions; (1) individual heavy metals (lead, arsenic, mercury, and cadmium), (2) pesticide residues (five pesticides of organic chlorine types), (3) sulfur dioxide, (4) mycotoxin (total aflatoxin and aflatoxin B1), (5) benzopyrene, (6) micro-organisms (total aerobic bacteria, total fungi, *E. coli*, salmonella, pseudomonas aeruginosa, and

staphylococcus aureus).

The strength of this review is that it is the first study that provided the hazardous material test items and criteria for the decoction types of PHMs and can be used as the basis for introducing a safety management system for the decoction types of PHMs by the government in the future.

The limitations of this review are as follows; First, this study is found wanting in terms of the credibility of the experts who selected the test items and criteria (there was no sampling) or their representativeness (only a handful of experts). Second, the literature review was limited to the data that were in English or Korean language. Therefore, the databases from the countries which have been using traditional decoction medicines were not included in the study. Finally, no pilot tests to apply the criteria set in this study were conducted.

In the future, it would be necessary to conduct a pilot test to ensure the validity and credibility of the test items, criteria, and methods, as well as their field relevance. Especially, a sufficient number of decoction monitoring, public hearings and gathering of the opinions from the field would have to be conducted. Finally, it would be necessary for the government to introduce the decoction safety management program so that the people of the country may use proven decoction medicines.

5. Conclusion

In this study, the researchers developed a set of safety management standards for the decoction type of PHMs, which included individual heavy metals, pesticide residues, sulfur dioxide, mycotoxin, benzopyrene, and micro-organisms. In the future, it would be necessary to verify the field relevance and applicability of the test items, criteria, and methods by monitoring the decoction medicines prescribed by actual TM clinics.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Funding

This study was supported by a grant from the Project of National Development Institute of Korean Medicine, Accreditation of External Herbal Dispensaries of Traditional Korean Medicine Clinics, funded by the Korea Ministry of Health.

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