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## Original Article

## Current status of the spontaneous reporting and classification/coding system for herbal and traditional medicine in pharmacovigilance

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## ABSTRACT

**Background:** While the use of herbal and traditional medicine (H&TM) has been extensive worldwide, the current status of H&TM management in pharmacovigilance remains to be investigated. To date, there is little information regarding the use of the classification/coding system (CCS) to detect signals for certain drugs within databases built on the basis of the spontaneous reporting system (SRS). The purpose of this study is to investigate the status of the SRS and CCS for H&TM in the pharmacovigilance systems of various countries around the world.

**Methods:** An e-mail survey was performed from late December 2018 to early January 2019 with 54 experts in pharmacovigilance. The results based on the information provided by the respondents were summarized.

**Results:** Fourteen experts from 13 countries responded to the survey. Eleven countries/regions were found to already include H&TM in their SRSs, managing only limited range of H&TM. Of the 9 countries/regions that provided the information on the status of CCS for H&TM in their domestic pharmacovigilance systems, only China had a separate CCS for H&TM.

**Conclusion:** Revising the current pharmacovigilance systems to include or expand the range of H&TM, and developing an internationally harmonized system to classify and code H&TM suitable to the unique characteristics of H&TM are critical and overall beneficial.

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## 1. Introduction

The use of herbal and traditional medicine (H&TM), experienced by more than 80% of the world's population, is not unusual anymore.<sup>1</sup> While H&TM are used extensively, information regarding its safety is still lacking. As the use of H&TM has been based on empirical tradition, rather than the premarketing research process, to date, only few of the H&TM have been entirely evaluated for their safety under modern scientific guidelines.<sup>2</sup>

Thus far, H&TM have been considered relatively less risky than conventional medicine, however, the complete absence of adverse reactions might not be feasible.<sup>3</sup> The safety of H&TM has become an issue worldwide, with the administration of some herbal products containing aristolochic acid resulting in reported nephropathy.<sup>4</sup> In the United States, marketing of dietary supplements, including

herbal medicines, containing ephedra alkaloids has been discontinued due to the reporting of cardiovascular and central nervous system events.<sup>5</sup> The vague belief that H&TM are safe solely based on their origin in nature, is no longer robust even in East Asia where H&TM have been widely utilized for a very long time. For example, in Japan, after a series of interstitial pneumonia cases were reportedly caused by *Sho-saiko-to*, the need for awareness about the safety of H&TM has been heightened.<sup>6</sup> According to a domestic statistics on over-the-counter H&TM in Japan, reports of adverse events (AEs) have tripled over the past decade, with serious AEs showing an increasing trend.<sup>7</sup> In China, 10%–15% of the adverse drug reactions (ADRs) identified by the national pharmacovigilance center are known to be related to H&TM.<sup>8</sup> Similarly, a prospective cohort study in a Korean traditional medicine hospital reported that AEs were found in about 10% of the patients who had been prescribed H&TM.<sup>9</sup>

Unlike conventional medicines that require active substance screening, preclinical studies, and large-scale clinical trials to get approval for marketing, most H&TM have been used empirically

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without going through these complicated procedures. Although pharmacological and toxicological evaluations of H&TM have been conducted using analytical chemistry, cell and animal experiments, and clinical trials, there is still insufficient information available on the safety of H&TM.<sup>2</sup>

In order to compensate for such a weak point, safety monitoring targeting H&TM based on clinical settings is essential.<sup>2,10</sup> As the level of awareness of the need to include H&TM in pharmacovigilance increased, the world health organization (WHO) officially suggested that the national pharmacovigilance systems should monitor H&TM along with conventional medicines.<sup>11</sup>

The primary method utilized to collect safety data in post-marketing surveillance is the spontaneous reporting system (SRS).<sup>12</sup> SRS can provide information on ADRs of drugs in the market at the population level. It is a starting point for the early detection of signals for new, unknown or serious ADRs.<sup>12</sup> Therefore, using this system, pharmacovigilance centers in several countries have collected AEs, and the WHO has been working on establishing and gathering these AEs into a large database, called VigiBase of Uppsala Monitoring Center (UMC), based on global reports through the Programme for International Drug Monitoring.<sup>13</sup> As of June 2020, 171 countries were participating this program as full or associate members.<sup>14</sup> Data gathered in VigiBase is accessible to anyone through a public access version called VigiAccess ([vigiAccess.org](http://vigiAccess.org)).

To analyze the data collected through the SRS, a classification/coding system (CCS) for drugs is required. In the absence of such an analytical tool, the detection of signals in large databases assembled using the SRS, and a meaningful utilization of knowledge for safe drug use, is challenging. Hence, UMC introduced the anatomical therapeutic chemical classification (ATC) system and standardized the classification of different kinds of drugs reported from around the world.<sup>15</sup>

With the formation of an international consensus that a pharmacovigilance system is needed not only for conventional drugs, but should also include H&TM, there is an increased interest in the SRS and CCS for H&TM.<sup>16</sup>

In the United States and Canada, for example, H&TM is categorized as dietary supplements or natural health products, respectively, rather than medicines, but both countries collect AEs for H&TM as well as conventional medicines using a single case report form in their SRS.<sup>17,18</sup> In Europe, the European Medicines Agency monitors the safety of drugs including H&TM,<sup>19</sup> but each country has its own specific SRS.<sup>20</sup> In the United Kingdom, its SRS, the yellow card scheme, treats both conventional medicines and H&TM,<sup>21</sup> while Italy has separate reporting routes and regulatory authorities to receive AEs for registered drugs and natural health products including herbal preparations.<sup>20</sup>

De Smet proposed the herbal ATC (HATC), compatible with the ATC system for conventional drugs, as a CCS for H&TM.<sup>22</sup> The WHO-UMC has accepted the HATC and issued its guidelines and index in 2004.<sup>23,24</sup> Currently, all the codes for H&TM are completely integrated into the ATC system of WHODrug Global, so a separate HATC system is not available.<sup>25</sup> In contrast to the original HATC that included mainly plant-derived products, the UMC has been working to expand the range of the registered H&TM to include animal or insect components in the WHODrug.<sup>26</sup> Several countries that have started using the existing pharmacovigilance system to monitor H&TM, have reported to be advancing to the stage of signal detection.<sup>27,28</sup>

However, the current situation of the introduction of the SRS and CCS for H&TM, in the pharmacovigilance system of each country, is not well known. The aim of the present study was to investigate the status of the SRS and CCS for H&TM in various countries around the world.

## 2. Methods

This study comprised an e-mail survey to investigate the current status of the SRS and CCS for H&TM in various countries. From December 26, 2018 through January 15, 2019, questionnaires were sent to experts of pharmacovigilance from 34 countries and the responses received via e-mail. The e-mail list was composed mainly of the members of the H&TM special interest group of the International Society of Pharmacovigilance (ISO-P), attendees of the UMC pharmacovigilance training course in 2017, also included corresponding authors of important articles related to the pharmacovigilance of H&TM. When the responders introduced other experts, additional e-mails were sent to those experts. We sent e-mails to a total of 54 individuals in 33 countries and one region. When two experts from the same country replied differently, we asked them to discuss and draw a conclusion.

The questionnaire consisted of seven major questions (appendix 1). The first question was about whether the domestic SRS included H&TM. The countries that responded 'yes' to the first question were considered as the main analysis subjects (MAS). The MAS were questioned in further detail about the status of H&TM management in the SRS, and about the use of any separate CCS for H&TM: whether the SRS included only pharmaceutical products authorized by the regulatory authority, raw materials, H&TM dispensed at medical institutions, or H&TM obtained through routes other than the above-mentioned methods; how H&TM were being named in the AE reports of the SRSs, whether official names registered in government documents such as pharmacopoeias were being adopted, or the use of other methods; whether the regulatory agency used any specific coding system when registering H&TM products; the type of CCS for conventional drugs and the existence of any separate systems for H&TM. Finally, they were asked to freely describe the challenges they experienced when reporting or analyzing the AEs related to H&TM, or their opinions to improve the current SRS.

The survey results were summarized in tables. The responses to the subjective questions were summed up in such a way that preserved the words used by the respondents.

## 3. Results

During the given period, responses were received from 13 countries including China, Singapore, South Korea, Thailand, Azerbaijan, Albania, Greece, the Netherlands, Morocco, Oman, Sudan, Costa Rica, Canada and one region from Hong Kong. Finally, the response rate was 41.2%, including information from five Asian countries/region including South Korea, four from Europe, three from Africa, one from North America, and one from South America. Ten (71%) of the respondents were staff in charge of regulatory authorities or national pharmacovigilance centers, while the other four (29%) were pharmacovigilance experts in hospitals or universities.

Table 1 shows the status of H&TM in SRSs of the countries/region that responded to this survey. In total, 11 countries/region (MAS) except for Albania, Sudan and Costa Rica have included H&TM in the SRS of drug regulatory authorities of each country. At a minimum, all countries in the MAS were receiving AE reports related to the pharmaceutical H&TM products authorized by the regulatory authorities. Five countries (Singapore, the Netherlands, Morocco, Oman, and Canada) were managing every type of H&TM, including raw materials, H&TM dispensed at medical institutions, and H&TM obtained through any other routes as well as the H&TM products that obtained marketing approval in their domestic SRS. Four countries/region (South Korea, Hong Kong, Thailand and Azerbaijan) were receiving the AE reports related to the licensed products

**Table 1**  
Inclusion of herbal/traditional medicine in spontaneous adverse event reporting system in each country/region.

Question	Hong Kong	China	Singapore	South Korea	Thailand	Azerbaijan	Albania	Greece	Netherlands	Morocco	Oman	Sudan	Costa Rica	Canada
Included in SRS	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y
Type of H&TM	Y	N	Y	Y	Y	Y	NA	Y	Y	Y	Y	NA	NA	Y
Y RA-approved PP	Y	N	Y	Y	Y	Y	NA	N	Y	Y	Y	NA	NA	Y
Raw materials	Y	N	Y	Y	Y	Y	NA	Y	Y	Y	Y	NA	NA	Y
Medicines prepared at MIs	Y	N	N	Y	N	N	NA	Y	Y	Y	Y	NA	NA	Y
The others	N	N	N	Y	N	N	NA	N	Y	Y	Y	NA	NA	Y

SRS: spontaneous adverse event reporting system, Y: yes, N: no, H&TM: herbal & traditional medicine, RA: regulatory authorities, PP: pharmaceutical products, MI: medical institutions, NA: not answered.

and raw materials, and two (China and Greece) were dealing with only the products approved by regulatory agencies (Table 1).

With regard to the nomenclature of the H&TM used in the AE reports of the domestic SRSs of each country, nine out of the MAS responded that they were using the official names registered in the government documents such as pharmacopoeia. Among the other countries, Singapore was using scientific names of plants, and Morocco was adopting trade names or vernacular names used by consumers or experts (Table 2).

The next question was whether the regulatory agencies of each country were using any specific coding system to register the H&TM products. Seven countries/regions (South Korea, Hong Kong, Thailand, Azerbaijan, Greece, and Netherlands) were assigning official registration codes to all the regulatory agency-approved products, including H&TM. In South Korea, not only was a product code set for registered products, but also a separate coding set (main ingredient codes) was prepared for raw materials of the H&TM, which were the constituent materials in the mixed type of H&TM products. Canada defined vitamins, minerals, herbal remedies, homeopathic medicines, traditional medicines, probiotics, amino acids, and essential fatty acids as natural health products (NHP) and assigned separate registration codes such as natural product number, homeopathic drug number etc. Singapore coded active ingredients of the drugs as the scientific names or botanical names, and described the used parts of the plants. Morocco stated that no codes were designated for H&TM products because the H&TM is not regulated by law. Oman is planning to assign Data Matrix 2-D bar codes to all registered pharmaceutical, herbal, health products and medicated medical devices beginning March 2019 (Table 2).

Among the 11 countries/regions constituting the MAS, nine, except Hong Kong and Canada, responded in regards to the kinds of the CCS used for conventional drugs in the pharmacovigilance system of each country. Eight countries, except China, were using the WHO-UMC ATC system. The national ADR center in China was using a separate CCS based on indications (Table 2).

Of the 10 countries/region forming the MAS, except Canada, all countries/region responded to the question regarding the CCS for H&TM in domestic pharmacovigilance systems. No responding countries, except China, had a separate system for H&TM. The responders from China and Hong Kong reported that the WHO-UMC HATC could not be adopted, as it did not fit the theory of traditional Chinese medicine (TCM). China classified the H&TM in accordance with their indications in the TCM theory. In case of Hong Kong, even though a specific CCS was not in use, the nomenclature and terms of TCM written in China were utilized when analyzing the reports. Thailand categorized single herb agents according to their composition, while mixture type preparations were classified as per indications or the reason for medication. Morocco was using vernacular names from the WHO dictionary, instead of adopting a separate classification system for H&TM. Oman divided the H&TM into herbal, traditional, homeopathic, Ayurvedic and Chinese, but no more sub-classification system existed (Table 2).

Among the MAS, all countries, except Hong Kong, reported that they were sending the AEs related to H&TM, as well as those related to conventional medicines, to the UMC. All the 10 countries were full member countries of the WHO program for international drug monitoring (Table 2).

In the final question, the responses received regarding the challenges faced were approximately divided into four categories. The identification of the offending ingredient was the most frequently reported issue (Singapore, Morocco, and Oman). Many H&TM are mixtures of several herbs, making it difficult to determine the suspected ingredient when an AE occurred. Furthermore, the lack of information on dose and the part of the plant used, complicated the analysis of the causative substance. Occasionally, unknown prod-

**Table 2**  
Current status of herbal/traditional medicine management in pharmacovigilance system in each country/region.

Question	China	Hong Kong	Singapore	South Korea	Thailand	Azerbaijan	Albania	Greece	Netherlands	Morocco	Oman	Sudan	Costa Rica	Canada
Nomenclature	ON	ON	TN or LN	ON	ON	ON	NA	ON	ON	TN or VN	ON	NA	NA	ON
Registration code	Y	Y	Y	Y	Y	Y	NA	Y	Y	N	Y	NA	NA	Y
Classification/coding system	CM	Indication	NA	ATC	ATC	ATC	ATC	NA	ATC	ATC	ATC	ATC	NA	NA
Report to UMC	CM	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	NA	NA
	H&TM	Y	N	Y	Y	Y	Y	NA	Y	Y	Y	Y	NA	NA

CM: conventional medicine, H&TM: herbal & traditional medicine, ON: official name, TN: trade name, LN: Latin/botanical name, NA: not answered, VN: vernacular name, Y: yes, N: no, I: Indication, ATC: anatomical therapeutic chemical classification system.

ucts or samples without labelling were received. In certain cases, no additional information about the drug, other than the H&TM nature, was reported. Secondly, complaints of under-reporting and an insufficiency of data to perform analysis, was established (Singapore, Oman). Some countries also mentioned the lack of a CCS for H&TM (China, the Netherlands). Cases reporting the problems of irregular naming of H&TM were also documented (China, Hong Kong). Doctors, pharmacists, and consumers often use different names for the same H&TM, hence necessitating a separate task to standardize the names of the H&TM was required when building up the database. This was listed as an obstacle to the automation of signal detection.

The most frequent suggestion on the improvement of the current system for H&TM was the necessity to introduce a CCS for H&TM (China, the Netherlands). The lack of a CCS made the classification and standardization of the data difficult, and an obstacle in signal detection. The importance of introducing a CCS suited to the characteristics of H&TM, to harmonize the global safety monitoring technology has been emphasized. The other suggestions included were the requirement to register all H&TM products actually in circulation in the domestic systems (Oman), an increased awareness of the pharmacovigilance for H&TM to activate the AE reports for H&TM (Singapore, Oman), and the composition of a global communication group specific for H&TM pharmacovigilance to share related information and updates on the latest knowledge (Oman).

#### 4. Discussion

This survey demonstrated the current state of the CCS for H&TM and the management of the H&TM in the SRS in various countries around the world. While some countries did not manage H&TM in the SRS, it is essential to note that even countries that included H&TM in the pharmacovigilance systems were in actuality managing only products approved by regulatory authorities. However, unlike conventional medicine, apart from the pharmaceutical products that obtained approval, there are several types of H&TM such as raw materials, medicines prepared at medical institutions, or drugs that consumers acquired through routes other than the above-mentioned methods. Eventually, it has been confirmed that many of the H&TMs distributed are still excluded from the current pharmacovigilance system. Considering the characteristics of H&TM distribution channels, it is necessary to receive the reports of AEs related to H&TM and revise the current pharmacovigilance system to include the whole range of H&TM that are in circulation.

Most of the countries that have been including the H&TM in their SRSs responded that the official names registered at government documents for the nomenclature of H&TM were being used. They also stated that they had the registration coding system for all the drugs, including H&TM, approved for marketing by regulatory authorities. However, some countries reported the use of only trade names of the products, Latin names of the plants, or vernacular names.

To classify and/or code the drugs reported to the SRS, all countries, except China, were using the ATC of WHO-UMC. However, none of the countries adopted the ATC to classify or code H&TM. All surveyed countries, except China, which has been using a CCS for H&TM according to the indication based on traditional medicine theory, reported that there were no separate systems available to classify or code H&TM.

Even though sufficient data regarding H&TM have been secured in the SRS databases, obtaining meaningful information from this data remains challenging, if no system to identify and classify the causative drugs has been established. The CCS for drugs is a basis for data standardization and automatic signal detection in large databases. Therefore, in the early 2000s, WHO-UMC had already launched HATC, a CCS for H&TM which is compatible with the existing ATC for conventional medicine<sup>23–25</sup> and currently is attempting to expand the reach of H&TM included in the WHO-UMC drug dictionary, WHODrug.<sup>26</sup> The WHODrug is continuously updated based on the drug information recorded in one or more reports submitted to Vigibase, so the increase in AE reports related to H&TM will contribute to the expansion of categories in the H&TM in the dictionary. Therefore, it is necessary to promote the reporting on H&TM and to develop the CCS for H&TM at the same time.

However, none of the surveyed countries adopted the HATC as a domestic system as of now. H&TM are usually used in the context of unique concepts and terminologies of traditional medicine. The ATC system does not perfectly fit into the theory of traditional medicine and is one of the main reasons why several countries have not adopted HATC as a CCS for H&TM.<sup>29</sup> This challenge has been confirmed in this survey. The general characteristics of many traditional medicines must be considered, including the use of a holistic approach to the human body and mind,<sup>30</sup> for example, a singular herb may target multiple indications or even the whole system of human body and mind. In this case, under the ATC system, the herb may require tens or hundreds of codes corresponding to indications/diseases of the whole system. In addition, as several types of traditional medicine use a combination of many herbs, the system may become overly complicated as several additional codes may be required. Moreover, H&TM is often prescribed as mixtures of various kinds of herbs and it may be difficult to define the main active substance of a single herb as the kinds of constituents in a herb are various, often inhomogeneous, or even unknown.<sup>31</sup> Taking into account such a characteristic of H&TM, the difficulty to apply a code to the last level of the ATC when an H&TM is defined according to chemical composition, can be estimated. Although there have been suggestions such as matching the indications of H&TM of traditional theory to the therapeutic indications in the classification of ATC even after HATC,<sup>32</sup> the results of this survey demonstrated that they have not been applied in practice at least in the surveyed countries.

Of the 14 countries that participated in this study, 10 countries reported that the HM-related AEs were being sent to UMC, even though they had no CCS for H&TM. The WHODrug dictionary published by WHO-UMC assigns code v90 (unspecified herbal and TM),

or v91 (homeopathic preparation) to the reported H&TM en bloc. In situations where the codes for H&TM are undifferentiated, even if there were numerous H&TM reports in VigiBase, it is difficult to identify and classify each type of the H&TM in the database. Hence, many respondents in this survey suggested that a separate CCS for H&TM other than HATC is ultimately required.

A recent study on the current status of the classification of H&TM in the European Union has pointed out that there are loopholes in the system for drug safety, due to the lack of harmonization in the classification method for H&TM.<sup>33</sup> Attempts to derive signals related to H&TM from drug safety databases have been made in some countries<sup>8,28</sup>; however, progress is still limited due to the lack of an internationally harmonized CCS for H&TM. Based on the international consensus for the need to improve safety and drug monitoring capabilities in H&TM, the ISO officially launched the H&TM special interesting group in October 2017, and one of the major agenda of this group, is the improvement and standardization of the CCS for H&TM.<sup>34</sup>

Finally, some respondents submitted under-reporting of H&TM related AEs as one of the challenges faced in this field. Under-reporting is one of the well-known limitations of SRS, and a greater a problem in H&TM than in conventional medicine, due to reasons such as lower frequency of especially severe AEs, and a tendency of patients to be reluctant to report about medicines being consumed.<sup>31,35,36</sup> Quantitatively insufficient data cannot guarantee reliable information.<sup>37</sup> Considering these characteristics of H&TM, detection of reliable signals from a database of a single institution or a single country is difficult. To overcome these problems, UMC and the national pharmacovigilance centers or drug regulatory agencies of each country need to encourage and increase the reporting of H&TM-related AEs and as suggested by the participants of this survey, the establishment of a global network of pharmacovigilance experts for H&TM to communicate with each other to share the latest information and updates on knowledge actively is required.

The limitations of this study are as follows. First, all countries worldwide were not covered in this survey, nor the included countries selected based on a rigorous sampling design. Therefore, this study is not a comprehensive representation of the SRS and CCS for H&TM throughout the world. Second, although the authors did their best to reach out to experts of pharmacovigilance in each country, this article has not originated from the official reports of each country. Hence, the situations and suggestions presented in this article may differ from the actual circumstances, or the official opinions, of each country. Especially, information of other important Asian countries where herbal medicine is widely used such as Japan, Taiwan, India, and Malaysia are missing. In addition, countries that currently had included herbal medicine in the pharmacovigilance system already or had a high interest in safety monitoring for herbal medicine would have more likely to reply than those who did not. Thus, the outcome of this study could be biased towards the situation of countries where the pharmacovigilance for herbal medicine has been settled or being prepared. Finally, although the authors of this study reached out to the experts of pharmacovigilance in each mentioned country, this article did not originate from the official report of the national regulatory agencies of national centers for pharmacovigilance. Depending on the unofficial data received from an expert individual, there may be slight differences or changes in detail. Therefore, the situations and suggestions presented in this article may differ from the actual circumstances or the official opinions of each country.

Nevertheless, the information provided in this study will be useful to, at a glance, evaluate the status of SRS as well as CCS for H&TM in different countries in different regions, and to establish a policy to monitor the safety of H&TM.

In conclusion, even though the use of H&TM has been extensive worldwide, this study shows that the pharmacovigilance system

for the safe use of H&TM is still inadequate. Some countries still do not include H&TM as targets in their drug monitoring system, and those that did include H&TM in the drug monitoring, managed only a limited range of drugs in actual circulation. Even most of those countries that collected the AEs of H&TM did not adopt a CCS for H&TM. The lack of a CCS for H&TM is an obstacle to effective signal detection. This further interferes with the effective decision making in order to provide safety information to drug users, and to quickly identify and act on the critical safety. Therefore, it is unquestionably necessary to include H&TM in the pharmacovigilance systems, and also develop an internationally harmonized system for the classification and coding for H&TM suitable for the unique characteristics of H&TM.

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### Author contributions

Conceptualization: CH. Methodology: YW. Investigation: MK. Writing – Original Draft: MK, Writing – Review & Editing: YW, CH. Visualization: MK. Supervision: CH. Project Administration: MK, YW. Funding Acquisition: CH

### Conflict of interest

The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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### Ethical statement

This research did not require an ethical approval and the approval was waived.

### Data availability

All data associated with this study is included within the article.

### Supplementary material

The survey questionnaire can be found in the online version, at doi:<https://doi.org/10.1016/j.imr.2020.100467>.

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