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ORIGINAL RESEARCH ARTICLE

Qualitative Interviews with Stakeholders in Herbal Pharmacovigilance and Recommendations for Best Practices to be Applied Worldwide

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Abstract

Background and Objective The use of herbal products globally is substantial, but varying definitions and regulatory frameworks have led to differences in their status as medicinal products and in approaches to monitoring their safety. This article explores the current landscape of herbal pharmacovigilance, drawing insights from interviews with global experts in the field, and offers recommendations for best practices to enhance the safety and benefit-to-harm balance of herbal products.

Methods This study comprised semi-structured interviews with members of the International Society of Pharmacovigilance-Herbal and Traditional Medicines Special Interest Group and the Nutrivigilance Information Exchange Network, recruited using purposive sampling. Data were stored and coded using NVIVO® and analysed thematically using a qualitative inductive approach.

Results Sixteen participants from 11 countries were interviewed, revealing diverse regulatory approaches and challenges in herbal pharmacovigilance. Key themes included legal status, awareness, identification and coding of herbal products, pre-/post-marketing product control, reporting of adverse drug reactions, causality assessment and signals of herbal products. This study yielded five general recommendations to further improve herbal pharmacovigilance worldwide.

Conclusions This study offers an overview of the global landscape of herbal pharmacovigilance, highlighting challenges in monitoring herbal products and presenting universal recommendations. These recommendations encompass increasing awareness, enhancing education and improving legislative frameworks. Given the growing use of herbal products, the implementation of strong pharmacovigilance practices is crucial to ensure consumer safety.

Key Points

Herbal products differ in status and approaches to monitoring their safety.

This study offers an overview of herbal pharmacovigilance, highlighting challenges and presenting universal recommendations.

1 Introduction

Herbal products are broadly used worldwide, for a variety of indications: for the maintenance of health and the prevention and treatment of minor illnesses as well as (serious) chronic conditions. However, considerable differences exist in their regulatory status between countries [1]. Herbal medicinal products can be marketed as registered medicines, following legislation for medicinal products, or as food supplements under food legislation. In this article, we use 'herbal products' as an umbrella term for both herbal medicinal products and herbal supplements. Globally, there is no consensus on how herbal medicines are defined [1]. The World Health Organization (WHO) defines herbal medicines to "include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations" [2]. In some countries, herbal products may contain, by tradition,

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natural organic or inorganic active ingredients that are not of a plant origin (e.g. animal and mineral materials). The Herbal Directive of the European Union defines the term "herbal medicinal product" as "any medicinal product, exclusively containing as active ingredients one or more herbal substances, or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations" [3]. Homeopathic medicines are distinct from herbal medicines, although they can be prepared from herbal sources. This distinction comes from the methods used in their preparation as well as the principles (similia rule) on which they are prescribed [4].

The large differences in legislation of herbal products between countries lead to differences in the status of these products and also in recognition, especially by healthcare professionals [5]. Most herbal products do not have the same legal status as conventional medicines, resulting in less strict regulation of herbal products, often leading to confusion. Because of the differences in legislation between countries worldwide, there may not be a requirement for herbal products to prove efficacy and safety in the way that is required for conventional medicines. In the European Union, herbal products can be marketed based on a traditional use registration, a well-established use marketing authorisation, or a stand-alone or mixed application, which have their own requirements on safety and efficacy [6]. As a result of limited regulation, the quality of herbal products may vary substantially. Because of inadequate quality control, inconsistent levels of biologically active compounds in herbal products may occur. Furthermore, contamination (e.g. with heavy metals, pesticide residues, microbes, radioactivity), adulteration (e.g. deliberate addition of synthetic compounds) and misidentification (e.g. deliberate or unintentional replacement of the plant species) will impair the quality of herbal products. This has implications for clinical efficacy as well as for safety [7]. In many countries, most herbal products can be purchased without a (doctor's) prescription and are meant for self-care purposes, although there are some herbal products with a prescription-only status [8].

Pharmacovigilance is defined as *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects of medicinal products or any other medicine-related problem* [9]. This definition is to be applied more broadly than for registered medicines only, and is also relevant for herbal products. Pharmacovigilance of herbal products, marketed as food supplements, may be designated as phytovigilance or nutrivigilance. To ensure the safety of herbal products and to protect consumers, optimal pharmacovigilance practices must be in place. Historically, little attention has been paid to the adverse effects induced by herbal products [8]. However, their global use, together with worldwide reports of quality issues, adulteration and contamination of these products raises questions around whether there is adequate protection of the consumer from poor-quality and unsafe products [8]. Pharmacovigilance of herbal products needs to further improve in order to ensure a favourable benefit-to-harm balance regarding their use [8].

The systematic monitoring of adverse drug reactions (ADRs) caused by herbal products, however, is far more complicated than for conventional medicines. First, the documents and methods to assess safety reports are designed for conventional medicines. However, herbal products can be very different from conventional medicines: whereas conventional medicines are mainly used for one specific disease, herbal products can be used for a variety of ailments. Second, different parts of the same plant (leaves, root, stem) can be used for different purposes or medical conditions [10, 11], and various production processes can be applied to process the same material. It is often difficult to identify the specific biologically active ingredients in a herbal product. Considerable quantitative variations may exist in the content of secondary metabolites in representatives of the same plant species. Additionally, constituents may differ qualitatively between parts of a plant. In contrast to conventional medicines, the precise chemical composition of herbal products is often unknown or at least less precisely characterised. The production process and the solvent used for extraction are important determinants for the final composition of the product. Herbal products are chemically rich complex mixtures and the composition and thus the biological activity, safety and quality may vary between batches of a product. Standardisation of herbal products is necessary to ensure a predefined spectrum of ingredients, quantitatively as well as qualitatively, and thus setting the expected therapeutic effect of each dose and ensuring safety. Standardisation is also important for guaranteeing a constant quality of products from different batches. Many herbal products even contain more than one herbal ingredient. Therefore, it can be difficult to directly link the ADRs of herbal products to their mode of action as these are often not (completely) known [8]. Third, misidentification of medicinal plants, adulterations (deliberate or undeliberate) or mislabelling of herbal products are sometimes responsible for observed ADRs or interactions [12].

Another big challenge for the pharmacovigilance of herbal products is the underreporting of ADRs of this class of products. This is owing to the common belief that herbal products are natural and therefore safe. As a result, consumers do not recognise and report ADRs that may come from herbal products. Furthermore, healthcare providers (physicians, pharmacists) are often unaware of the use of herbal products by their patients and their knowledge about various aspects of herbal products can be limited. Patients do not mention their use because they consider herbal products to be harmless. When collecting information from patients for counselling or for conducting a medication review, they

should be explicitly questioned about the possible use of herbal products. This underreporting results in a scarcity of data and incomplete knowledge regarding the safety of herbal products (or the risks involved) [13]. The aim of this study was to create an overview of the current state of herbal pharmacovigilance and to provide recommendations about best practices of herbal pharmacovigilance based on interviews held with experts in herbal pharmacovigilance from different countries across the world.

2 Methods

This research used a qualitative inductive methodology through a thematic analysis [14]. The first step was to develop a semi-structured interview guide. Purposive sampling was used to recruit the interview participants. Purposive sampling is a technique widely used in qualitative research for the identification and selection of information-rich cases and to gather in-depth data on the topic of interest with the most effective use of limited resources [15].

2.1 Interview Guide Design

First, a format of the interview guide was designed based on a rapid review [16]. In this review [17], we made an assessment of what is already known about the topic of herbal pharmacovigilance by using systematic review methods to search for impactful articles on "pharmacovigilance" OR/AND "herbal products" OR "herbal medicines" through PubMed, Web of Science, and Google Scholar and regulator websites. The concept interview guide made by SHPW, FvH, SvdK and HJW was field tested among clinical assessors and interns working at the Netherlands Pharmacovigilance Centre Lareb and an external expert in the field of PV (SS) and subsequently modified and improved (Fig. 1). This resulted in a final interview guide that contained 11 main themes: (1) General information about the participants; (2) Pharmacovigilance; (3) Herbal medicinal product definition; (4) ADRs or herb–drug interactions; (5) Assessing and analysing ADRs related to herbal medicinal products; (6) Identification; (7) Causality assessment; (8) Signals on ADRs related to herbal products; (9) Best practices; (10) Possible improvements and challenges; (11) Referral to other qualified persons to participate as well. The final interview guide consisted of 55 questions in total and is available in Addendum A in the Electronic Supplementary Material (ESM).

2.2 Participant Selection and Interview Process

In order to find participants who were knowledgeable on herbal pharmacovigilance, we purposively selected potential participants through two different networks; the International Society of Pharmacovigilance-Herbal and Traditional Medicines Special Interest Group [18] and the Nutrivigilance Information Exchange Network [19] (members of the *Nutrivigilance Newsletter*, sent by the French Agency for Food, Environmental and Occupational Health & Safety). In total, 46 experts in herbal pharmacovigilance were invited via e-mail to participate. By using a snowballing technique,

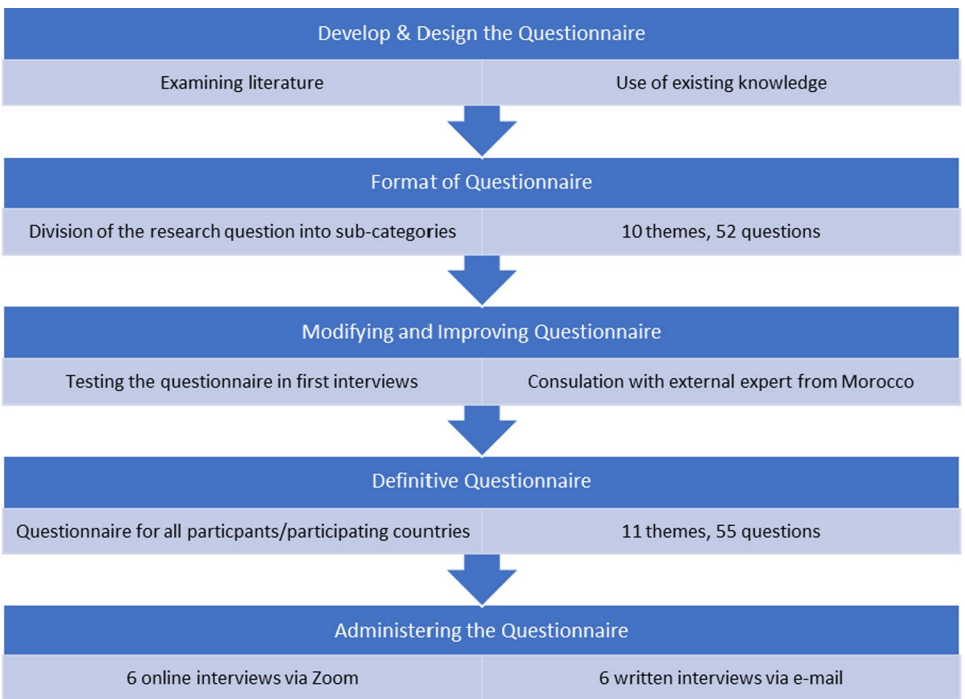

Fig. 1 Flowchart of the process of creating and administering the interview guide

more potential participants were reached [20, 21]. From November 2021 until February 2022, participants were interviewed. The interviews were originally performed face to face via Zoom®, but to increase the number of participants, the possibility to hand in written answers to the questions was added. The number of participants was determined based on data saturation, defined as the point at which no new codes emerge from the data [22]. At the point of data saturation, snowballing was stopped, and only earlier scheduled interviews were completed. In this context, data saturation is normally reached between 7 and 12 interviews in qualitative research where interviews are used as a data source [23, 24].

2.3 Coding and Data Analysis

After the interviews had taken place and transcribed, the data were analysed. Data coding in a thematic analysis consisted of identifying fragments of data by their meaning and labelling them with a code [25, 26]. For the elaboration of the transcripts, NVIVO® was used. NVIVO® is a computer program that can be used for encoding and is often applied in a qualitative data analysis [27, 28]. As the process continues, a relationship or connection between the codes can be depicted, which generates high-level concepts. Groups of related high-level concepts are then placed together under larger concepts to create themes.

The coding of the first two interviews was completed by two researchers (SW and FvH). Throughout the analysis, codes were modified and merged based on discussions between the authors while working in NVIVO®. In NVIVO®, eight themes of the questionnaire were used as main codes to create an overview. The questions of the interview guide were coded as sub-codes to the corresponding theme. The answers on the questions were then coded as sub-sub-codes to the main codes. An answer could be assigned to multiple codes. These codes were registered as keywords.

To ensure that all data from the interviews were interpreted correctly, the results were sent to the respective participants and their opinion/feedback was asked and subsequently elaborated. This study was created to adhere to the Consolidated Criteria for Reporting Qualitative Research [29].

3 Results

Sixteen participants from 11 countries (China, Ethiopia, Italy, Japan, Malawi, Morocco, New Zealand, Portugal, Saudi Arabia, Thailand and the Netherlands) participated in 12 interviews (six online interviews and six participants provided written answers to interview questions) [Table 1].

Table 1 Overview of participants, their country, organisations and job description

Interview	Country	Organisation	Number of participants
1	The Netherlands	Regulator	2
2	Malawi	Academic	1
3	Morocco	Academic	1
4	Thailand	Academic	1
5	Portugal	Regulator	1
6	China	Manufacturer	1
7	China	Academic	1
8	Japan	Academic	1
9	Ethiopia	Regulator	1
10	Italy	Academic	1
11	New Zealand	Regulator	1
12	Saudi Arabia	Regulator	4

Based on the outcome of all interviews, we grouped the results into eight themes: Pharmacovigilance Organization, Herbal Products, Identification, Coding, Causality assessment, Reporting ADRs, Signals of ADRs for Herbal Products and, Possible improvements, each with corresponding sub-themes (see Fig. 2). A selection of these (sub-) themes is presented and discussed in detail below. In addition, selected quotes from the interviews, being illustrative for the theme, are given.

3.1 Herbal Products

3.1.1 Legal Status

The legal status of herbal products differs among participating countries. This can potentially cause difficulties for pharmacovigilance systems in collecting data because regulations usually place obligations on manufacturers to undertake pharmacovigilance activities for their products that are authorised, approved, listed or registered [8]. There are countries with no regulation at all for herbal products ($n = 4$), countries with a distinction in regulation between conventional medicines and herbal products ($n = 4$), countries where the regulation is the same for conventional medicines and herbal products ($n = 2$) and countries where legislation of herbal products is in progress ($n = 2$). The most common way to obtain herbal products in the participating countries is on prescription ($n = 8$) followed by 'over the counter' (without a prescription).

> "It is in a gray zone, mixed with foods, different countries/cultures different rules. People can get them from the pharmacy but also on the market." Participant

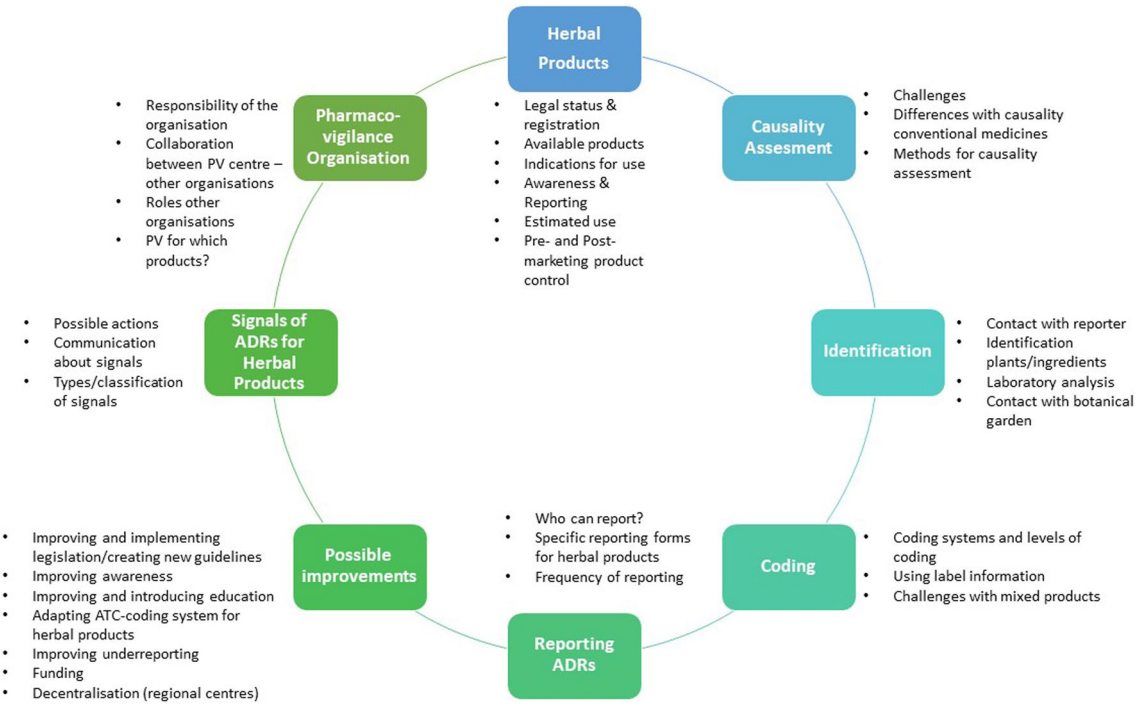

Fig. 2 Overview of the main themes emerging from the interviews and their sub-themes. *ADRs* adverse drug reactions, *ATC* Anatomical Therapeutic Chemical, *PV* pharmacovigilance

"Consumers in China can get the herbal products by physicians' prescription. Some herbal products are available over the counter. In China, traditional Chinese medicines (most are herbals) have always been legal." Participant

"None has been registered and marketed so far in Ethiopia and home remedies are not regulated. Therefore, no adverse event reporting." Participant

"The most used products containing herbals are food supplements made by manufacturers, but in Italy a doctor can also prescribe mixtures of crude herbs, that the pharmacy prepares for specific patients, for example for weight loss indication." Participant

3.1.2 Awareness

As many people believe herbal products to be safe because they are natural, it is important to create awareness for possible adverse reactions to herbal products. This applies to pharmacists, doctors and other healthcare professionals as well as patients and consumers.

Awareness of herbal pharmacovigilance has been actively appointed by eight countries and one country mentioned doing so in the future. Awareness is created via articles in journals ($n = 4$), education ($n = 4$), websites ($n = 2$), radio ($n = 2$) and conventions ($n = 2$).

"Yes, for all licensed medicines, however, not particularly awareness just for licensed herbal medicinal products, because they are all treated as licensed medicines. It is important to create awareness of unlicensed herbal products." Participant

"The main problem is to create awareness, that is the key. Because I know from trainings for health workers, but I believe the public also needs some health education to know about the ADR reporting form that can be accessed via this website. People should be aware and they need an explanation of why they should report ADRs associated with herbals. They got the right for an explanation. And they are going to respond. This is important." Participant

"A good way is a web application, they don't download anything in their smartphone, now smartphone is popular in Thailand. I think if we create web application for consumer report is good. They need to choose a simple design, with no extra buttons.

First we should control television and radio and second every time that healthcare professional dispense a herbal product, you should tell them what its serious adverse effects are and how to deal with them." Participant

"Saudi Food and Drug Authority (SFDA) publishes awareness posts and recorded video about potential drug-herbal interactions for the public." Participant

Recently, the Saudi Food and Drug Authority published the Herb-Drug Interaction Project to detect and assess potential herb–drug interactions to ensure safety [30].

3.1.3 Pre-/Post-Marketing Product Control

Between countries, there are differences in the pre-/post-marketing control of herbal products. Pre-marketing control of herbal products is performed by some of the participating countries, although it depends on the type of herbal product and the regulatory status in the country. For instance, in Italy, there is a difference in quality controls between food supplements and drugs. In China, new decoctions may follow the same steps as conventional medicines, whereas some classical decoctions could skip preclinical studies. In Ethiopia and Malawi, no pre-marketing control occurs, but in Malawi this will be addressed by future guidelines. In Morocco, pre-marketing control is performed for natural products that have a regulatory status. All participants except one mention that post-marketing control is carried out in their country.

> "None has been registered and marketed so far in Ethiopia and home remedies are not regulated. Therefore, no post-marketing surveillance for herbal medicinal products." Participant
>
> "Some classical decoctions which had been used for hundreds or thousands of years with certain efficacy could skip the preclinical studies, while some new decoctions may follow the same steps on conventional medicine." Participant

3.2 Identification and Coding of Herbal Products

The identification of the ingredient(s) that is (are) suspected to cause the ADR is identified differently across the participating countries. Methods that were mentioned in the interviews were: a literature search ($n = 2$), integrated evidence chain ($n = 1$), based on experience ($n = 1$) or intuition ($n = 1$), through a thin-layer chromatography fingerprint ($n = 1$) and follow-up information from the reporter ($n = 1$).

> "There are a lot of crudes in one capsule, that is a problem. We have TLC fingerprint, but only 60 recipes have TLC fingerprint. And of that a single herbal. We cannot identify the exact compound of mixtures." Participant

Coding herbal products in order to store the data of the reports in a pharmacovigilance database can be challenging for several reasons. Herbal products often come from a wide variety of sources and may not be standardised in terms of ingredients, concentrations or formulations. Furthermore, herbal products have complex compositions and they can contain numerous active and inactive ingredients, making it hard to accurately identify and code each component. To store reports on herbal products in a database, one needs to code and be able to analyse reports at all the different hierarchical levels, such as plant species, specific plant part used, type of extract and specific manufacturer's product. For regular drugs, a fixed structure is in place (the Anatomical Therapeutic Chemical [ATC] classification system). However, such a structure is lacking for herbal products. For the classification of herbal medicines, a system based on the ATC system is available, the Herbal-ATC (HATC) classification developed by the Uppsala Monitoring Centre. Although the HATC system represents a valuable attempt at coding herbal medicines, it may not be perfect for covering all types of herbal medicinal products [6]. For instance, not all indications can be captured with the HATC. In many countries, herbal medicines are used in the form of raw or crude herbal substances, also making it difficult to apply the HATC to code their ingredients. In the interviews, it was mentioned that two participating countries use (herbal) ATC coding and six countries use their own coding system. Participants mentioned that important items to code were the product name ($n = 8$), plant parts used ($n = 2$), method of preparation ($n = 2$), exposure [dose, frequency, duration] ($n = 2$) and the manufacturer ($n = 2$).

> "When an herbal product is in finished form, we use the same assessment and the same form as conventional drugs. If it's raw material we precisely ask please state the vernacular name, the quantity used, the part used and mode of preparation." Participant

3.3 Reporting of ADRs for Herbal Products

Differences exist in the frequency and reporting of ADRs of herbal products compared with conventional medicines. Underreporting of ADRs related to herbal products because of cultural beliefs, a lack of awareness or self-medication can hinder pharmacovigilance. In the interviews, the main reasons for the higher percentage of underreporting of ADRs of herbal products compared with conventional medicines were: a lack of awareness that reactions to herbal products should be reported ($n = 3$), a lack of information because herbal products are not under legislation ($n = 1$), a lack of recognition of herbal products being a cause of ADRs ($n = 1$) and an unawareness where to report ADRs of herbal products ($n = 1$). In most participating countries, healthcare professionals as well as consumers were able to report ADRs of herbal products. Six countries mentioned having the same reporting form for herbal products as for conventional medicines (China, Thailand, Morocco, New Zealand, Saudi Arabia and the Netherlands). Frequencies of reports of ADRs of herbal products received by national pharmacovigilance

centres ranged from 8 per year to 400,000 per year between the participating countries.

> "Because herbal products are not registered now, it means most of the information may not be there. One of the questions that, it is all part of the project I am doing, when I speak to the legislators about how many reports for example. 2019 literally none. So, part of the reason is awareness, people need to report." Participant
> "All stakeholders can report ADRs, this includes the public, healthcare providers (HCPs) and pharmaceutical companies. There is a difference between requirements when it comes to pharmaceutical companies, however, the public and HCPs can both report using the online platform and it is worth mentioning that we receive public reports through the phone as well." Participant

3.4 Causality Assessment

Case reports of suspected ADRs associated with the use of herbal products are submitted to the manufacturer and/or regulatory agencies on a voluntary basis. Many such case reports are of limited quality and lack essential information. This makes pharmacovigilance for herbal products challenging because a robust causality assessment depends primarily on the quality of the reports received by national pharmacovigilance centres [8]. Pharmacovigilance evaluation for herbal medicines requires complete data sets and sophisticated causality assessment methods. Causality assessment methods show substantial variabilities in their characteristics and each has their own limitations as discussed by Barnes et al. [8] and Khan et al. [31].

Among the participating countries, different methods were used to assess causality. They included: the causality method of the WHO ($n = 6$), Naranjo ($n = 2$), French method ($n = 1$), Thai algorithm ($n = 1$), Chinese National Adverse Drug Reactions Monitoring System assessment ($n = 1$), integrated evidence chain ($n = 1$), the Drug Interaction Probability Scale to assess the probability of a causal relationship between the interacting herb and drug and the event ($n = 1$), and no standardised methods ($n = 2$). Challenges in the causality assessment of herbal product–ADR associations were the complex composition of herbal products ($n = 4$), a lack of information in the report ($n = 2$), the exact name of the product ($n = 2$), experience ($n = 2$), an unsuitable algorithm ($n = 1$) and time-consuming work ($n = 1$).

> "We use Naranjo, but actually we have three algorithms. WHO UMC, Thai algorithm as well. But it's not popular, we only use Naranjo. We find it hard to interpret from the WHO UMC." Participant
> "The composition of herbal products is complex and the herbal components are various. What's more, ADRs of herbal products are always delayed and hidden." Participant
> "It will be a bit difficult I mean to assess especially the actual active ingredient. So herbal product is complex, because of combining two medicinal plants. There are a lot of compounds in there, so you may not be sure what is causing the effect. So, we need a lot work on that. But with current technology and metabolomics, DNA sequencing for traditional medicine, so we can exactly know what is in the medicine. For scientist it is not a big deal, but it is the public that is reporting and it is difficult for them to come up with the scientific name. This is a challenge." Participant

3.5 Signals of Herbal Product ADRs

After receiving a report of a herbal product ADR by a pharmacovigilance centre, all available information is analysed. For example, it is checked whether similar reports have been received, if the association is described in the literature and if there is a plausible mechanism which can explain the observed ADR. When the causality assessment is completed and a new signal (new information on a new or known adverse event that may be caused by a medicine and requires further investigation [32]) of an ADR of an herbal product is found, pharmacovigilance centres must communicate this finding to health professionals, organisations responsible for the safety of herbal products and, most importantly, to consumers. This is done differently across the participating countries.

> "Medsafe does not routinely communicate all safety signals that are detected. Medsafe informs healthcare professionals and the public about relevant confirmed safety signals via safety communications on the Medsafe website. Medsafe informs the expert advisory committee in a quarterly summary about all signals logged and closed by Medsafe." Participant
> "We send the signal to the Netherlands Food and Consumer Product Safety Authority, Health and Youth Care Inspectorate or the National Poison Information Centre to inform them. Then it's their task to take action. We also publish our findings on our website, that is also important." Participant

3.6 Best Practices

In this study, a best practice was defined as a recommended possible improvement when three or more participants named it. Out of the 12 interviews, five general recommendations applicable worldwide emerged (Table 2).

Table 2 Recommendations of best practices

Recommendations
Improving and implementing legislation/creating new guidelines
Improving awareness
Improving and introducing education
Adapting an ATC coding system for herbal products
Improving underreporting

ATC Anatomical Therapeutic Chemical

3.6.1 Improving and Implementing Legislation/Creating New Guidelines

Legislation is one of the biggest issues and the hardest to solve owing to the distinction in the status of conventional medicine, food supplements and herbal products. Many products on the market are used for medicinal purposes, but marketed as food supplements of which the market authorisation is much cheaper and easier compared with conventional medicines [33]. Legislation can be improved in three ways. The first method is categorising each product, for instance as a conventional medicine, a complementary alternative medicine or a food supplement. Perhaps even more categories (sub-categories) are justified. Creating clear legislation for each category is essential. This is a time-consuming and costly task. Furthermore, exploring possibilities for introducing a notification system for these products may contribute to their safety [34]. The second method to improve legislation is to look at the organisations that are responsible for this. There should be a clear division of responsibilities connected to the various types of products available on the market. An option could be a system with two organisations in every country: a food safety organisation and a pharmacovigilance centre. However, a drawback of two separate organisations is that it can be hard for consumers to tell the difference between these different products. Establishment of good and timely communication between such two organisations is a prerequisite. The third method to improve legislation is to demand strict requirements regarding the labels on which all the ingredients, doses, instructions for use and warnings must be displayed. This will improve the safety of these products and ultimately improve causality assessments of reported ADRs. Nevertheless, this will remain a big challenge with the plethora of online web shops, where people can buy herbal products (or assumed herbal products) from all over the world including from countries with less strict or different legislation. Ther is a need for an internationally recognised quality label, with qualitative as well as quantitative information, for herbal products under the auspices of WHO (worldwide) and/or under the auspices of larger multi-country bodies such as the European Medicines Agency, the European Food Safety Authority or the US Food and Drug Administration. The establishment and implementation of international guidelines acknowledged by individual countries are essential here [35].

3.6.2 Improving Awareness

Awareness among both users and healthcare providers of the correct use and possible health risks of herbal products is often limited and too low [36–38]. Improving awareness is needed, for instance via post-academic training of healthcare professionals, websites, social media campaigns and television advertisements. A government campaign could be beneficial.

3.6.3 Improving and Introducing Education

Education can be improved by incorporating pharmacovigilance of herbal products in the curriculum of academic health-related studies such as pharmacy and medicine. Experiences of implementing a university curriculum for the pharmacovigilance of herbal medicines from Morocco were recently published [39]. More generally, there are huge differences in the share of natural product-related courses in these curricula worldwide. Education will automatically increase the awareness among healthcare providers. This is a time-consuming solution, but by educating future generations and providing objective and qualitatively good information, pharmacovigilance of herbal products would over time improve significantly. Consumers should also be educated by, for example, creating a user-friendly and easily accessible website or formulary that would also be accessible for healthcare providers.

3.6.4 Adapting an ATC Coding System for Herbal Products

The development and availability of a specific ATC coding system for herbal products would be a great improvement. The WHO has a herbal ATC coding, but this needs to be improved so that all indications can be captured and all ingredients can be coded in order to be applied globally. Reliable declarations of content (including the origin and identity of the plant material and the production process applied) are essential in this context.

3.6.5 Improving Underreporting

Underreporting of adverse reactions related to the use of herbal products is also one of the main problems and is largely caused by the common belief that herbal products are harmless because they are natural. This can be solved by improving the awareness as described earlier and by using an easily accessible reporting system. Encouragement of

patients or consumers to participate in pharmacovigilance would increase spontaneous reporting and early detection of serious ADRs. The use of herbal medicine is strongly rooted in various cultures, especially in non-Western countries. This traditional use (and the well-accepted status) may impede the stimulus to report adverse reactions possibly attributed to the use of herbal products.

4 Discussion

This international qualitative study with participants from 11 countries worldwide found that pharmacovigilance for herbal products is considered to be a highly relevant topic that still faces many relatively unknown challenges. We identified a large variation in the status of pharmacovigilance of herbal products between various countries. Five general recommended best practices that are applicable in every country emerged. Categorising the different products and clearly dividing responsibility between organisations would remove the 'grey area' in which herbal products find themselves right now. By enforcing an ingredient declaration on the packaging/labels, pharmacovigilance of herbal products would improve significantly. For these recommendations, (international) legislation and guidelines are needed. Furthermore, awareness about herbal products needs to be improved. This will require a change in mindset of both healthcare providers and consumers and therefore education is needed. This is a time-consuming task that requires long-term planning. By creating a specific ATC coding system for herbal products and food supplements, recording of reports of ADRs of herbals in databases would improve. By creating awareness and an easily accessible reporting system, the problem of underreporting would probably diminish. This will lead to safer and more rational use of herbal products and favours the protection of the consumer or patient.

There are clear geographical differences when it comes to pharmacovigilance of herbal products. One of the biggest differences is the fact that in Asian countries that participated in this study, herbal products are much more established and recognised in healthcare than in European countries. In many Asian countries, there is distinct legislation for herbal products and there are even two different types of hospitals in countries such as China. One "conventional" hospital and one hospital where herbal products are used as medicines. African countries mention widespread use of traditional medicines and home remedies; however, in an interview it was stated that home remedies and traditional practitioners prescribing herbal products are not yet regulated. For example, in Malawi, the market is replete with unregulated herbal medicines of questionable quality [40]. Other articles have also stressed the importance of herbal pharmacovigilance and improving awareness and regulatory oversight [41, 42]. Several authors have described herbal pharmacovigilance systems in their country [7, 38, 43]. Our study adds expert opinion through in-depths interviews with experts in the field of herbal pharmacovigilance.

Recently, two books about herbal pharmacovigilance were published: *Pharmacovigilance for Herbal and Traditional Medicines. Advances, Challenges and International Perspectives* [8] and *Evidence Based Validation of Traditional Medicines* [44]. These books underpin the significance of the topic and provide easily accessible literature for healthcare providers on (pharmacovigilance of) herbal and traditional medicines.

4.1 Recommendations

A good approach to optimise pharmacovigilance of herbal products would be to provide more guidance internationally [45, 46] for the registration of herbal product ADRs and for the causality assessment and to optimise the WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems of 2004 [2]. This guidance could be based on a larger follow-up study of our current research, for instance by including questionnaires sent to members of the WHO Program for International Drug Monitoring.

It could be investigated if a format for a standardised online reporting form for ADRs of herbal products would be applicable worldwide, despite geographical and cultural differences. Such a standardised online reporting form should be easily accessible, and as conclusive as possible. Both consumers and healthcare professionals should be able to fill in this form, regardless of education or background. This form should ideally be integrated in the standard reporting systems and forms that countries already have. In 2004, the WHO published guidance on safety monitoring of herbal medicines in pharmacovigilance systems [2]. This guideline already mentions elements of information that should be present in a reporting form for herbal medicines.

A study into the design and implementation of a general international guideline for herbal products may be initiated. Such a guideline could be implemented on a national level and may be a new GxP guideline called Good Herbal Medicinal Products Pharmacovigilance Practice. For the Netherlands, it has been studied whether and how a vigilance framework can contribute to protecting consumers from adverse reactions to presumably health-enhancing food products [34]. In recent years, national and international legislation is improving for pharmacovigilance in general [47]. This is a good development and needs to be extended, especially for herbal products.

4.2 Strengths and Limitations

A main strength of this study is the participation of 11 countries from four different continents. The questionnaire was extensive and broad and provided in-depth insight regarding the current state of pharmacovigilance of herbal products and future opportunities. The selection of participants proved challenging as specific knowledge about herbal pharmacovigilance was needed to answer the questions. This resulted in the choice to select potential participants from two international networks, resulting in a limited number of participants. A limitation of our study is that we did not include authors from scientific papers on herbal pharmacovigilance, which were not part of the aforementioned network, as potential participants. However, we did use a snowballing technique to increase our sample. Sample adequacy in qualitative research relies on both the appropriateness of the sample composition and the size. We relied on purposive sampling, by selecting individuals as potential participants based on their capacity to provide richly textured information relevant to the topic we were investigating. Purposive sampling, as opposed to probability sampling used in quantitative research, selects potential candidates on their features. Often, sample size determination is guided by the criterion of informational redundancy, that is, sampling can be terminated when no new information is elicited by sampling more units [48]. A review of sample sizes for saturation in qualitative research found that qualitative studies can reach saturation at relatively small sample sizes. Results from this review showed that 9–17 interviews or four to eight focus group discussions were needed to reach saturation [49]. In our study, we included 16 participants from 11 countries.

Online face-to-face interviews provided more information in comparison to written interviews. A reason for this is that clarifications could be obtained if there were any uncertainties in the questions or answers. However, the written interviews were a good addition to the online interviews, as they resulted in a larger number of participants that could be included in our study. Additionally, the language barrier could have potentially been a limitation as questions and answers could be misinterpreted. From most participating countries, only one person was interviewed, and personal views might differ in some respect from standpoints of the official pharmacovigilance centre. As a result of the coronavirus disease 2019 pandemic, many pharmacovigilance centres were highly occupied with vaccine pharmacovigilance in 2021 and 2022 and less focus could be given to pharmacovigilance of herbal products. This might also have resulted in less participants joining the study. Despite these limitations, we have tried to make sure that we reached data saturation, which is one of the most used methods in qualitative research for determining a sample size and evaluating its sufficiency. With the number and expertise of the participants in our study, we believe we have the main topics of concerns and best practices about pharmacovigilance of herbal medicines covered.

5 Conclusions

This study showed the current state of herbal pharmacovigilance in a number of countries across the world, identified barriers in the pharmacovigilance of herbal products and yielded recommendations of best practices of pharmacovigilance of herbal products. The principal recommendations are applicable worldwide and include: increasing awareness, improving education, and improving and creating applicable legislation and guidelines. As the use of herbal products is becoming increasingly popular, good pharmacovigilance practice focusing on these products is imperative for the sake of consumers' safety.

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Data Availability The data for this manuscript (transcribed interviews and NVIVO coding) are not publicly available because of the Lareb data protection policy. Requests to access the datasets should be directed to the corresponding author and will be granted upon reasonable request.

Code availability The NVIVO coding for the data used in this article are not publicly available because of the Lareb data protection policy. Requests to access the datasets should be directed to the corresponding author and will be granted upon reasonable request.

Declarations

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Conflicts of interest/competing interests The authors have no conflicts of interest that are directly relevant to the content of this article. Some of the authors were also interviewees. Statements about opinions are those of the interviewees alone, and not necessarily reflecting their institution.

Disclaimer The views expressed in this paper are those of the authors and not do not necessarily reflect those of the authors' institutions or their stakeholders. Guaranteeing the accuracy and the validity of the data is a sole responsibility of the research team.

Ethics approval If a study in the Netherlands is subject to the Medical Research Involving Human Subjects Act (WMO), it must undergo a review by an accredited Medical Research Ethics Committee or the Central Committee on Research Involving Human Subjects (CCMO). This study does not fall under the WMO.

Consent to participate Participants in the study were informed in writing of the study purposes, including publication of the results, and provided a statement of informed consent prior to participating in the study.

Consent for publication All participants were provided with the finalised version of the results. Feedback of the participants on the results was incorporated.

Availability of data and material The data for this article (transcribed interviews and NVIVO coding) are not publicly available because of the Lareb data protection policy. Requests to access the datasets should be directed to the corresponding author and will be granted upon reasonable request.

Code availability The NVIVO coding for the data used in this article is not publicly available because of the Lareb data protection policy. Requests to access the datasets should be directed to the corresponding author and will be granted upon reasonable request.

Authors' contributions The original study protocol was designed by FvH, SHPW, SvdK and HJW. The study protocol was reviewed by SS. Interviews were held by SHPW. Data analysis was performed by SHPW, FvH and CE. The first draft of the manuscript was written by CE. All authors contributed to manuscript drafting and revision. All authors approved the final version to be published.

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