



# Signals of Adverse Reactions to Herbal Medicines: Evidence and Document Analysis Based on a Scoping Review

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## Abstract

**Background** To date, signals of adverse reactions to herbal medicines have not been systematically reviewed, limiting pharmacovigilance of herbal medicines because of a lack of data.

**Objectives** We sought to analyse the available evidence on signals involving herbal medicines and to determine to what extent they had been documented at the European Union (EU) level and in the USA.

**Methods** We used the results of a published scoping review of interventional and non-interventional studies that reported signals of adverse reactions to drugs. We assigned Anatomical Therapeutic Chemical classification to all drugs, and identified herbal medicines when they fell under the Anatomical Therapeutic Chemical V90. We ascertained the presence of the adverse reaction, or related adverse reactions, for each signal in reference documents for healthcare professionals: the *US Botanical Safety Handbook* and the EU monographs and *US Dietary Supplement Fact Sheets*; and in those for consumers: the US Dietary Supplement Label Database. We summarised the data descriptively, treating US documents as one and comparing harms across pairs of US and EU documents by signal. Documents were deemed concordant if they both included the same or related adverse reactions, or if neither did. We also compared adverse reactions across US documents for healthcare professionals with those for consumers.

**Results** Of the 10,861 signals covered by the scoping review, 53 (0.49%) concerned herbal medicines, all based on case reports. Reference documents from both the US and EU were available for 37 signals. Most of the documents were concordant (73%), and ten (27%) were discordant: six adverse reactions were mentioned only in US documents, three only in EU monographs, and one was warned against in US documents but not in EU documents. Twenty-one signals could be followed up in the *Botanical Safety Handbook* and *Dietary Supplement Fact Sheets*. Most (68%) US documents for healthcare professionals were concordant. When the *Botanical Safety Handbook* and *Dietary Supplement Fact Sheets* did not include an adverse reaction, neither did the Dietary Supplement Label Database. However, when they did, only 20% of the labels for consumers did too. The proportion of labels mentioning adverse reactions otherwise available in documents intended for healthcare professionals ranged widely, reflecting differences across multiple labels for the same products.

**Conclusions** Very few signals of adverse reactions from the wider scoping review concerned herbal medicines, and were all based on case reports. Information was mostly concordant across documents in the EU and USA. As manufacturers are solely responsible for the contents of the Dietary Supplement Label Database, regulatory oversight may be required to ensure that consistent and comprehensive information on the harms of herbal medicines is made available to consumers in the USA.

## Plain Language Summary

In this study we looked at how adverse effects (side effects) of herbal medicines are reported in official documents in the USA and the European Union (EU). We used data from a previous review of studies of medicinal drugs to select those that reported signals, i.e. possible associations of herbal medicines with adverse effects. We then checked if the adverse effects were listed in official documents for healthcare professionals and consumers in the two regions. We also checked the adverse effects in US documents for healthcare professionals matched with those in product labels for US consumers. We found 29 studies in which 53 signals of adverse effects to herbal medicines were mentioned, all of which were based on anecdotal case

reports. Of the 37 signals for which documents were available in both the USA and the EU, most had matching information about adverse effects, but about a quarter did not: some adverse effects were mentioned only in US documents, others only in EU ones. US documents for healthcare professionals were mostly consistent, but product labels mentioned fewer adverse effects in comparison. This suggests that consumers may not always be getting all relevant information on the possible adverse effects of herbal medicines. To sum up, possible adverse effects of herbal medicines are probably being under-reported. Stronger regulation may be needed to make sure that product labels for herbal medicines give consumers complete information on possible adverse effects.

### Key Points

Of 10,861 signals reviewed, 53 (0.49%) concerned herbal medicines, all derived from case reports.

US and European Union documents were mostly concordant (73%), but only 20% of US labels for consumers included adverse reactions information provided to healthcare professionals.

Regulatory oversight may be needed to inform US consumers of the benefits and harms of herbal medicines.

## 1 Introduction

Adverse reactions to herbal medicines may result in serious harms [1]. Their mechanisms vary; for example, they can occur through accumulation of active constituents or their metabolites (e.g. renal failure and urothelial carcinoma due to *Aristolochia clematitis* L. [2]) because of the methods of extraction of the active constituents (e.g. supercritical carbon dioxide extracts of *Artemisia annua* L. and hepatotoxicity [3]), or herb–drug interactions [4]. Often, but erroneously, herbal medicines are perceived as being completely safe [5–7]. Despite the potential for adverse reactions, they have been used widely and for millennia [8], as sole treatments or as adjuncts to conventional medicines [9, 10]. How consumers perceive herbal medicines affects the likelihood that suspected adverse reactions are reported by them spontaneously or via healthcare professionals [11]. Furthermore, consumers may not be aware of reporting practices [1, 12], which healthcare professionals themselves may not have been trained to follow [13].

Products containing active constituents sourced from (parts of) plants can be regulated as health or functional foods, dietary supplements, prescription medicines or over-the-counter products [14]. Unlike the increasingly harmonised regulation of conventional medicinal products [15, 16], products sourced from plants are categorised differently in the European Union (EU) and USA [1, 17, 18]. For instance, *G. biloba* L. is regulated as a supplement in the USA, and

both as a herbal medicinal product and a supplement in the EU, with different therapeutic claims or indications [19, 20]. In some cases, tolerable upper intake levels differ too, as for alpha-tocopherol, for example from *C. sinensis* (L.) Kuntze extracts (1000 mg/day in the USA, 300 mg/day in the EU) [21]. The European Medicines Agency (EMA) regards herbal medicines as “herbal medicinal products”, while the European Food Safety Authority regards products that contain whole plants, parts thereof or their extracts as “food supplements”. In the USA, herbal medicines are regulated either as “botanical dietary supplements”, a subcategory of dietary supplements, or as “botanical drugs”. The Centre for Food Safety and Applied Nutrition of the US Food and Drug Administration (FDA) is responsible for assessing potential harms from botanical dietary supplements, while the FDA’s Centre for Drug Evaluation and Research is responsible for assessing harms from botanical drugs.

Information that a medicine, including a herbal medicine, may cause an adverse reaction may derive from any type of study design. Information that may require subsequent verification or regulatory action is known as a “signal” in pharmacovigilance [22]. Reports of suspected adverse reactions, whether spontaneous, solicited or published in journals or social media, have remained the main type of evidence supporting signals over the past 30 years [23, 24]. Nevertheless, given the differences in the monitoring of harms from herbal medicines, the evidence base of signals of adverse reactions to herbal medicines remains unclear, as do regulatory actions that result. We therefore aimed to review the evidence base of relevant signals, to compare whether and how the suspected adverse reactions had been made available in EU and US documents for healthcare professionals, and to examine the differences between US documents for healthcare professionals and those for consumers.

## 2 Methods

### 2.1 Terminology

As discussed earlier, regulatory systems differ in terminology for products sourced from plants, parts thereof and extracts. We use “herbal medicine(s)” as a generic expression to encompass the concepts of “herbal medicinal

product”, “dietary supplement”, “food supplement”, “botanical drugs” or “botanical dietary supplements”. Where needed, we refer to these categories using terms specific to the regulatory context. Specifically: a “herbal substance” consists of mainly whole, fragmented or cut plants, plant parts, algae, fungi or lichen in an unprocessed, usually dried form but sometimes fresh; a “herbal preparation” is one that is obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation; a “herbal medicinal product” is 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 [25, 26].

## 2.2 Study Base

We extracted information on studies of signals and signals of disproportionate reporting (SDRs, i.e. statistical associations between medicinal products and adverse events obtained through a disproportionality analysis [27]) from our previously published scoping review [23]. This review characterised the evidence base of published and unpublished studies of any design, up to August 2020, to the extent they concerned SDRs or signals of suspected adverse reactions. Because the concept and definition of a signal have changed over time, and to avoid introducing biases, we did not determine whether the findings of a study constituted a signal. Rather, we considered a signal as any finding described as such in the studies and corresponded with original authors when uncertain. We also requested records from authors who could be deemed to have reported signals, even when they did not use the term [28]. When records were in languages other than English, or languages we could not translate ourselves, we asked the authors for a translation. The scoping review concerned medicinal products (see [29] for definition), and by extension herbal medicinal products. Interactions were also included, provided they involved at least one medicinal product. To account for diversity among regulatory systems, we included herbal medicines that did not fall under the EU definition of a herbal medicinal product, if the provisions under which they were approved required evidence of efficacy or traditional use, and admitted therapeutic claims. We independently verified the relevant regulations, if this information was unavailable in the included studies.

We retrieved the type of publishing stakeholder (academia, regulatory agency, research organisation, health carer, marketing authorisation holder), the medicinal product (mapped to the Uppsala Monitoring Centre’s [UMC’s] *Drug Dictionary*, WHODrug Global, B3/C3-format, September 2020) [30], the adverse reaction (coded to the *Medical Dictionary for Regulatory Activities*, v. 23.1) and the

year of communication. The UMC Drug Dictionary assigns common or scientific synonyms of bespoke “herbal ingredients” to an accepted scientific name, determined in collaboration with the Medicinal Plant Names Services of the Royal Botanic Gardens in Kew [31]. In UMC’s *Drug Dictionary*, “herbal ingredients” adopt a Latin binomial classification, without standard author abbreviations, parts of plants are also available at granular levels of the dictionary. For example, the herbal ingredient “*Chrysanthemum indicum*” is assigned to the synonyms *Tanacetum indicum*, *Martaria indica* and *Dendrathera indicum*, among others, and subsumes entries for its flowers, flower head, inflorescence and whole plant. For purposes of standardisation, we used herbal ingredients.

We assigned an Anatomical Therapeutic Chemical (ATC) level 5 code to all medicinal products, including herbal medicines, expanded by the UMC’s Herbal ATC classification [30]. This expansion follows the same principles of the ATC classification system, providing additional branches to the hierarchy. It assigns “herbal ingredients” to ATC codes based on their therapeutic indication across countries, in addition to the ATC level 2 V90: “Unspecified herbal and traditional medicine”. We identified all signals/SDRs concerning herbals based on ATC V90. Fixed-dose combinations were eligible, provided at least one of its constituents fell under ATC V90 in isolation. Drug–herb interactions were also eligible.

## 2.3 Retrieval of Information on Adverse Reactions to Herbal Medicines from Reference Documents

Using “herbal ingredients” of each signal/SDR we searched the EMA’s herbal monographs (<https://www.ema.europa.eu/en/human-regulatory-overview/herbal-medicinal-products/european-union-monographs-list-entries>), compiled by the Committee on Herbal Medicinal Products [32]. We selected the EMA’s monographs because they were the only repository of information on harms from centrally approved herbal medicinal products, and because EU dietary supplements are regulated by national procedures [33]. In the USA, the monographs in the Herbal Medicines Compendium report tests for identity, strength and purity, or prescriptions to adhere to good manufacturing practices for dietary supplements, but no information on harms [34]. We therefore resorted to the US *Dietary Supplement Fact Sheets* (DSFS, <https://ods.od.nih.gov/> [35]), developed by the Office of Dietary Supplements at the National Institutes of Health, and the US Dietary Supplement Label Database (DSLDD, <https://dslld.od.nih.gov/> [36]), maintained by the same institute. For the DSLDD, we exported all records for marketed botanical products, inclusive of information on DSFS and Label Statements. We further searched the online version of the *Botanical Safety Handbook* (BSH) curated by the American Herbal Products Association, which

provides information on the pharmacology, toxicology, clinical trials and published case reports of 500 species [37]. We retrieved all reference documents as of May 2024. The EMA and FDA are members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and as such are deemed “listed authorities” by the World Health Organization [38]. Listed authorities, which include ICH observers, are a reference for other agencies or authorities in matters relating to reliance procedures. These procedures, when implemented efficiently, facilitate adoption of regulatory decisions and the exchange of information, including those that pertain to pharmacovigilance [39].

For signals/SDRs concerning herb–drug interactions, we consulted the most recent version of the EU Summaries of Products Characteristics or the FDA product information of the relevant medicinal products, which are compiled by marketing authorisation holders, submitted to and approved by the competent agencies [40, 41]. For EU centrally authorised medicinal products, we used the European Commission’s website (<https://ec.europa.eu/health/documents/community-register/html/>), and for nationally authorised medicinal products, we used the Medicines and Healthcare products Regulatory Agency website (<https://products.mhra.gov.uk/>). When no relevant Summaries of Products Characteristics were available there, we used the Health Products Regulatory Agency website (<https://www.hpra.ie/find-a-medicine/for-human-use/authorised-medicines>). For US product information, we accessed the repository at <https://www.accessdata.fda.gov/scripts/cder/daf/>. We categorised the EMA’s monographs, the BSH and DSFS, and Summary of Product Characteristics or product information as references for healthcare professionals, and entries in the DSLD as references for consumers.

## 2.4 Ascertainment of Amendments to EU and US Reference Documents

One researcher (DS) verified whether the adverse reactions conveyed in the signal/SDR had become available in reference documents, deeming a signal/SDR to have been followed up if the same *Medical Dictionary for Regulatory Activities* term, or any clinically related term, was present in the documents. See the Electronic Supplementary Material (ESM) for a complete list of adverse reactions and clinically related terms.

## 2.5 Determination of the Consistency of Information on Harms for Healthcare Professionals between the EU and the USA

Reference documents were categorised based on whether they included the adverse reactions of interest or clinically related terms. European Union monographs concern one herbal medicinal product, and BSH and DSFS concern one

herbal medicine. However, there can be multiple DSLD entries referring to the same herbal medicine. To enable pairwise comparisons between the USA and the EU, we treated all information pertaining to the same herbal medicine in all the entries of the DSLD as one reference document, combined with the information in the entries from the BSH and DSFS. Paired US-EU reference documents were concordant if their categories were the same across the same signal/SDR.

## 2.6 Determination of the Consistency of Information on Harms Between US Reference Documents for Healthcare Professionals and Consumers

European Union legislation mandates that information on harms attributed to centrally approved herbal medicinal products should be based on EU herbal monographs, for both healthcare professionals and consumers [42]. No such requirement exists in the USA [43]. Hence, we assumed consistency across EU information for healthcare professionals and consumers, while for US-based products we further evaluated whether information on harms across the BSH, DSFS and DSLD was consistent, treating all documents as separate. The DSLD entries that concerned products for “dispensing purposes only” were excluded, as they contain no information on harms.

## 2.7 Data Analysis

To provide an overview of signals/SDRs relating to herbal medicines, we calculated the frequency of signals/SDRs over the total dataset of the scoping review. We presented descriptive statistics for signals and SDRs separately, as was done in the scoping review because SDRs rarely lead to regulatory action without a clinical assessment of the information contained in reports of suspected adverse reactions [44].

To assess the consistency of information between US and EU documents, we calculated the frequency of concordant documents over total pairs. To assess the consistency of information for healthcare professionals with that for consumers in US documents, we first quantified the concordance across BSH and DSFS, as done for the international comparison. As there could be more than one label for a herbal product in the DSLD, we recorded the frequencies of labels that included the adverse reaction out of the total available labels in the DSLD for each product. We appended these frequencies to classifications of BSH and DSFS.

We managed the data and computed descriptive statistics in Microsoft Excel (v. 2308). We produced stacked bar charts in R (v. 3.4.2, [45]), using the *ggplot2* package [46], and flowcharts using Microsoft PowerPoint.

### 3 Results

#### 3.1 Descriptive Analysis

The original scoping review concerned, among others, 1683 studies including clinical assessments of reports of suspected adverse reactions and 181 disproportionality analyses alone, communicated between 1986 and 2020. We identified 29 studies involving herbal medicines, based on 25 (1.5% of 1683) clinical assessments of reports of adverse reactions, and four (2.2% of 181) disproportionality analyses, communicated between 1995 and 2020. For the full list of studies, please see the ESM.

The frequency of studies on herbal medicines appeared consistent over the years, never exceeding three studies per year, unlike that of other medicinal products (see Fig. 1). Research organisations authored most of the studies ( $n = 18/29$ , 62%), followed by regulatory agencies ( $n = 6$ , 21%), academia ( $n = 4$ , 14%) and healthcare professionals ( $n = 1$ , 3%).

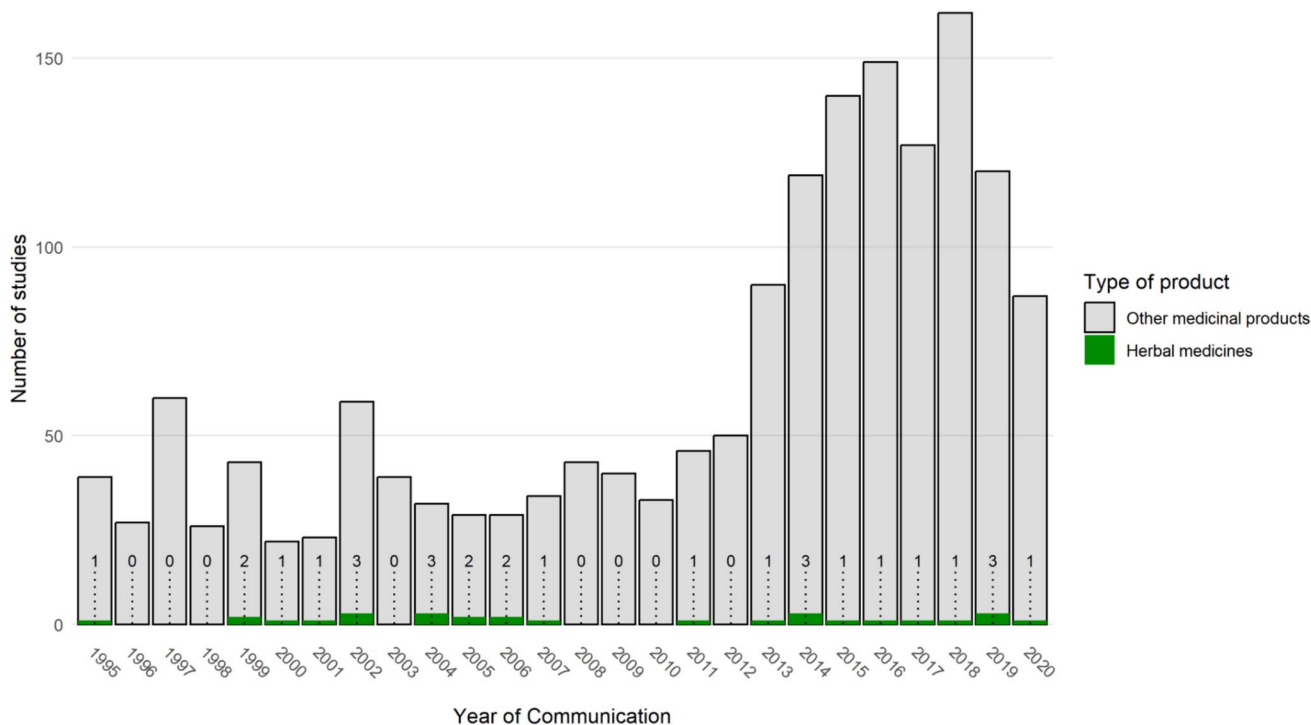
The 29 studies included a total of 53 signals, or 0.46% of the dataset in the published scoping review ( $n = 10,861$ ): 41 were detected from clinical assessments and 12 from disproportionality analyses alone. The herbal medicines associated with the largest number of signals were *Ginkgo biloba*, either alone or in interactions with other medicinal products

( $n = 8$ , 15%), *Hypericum perforatum* (including interactions with oral contraceptives:  $n = 5$ , 9%), preparations containing *Gardenia jasminoides* alone, in fixed-dose combinations with other medicinal products, or in interactions with medicinal products ( $n = 3$ , 1%), and *Trigonella foenum-graecum* ( $n = 2$ , 0.04%). Thirteen signals (25%) concerned possible herb–drug interactions, nine of which came from a single disproportionality analysis.

#### 3.2 Follow-Up of the Signals/SDRs in EU and US Reference Documents

To avoid duplicate counting of adverse reactions in reference documents, we restricted the 53 signals to 49: *Ginkgo biloba* and thrombocytopenia was communicated three times, in either the same substance or form by separate authors, including a fixed-dose combination of *G. biloba* and troxerutin. *T. foenum-graecum* and congenital anomalies was communicated by two separate groups of authors, the signal of *H. perforatum* and unintentional pregnancy was extended to the interaction between *H. perforatum* and oral contraceptives in the same study.

For five signals [47–50], we identified no reference documents, either because signals involved products not marketed in the EU or the USA, or because of the withdrawal of marketing authorisations. Of the 44 signals with reference documents, US reference documents were the only documents



**Fig. 1** Numbers of clinical assessments of reports of adverse reactions and disproportionality analyses across year of communication, colour coded by type of product. Studies on herbal medicines = 29, with yearly counts above the dotted lines

available for seven [50–52]. Thus, 37 signals could be followed up in both the EU and US documents (see Fig. 2).

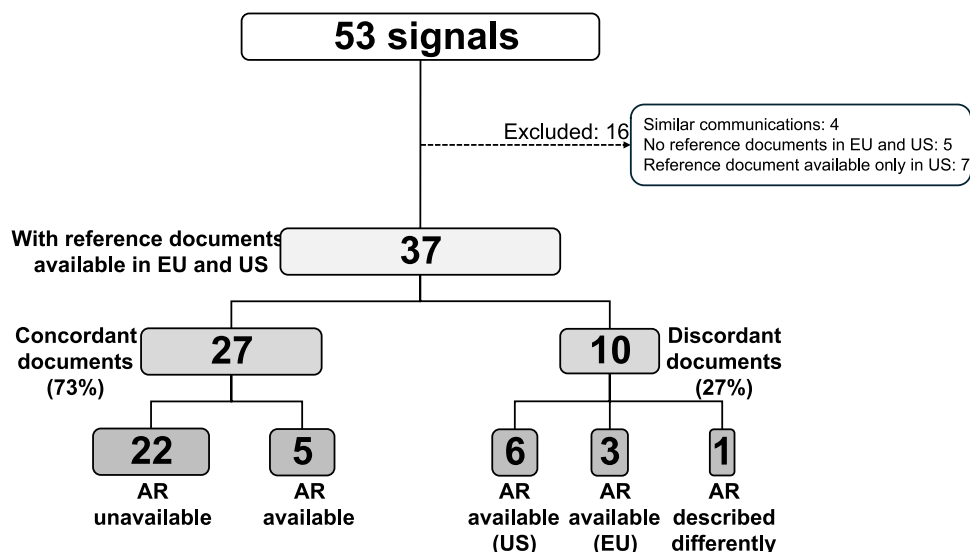
Reference documents were concordant for 27/37 (73%) signals. Ten (27%) were not: six adverse reactions were mentioned only in US documents, three only in EU monographs. Moreover, one signal was described differently in US documents and EU documents: the potential teratogenicity of *T. foenum-graecum* resulted in a recommendation against its use in women of childbearing potential not using contraception in the EU monograph, while the US documents contraindicated its use during pregnancy. Table 1 reports the signals for which reference documents were available in both the USA and the EU; for the full list of signals, please refer to the ESM.

### 3.3 US Reference Documents for Consumers and Those for Healthcare Professionals

Thirteen signals concerned herb–drug interactions, and so they were followed up in the product information of the relevant medicinal products (see Table 1). For ten signals, information was available in the DSFS but not in the BSH ( $n = 7$ ), or vice versa ( $n = 3$ ). For a complete overview, please refer to Table 4s of the ESM. In total, there were reference documents available across BSH, DSFS and DSLD, for 21 signals of adverse reactions to herbal products (see Fig. 3).

The BSH and DSFS were concordant for 14/21 signals (66%) and discordant for seven (33%); five adverse reactions were mentioned only in the BSH, one only in the DSFS, and the description of one adverse reaction differed: for *G. biloba* L., the BSH reported cerebral haemorrhages and thrombocytopenia, while the DSFS reported “increased risk of bleeding”.

**Fig. 2** Flowchart of the signals of adverse reactions (ARs), including signals of disproportionate reporting, for which there were reference documents across the European Union (EU) level and the USA (US). European Union documents included the herbal monographs, and US documents were the *Botanical Safety Handbook*, the *Dietary Supplement Fact Sheets* and the *Dietary Supplement Label Database*, treated as one. Documents were categorised as concordant when the ARs were available or not in both the EU monographs and the US set of documents



When the BSH and DSFS both did not mention a given adverse reaction, neither did the DSLD (eight signals, see Table 2). However, when the BSH and DSFS both mentioned an adverse reaction (six signals), the DSLD labels of each product never uniformly included the reaction underpinning the signals: of the corresponding 806 DSLD labels, only 159 (20%) contained the adverse reactions available in the BSH or DSFS. The relative frequency of DSLD labels that mentioned the reactions underpinning the signals ranged from 5% (*G. biloba* L.) to 78% (*T. foenum-graecum* L.). Thus, for 106 labels of products containing *T. foenum-graecum*, 83 included warnings that pertained to congenital anomalies also included in the BSH and DSFS.

When the BSH and DSFS were discordant, the relative frequency of DSLD labels whose contents agreed with either source ranged from 0.39% (*C. longa* L.) to 5% (*G. biloba* L.). We also found that 5–22% of the DSLD’s labels we considered lacked information on harms entirely, depending on the supplement. For instance, of the 98 labels for *P. ginseng* (C. A. Mey.), 21 contained no warnings at all.

## 4 Discussion

### 4.1 Summary of Key Findings

In the data set of the previously published scoping review, the proportions of clinical assessments of reports of adverse reactions and disproportionality analyses that related to herbal medicines were low (25/1683, 1.5% and 4/181, 2.2%). Furthermore, the number of studies on herbal products was three per year at most, in contrast to what we observed for conventional medicinal products (see Fig. 1). The EU and US reference documents were mostly concordant (73%), primarily for the absence of the adverse events involved in

**Table 1** List of 37 signals/signals of disproportionate reporting of adverse reactions or herb–drug interactions that could be followed up in the EU and US reference documents, with citations to the studies in which they were communicated, and whether the reactions to which they referred were documented (Y) or not (N), or whose description was unclearly reported (U)

Herbal ingredient	Adverse reaction terms	US documents	EU documents	Citation
<b>Information concordant in the USA and EU (n = 27)</b>				
<i>Allium sativum</i> + chemotherapy <sup>a</sup>	Musculoskeletal and connective tissue disorders	N	N	[53] <sup>n</sup>
	Nervous system disorders	N	N	[53] <sup>n</sup>
<i>Camellia sinensis</i> + chemotherapy <sup>a</sup>	Gastrointestinal disorders	N	N	[53] <sup>n</sup>
	Nervous system disorders	N	N	[53] <sup>n</sup>
<i>Euterpe oleracea</i> + chemotherapy <sup>a</sup>	Vascular disorders	N	N	[53] <sup>n</sup>
<i>Ginkgo biloba</i> alone or in a fixed-dose combination with troxerutin	Agranulocytosis <sup>b</sup>	N	N	[54] <sup>n</sup>
	Cardiac arrhythmias <sup>b</sup>	N	N	[55]
	Depression	N	N	[56]
<i>Hedera helix</i>	Anxiety	N	N	[56]
	Lip ulceration	N	N	[56]
	Malaise	N	N	[56]
	Muscular weakness	N	N	[56]
	Peripheral neuropathy	N	N	[56]
	Nocturia	N	N	[56]
	Hepatitis and hepatic failure <sup>c</sup>	N	N	[57]
<i>Senna alexandrina</i>	White blood cell disorder	N	N	[58]
	Tooth discolouration	N	N	[52]
Qingkailing <sup>d</sup> + benzylpenicillin	Anaphylactic shock/reaction	N	N	[59]
<i>Vaccinium macrocarpon</i> + chemotherapy <sup>a</sup>	Musculoskeletal and connective tissue disorders	N	N	[53] <sup>n</sup>
	Respiratory, thoracic and mediastinal disorders	N	N	[53] <sup>n</sup>
<i>Zingiber officinale</i> + chemotherapy <sup>a</sup>	Musculoskeletal and connective tissue disorders	N	N	[53] <sup>n</sup>
	Skin and subcutaneous tissue disorders	N	N	[53] <sup>n</sup>
<i>Hypericum perforatum</i> + oral contraceptives <sup>e</sup>	Unintended pregnancy	Y	Y	[60]
<i>Echinacea pallidal</i> / <i>Echinacea purpurea</i> / <i>Echinacea</i> spp.	Bronchospasm	Y	Y	[61]
<i>Ginkgo biloba</i> alone or in a fixed-dose combination with troxerutin	Cerebral haemorrhage	Y	Y	[62]
	Thrombocytopenia	Y	Y <sup>f</sup>	[56, 63, 64]
<i>Pelargonium sidoides</i>	Anaphylactic shock <sup>g</sup>	Y	Y	[65]
<b>Information discordant in the USA and EU (n = 10)</b>				
<i>Ginkgo biloba</i> + efavirenz; emtricitabine; tenofovir	Viral load increased	N	Y	[66]
<i>Ginkgo biloba</i> + efavirenz	Viral load increased	N	Y	[66]
<i>Hedera helix</i>	Bullous dermatitis	N	Y <sup>h</sup>	[56]
<i>Curcuma longa</i>	Diarrhoea	Y	N	[50]
	Nausea	Y	N	[50]
	Vomiting	Y	N	[50]
<i>Hypericum perforatum</i>	Anxiety	Y	N	[67]
<i>Panax ginseng</i> / <i>Ginseng</i> not otherwise specified	Hypertension	Y <sup>i</sup>	N	[68]
<i>Valeriana officinalis</i>	Sleep-related events <sup>j</sup>	Y <sup>k</sup>	N	[69]
<i>Trigonella foenum-graecum</i>	Congenital anomalies	Y <sup>l</sup>	U <sup>m</sup>	[70, 71] <sup>n</sup>

BSH Botanical Safety Handbook, DSFS Dietary Supplement Fact Sheets, DSLD Dietary Supplement Label Database, EU European Union, MedDRA<sup>®</sup> Medical Dictionary for Regulatory Activities, UMC Uppsala Monitoring Centre

US documents = BSH, DSFS and DSLD, with US product information for drug–herb interactions, all treated as one. EU Documents = EU herbal monographs, with EU product information for drug–herb interactions

Plus signs: herb–drug interaction; semicolons indicate fixed-dose combinations; solidi indicate “OR” logic. The first column shows herbal ingredient names, as coded by the UMC’s *Drug Dictionary*. In some cases, no additional information was available to ascertain them (and in all instances, the parts of plant that they concerned). The UMC’s *Drug Dictionary* is not equipped with standard authors’ abbreviations, so they were omitted

<sup>a</sup>Abiraterone, anastrozole, bortezomib, cetuximab, cisplatin, crizotinib, cyclophosphamide, docetaxel, doxorubicin, erlotinib, etoposide, gemcit-

**Table 1** (continued)

abine, ifosfamide, imatinib, irinotecan, lenalidomide, methotrexate, nilotinib, paclitaxel, pazopanib, ruxolitinib, sorafenib, sunitinib, tamoxifen, vemurafenib, vincristine

<sup>b</sup>Standardised MedDRA<sup>®</sup> Query, broad scope

<sup>c</sup>Includes the MedDRA<sup>®</sup> Preferred Terms: hepatitis, hepatocellular injury, jaundice, alanine aminotransferase increased, aspartate aminotransferase increased, hyperbilirubinaemia, hepatic failure, hepatitis cholestatic

<sup>d</sup>Combination of baicalin; buffalo horn; cholic acid; *Concha margaritifera*; *Gardenia jasminoides*; hyodeoxycholic acid; *Isatis tinctoria*; *Lonicera japonica*

<sup>e</sup>Ethinylestradiol; levonorgestrel or ethinylestradiol; norethisterone

<sup>f</sup>“increased risk of bleeding”

<sup>g</sup>Includes the MedDRA<sup>®</sup> Preferred Terms: hypersensitivity, anaphylactic shock, dermatitis, rash, flushing, face oedema, tongue oedema, oedema mouth, oedema peripheral, dermatitis bullous, pruritus, rhinitis, urticaria, conjunctivitis

<sup>h</sup>“hypersensitivity”

<sup>i</sup>“high blood pressure”

<sup>j</sup>MedDRA<sup>®</sup> High Level Term hallucinations (excluding sleep related), and Preferred Terms: nightmare, abnormal dreams, mental disorder

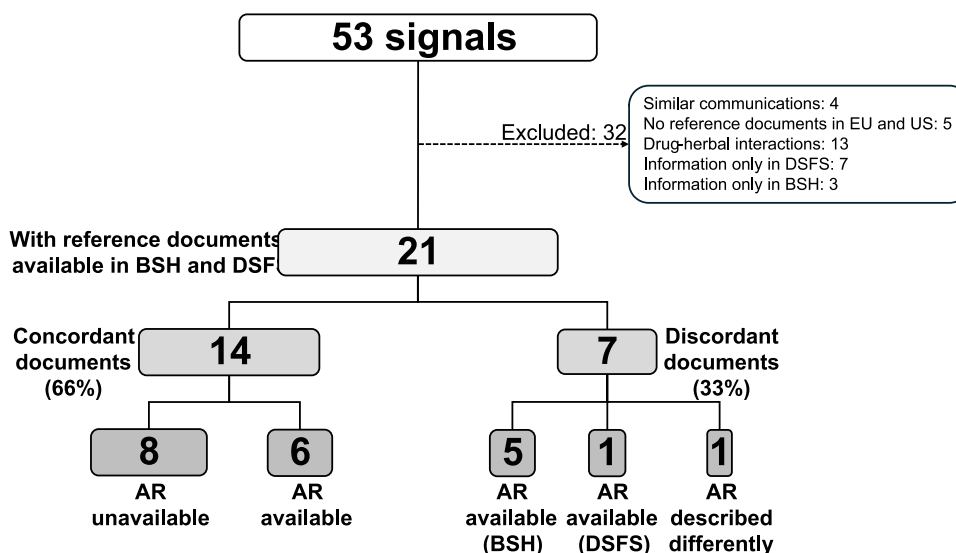
<sup>k</sup>“vivid dreams”

<sup>l</sup>“birth defects”

<sup>m</sup>“use not recommended in pregnancy and lactation”

<sup>n</sup>Signal of disproportionate reporting

**Fig 3** Flowchart of the signals of suspected adverse reactions (ARs) for which there were reference documents for health-care professionals across the USA. These were the *Botanical Safety Handbook* (BSH) and the *Dietary Supplement Fact Sheets* (DSFS). Documents were categorised as concordant when the ARs were available or not in both. EU European Union, US USA



the signals. Most of the differences (9/10, 90%) between the EU and US reference documents occurred because of the absence of the adverse reaction in one or the other resource. Only 20% of the labels for consumers included the same information on adverse reactions also available to healthcare providers, and some (5–2%) did not include information on harms at all.

## 4.2 Signals of Adverse Reactions to Herbal Medicines are Under-Reported

Reports of suspected adverse reactions were the main type of evidence supporting signals in this study, which is in line with previous findings. We have also shown a yearly increase in the number of studies of any medicinal product

[23]. Conversely, this study shows that the number of studies on herbal products per year was consistently low. A recent systematic review of cross-sectional studies based on spontaneous reports of adverse events to herbal medicines similarly found 26 eligible records published between 2005 and 2021, four of which in 2014, albeit with different inclusion criteria [72]. Additionally, an overview of 50 systematic reviews on adverse effects of herbal medicines identified major methodological flaws in 15, particularly the failure to report the numbers of retrieved records and reasons for exclusions [73]. At the same time, unpublished case reports concerning herbal medicines are lacking: a 2019 descriptive analysis showed that VigiBase, the World Health Organization’s global database of adverse events for medicines and vaccines, contained 128,000 reports featuring at least one

**Table 2** Consistency of information available in US reference documents for healthcare professionals (BSH; DSFS), and the relative frequencies of 21 sets of labels obtained from the DSLD

Herbal ingredients	Adverse reaction terms	BSH	DSFS	DSLDD Y/total (%)
<b>Information concordant in BSH and DSFS (n = 14)</b>				
<i>Gardenia jasminoides</i> fruit and preparations thereof	Mesenteric phleboscrosis	N	N	0/4
<i>Ginkgo biloba</i> alone or in a fixed-dose combination with troxerutin	Agranulocytosis	N	N	0/261
	Cardiac arrhythmias	N	N	0/261
	Depression	N	N	0/261
<i>Hypericum perforatum</i>	Hepatitis and hepatic failure	N	N	0/111 <sup>a</sup>
	White blood cell disorder	N	N	0/111 <sup>a</sup>
<i>Hydrastis canadensis</i>	Tooth discolouration	N	N	0/115 <sup>b</sup>
<i>Senna alexandrina</i>	Tooth discolouration	N	N	0/85 <sup>c</sup>
<i>Andrographis paniculata</i>	Face oedema	Y	Y	9/66 <sup>d</sup> (14%)
	Urticaria	Y	Y	9/66 <sup>d</sup> (14%)
<i>Echinacea pallidal</i> / <i>Echinacea purpurea</i> / <i>Echinacea</i> spp.	Bronchospasm	Y	Y	51/273 <sup>e</sup> (19%)
<i>Ginkgo biloba</i> alone or in a fixed-dose combination with troxerutin	Thrombocytopenia	Y	Y	12/261 <sup>f</sup> (5%)
<i>Panax ginseng</i> / <i>Ginseng</i> not otherwise specified	Hypertension	Y	Y	4/98 <sup>g</sup> (4%)
<i>Trigonella foenum-graecum</i>	Congenital anomalies	Y	Y	83/106 <sup>h</sup> (78%)
<b>Information discordant in BSH and DSFS (n = 7)</b>				
<i>Hypericum perforatum</i>	Anxiety	N	Y	0/111 <sup>a</sup>
<i>Andrographis paniculata</i>	Anaphylactic shock	Y	N	0/66 <sup>d</sup>
<i>Curcuma longa</i>	Diarrhoea	Y	N	0/258 <sup>i</sup>
	Nausea	Y	N	1/258 <sup>i</sup> (0.39%)
	Vomiting	Y	N	1/258 <sup>i</sup> (0.39%)
<i>Valeriana officinalis</i>	Sleep-related events	Y	N	0/145 <sup>j</sup>
<i>Ginkgo biloba</i> alone or in a fixed-dose combination with troxerutin	Cerebral haemorrhage	Y	U	12/261 <sup>f</sup> (5%)

BSH Botanical Safety Handbook, DSFS Dietary Supplements Fact Sheets, DSLDD Dietary Supplement Label Database, N adverse reaction unavailable, U unclear, UMC Uppsala Monitoring Centre, Y adverse reaction available

Solidi indicate “OR” logic. The first column shows the herbal ingredient names, as coded by the UMC’s *Drug Dictionary*. In some cases, no additional information was available to ascertain them (and in all instances, the parts of plant that they concerned). The UMC’s *Drug Dictionary* is not equipped with standard authors’ abbreviations, so they were omitted

<sup>a</sup>6/111 (5%) without any precautions

<sup>b</sup>18/115 (16%) without any precautions

<sup>c</sup>12/85 (14%) without any precautions

<sup>d</sup>Allergic reactions only; 9/66 (14%)

<sup>e</sup>Allergic reactions only. 47/273 (17%) without any precautions

<sup>f</sup>Unspecified bleeding; 33/261 (13%) without any precautions

<sup>g</sup>21/98 (21%) without any precautions

<sup>h</sup>23/106 (22%) included no warnings at all, or no warnings on use in pregnancy; the rest included warnings to consult doctors if the consumer is pregnant, before becoming pregnant or before taking any supplement (56); explicit warnings of teratogenicity (27)

<sup>i</sup>15/258 (6%) without any precautions

<sup>j</sup>14/145 (10%) without any precautions

suspected or interacting herbal ingredient; however, this figure fell to 24,000 when restricted to case reports that included a sole suspected or interacting herbal ingredient. To give this context, as of 2019, there were over 21 million reports in VigiBase that concerned other suspected/interacting medicinal products. Nevertheless, reports with a sole suspected herbal medicine may help detect signals [74]. Despite the availability of global data, signal detection

activities concerning herbal medicines have been limited to specific countries [50, 75, 76].

Taken together, the available evidence from published and unpublished reports may be methodologically weak and insufficient for a comprehensive understanding of the adverse effects of herbal medicines. Should signal detection activities be extended internationally, we agree with van

Hunsel et al. that VigiBase may provide additional information on herbal medicines [74].

### 4.3 Evidence for and Presumed Relevance of Discrepancies Across Reference Documents

Our results suggest that, as for medicinal products [77–79], there are international discrepancies in harms reported in reference documents of herbal medicines. More research would be required to better understand the national regulatory practices or requirements that may affect the compilation of product information [80–82], and their impact on healthcare professionals and patients [83–85].

We noted that information for US-based consumers tended to lack information on harms, extending prior research on EU products [86]. Currently, only manufacturers are responsible for compiling DSLD entries, and the US FDA does not verify whether information in the DSLD is compliant with regulations [36]. Applying regulatory oversight may ensure that reference documents for consumers also report harms, in contrast to online information, which mostly focuses on benefits [87–91]. Regulatory oversight might also mitigate possible effects of, for example, missing information on the teratogenicity of *T. foenum-gracum* L., contraindicated in pregnancy in the BSH but unavailable in some labels for patients, or anaphylactic reactions to *A. paniculata* (Burm. f.) Wall. ex Nees, which is absent from all DSLD labels but warned against in Australia [92].

### 4.4 Strengths and Limitations

To our knowledge, this is the first review that examines patterns of reporting of signals attributed to herbal medicines. Our overview was compiled using data retrieved systematically, covering over three decades of communications. As far as herbal medicines are concerned, we are not aware of any follow-up analyses of regulatory actions after signal communication, nor of possible international discrepancies across distinct regulatory settings.

The results we have presented should be evaluated within the definitions we adopted to obtain a set of signals of adverse reactions in the broader scoping review. Specifically, we considered only signals that involved medicinal products, and herbal medicinal products by extension. While the inclusion criteria of the scoping review required evidence of efficacy or traditional use, and of therapeutic indications for herbal medicines, we may have missed records relevant to herbal medicines regulated differently, for example, signals of liver damage or rhabdomyolysis with ‘Red yeast rice’ [93] could not be retrieved because where they originated the product containing *Oryza sativa* L. fermented with *Monascus purpureus* was not allowed to have therapeutic claims; similar to *Artemisia annua* L. in New Zealand [3]. The

well-known case of hepatotoxicity due to *Piper methysticum* G. Forst. was not described as a signal [94], and neither was that of *Actaea racemosa* L. [95]. The records in which these adverse reactions were described were ineligible, as we required findings to be explicitly described as signals. Thus, while these records were retrieved by our search strategy they did not meet our inclusion criteria. Furthermore, we only considered “herb–drug” interactions, so signals of interactions between herbal medicines (“herb–herb”) were omitted when both herbal medicines were ineligible. Therefore, our findings may underestimate the true number of studies of signals that concern herbal medicines. In addition, the scoping review excluded studies for which we did not receive a translation to English by the authors. We therefore excluded studies that we could not translate ourselves, written in Chinese, Japanese or Thai. Moreover, our search strategy may not have retrieved articles published in national journals. Because these countries have strong traditions of herbal medicine, some relevant signals may have been missed.

There are currently no benchmark countries for assessing international discrepancies across reference documents, although countries without medicines compendia tend to use foreign compendia [96]. It is therefore possible that reference documents may be more similar in another set of countries. It is also possible that our assumptions that information for EU consumers is faithful to that in EMA monographs may not hold. To verify this would require comparing information across all member states. Relatedly, most herbal medicines in the EU are licensed by individual member states; therefore, our choice of following up signals in EU monographs may have led us to miss nationally available sources of information intended for healthcare providers or consumers [97].

Finally, only one of the authors (DS) determined the consistency across documents, but two or more independent reviewers may have yielded different results. To improve the transparency of the judgements, we have made the author’s decisions available directly in the results, or as part of the ESM.

## 5 Conclusions

This study has shown that there were very few signals concerning herbal medicines identified in a published scoping review, all based on disproportionality analyses or clinical assessments of reports of adverse reactions. European Union and US reference documents were mostly consistent. Regulatory oversight in the compilation of entries in the DSLD may help keep information for consumers about harms from herbal products consistent.

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## Declarations

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**Conflicts of Interest/Competing Interests** Jeffrey K. Aronson has written and edited articles and textbooks on adverse drug reactions, including *Meyler's Side Effects of Drugs* (16th edition, 2016), its companion volumes the *Side Effects of Drugs Annuals*, and *Stephens' Detection and Evaluation of Adverse Drug Reactions* (6th edition, 2011). Daniele Sartori, Judith S. Brand, Oskar Gauffin, Sara Hedfors Vidlin and Igho J. Onakpoya have no conflicts of interest that are directly relevant to the content of this article. G. Niklas Norén is an Editorial Board member of *Drug Safety*. G. Niklas Norén was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

**Ethics Approval** This research relied on previously collected, anonymised, non-National Health Service data. As such, ethics approval was not required.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Availability of Data and Material** Research data on the included studies in the published scoping review are available here [https://static-content.springer.com/esm/art%3A10.1007%2Fs40264-022-01258-0/MediaObjects/40264\\_2022\\_1258\\_MOESM5\\_ESM.xlsx](https://static-content.springer.com/esm/art%3A10.1007%2Fs40264-022-01258-0/MediaObjects/40264_2022_1258_MOESM5_ESM.xlsx). For the specifics of the studies in this research, please refer to the ESM.

**Code Availability** The R code used to produce the figures is available upon request.

**Authors' Contributions** DS, IJO, NN and JKA conceptualised the study. DS undertook the data collection and analysis, and was supervised by IJO, JKA and NN. DS, JSB, OG and SHV contributed to the data visualisation and provided input for the data analysis. All authors have contributed to the original draft and to the revision of subsequent versions of the manuscript, and have read and approved the final version.

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