Supplementary Materials

Signals of Adverse Reactions to Herbal Medicines: evidence and document analysis based on a scoping review

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1 Additional information on the included studies

Table 1s: Characteristics of the 29 studies included in the review, with herbal products and adverse drug reactions of the 53 signals they communicated. Each publication could include more than one study. For example, where multiple clinical assessments were conducted separately on distinct series of case report, concerning separate herbal ingredients as coded by Uppsala Monitoring Centre's Drug Dictionary. For completeness, we present the accepted scientific name as per the Medicinal Plant Names Services by the Royal Botanic Gardens, Kew, to refer to herbal medicines; we note that the original publications may not present such details. Each entry assigns sequential identifiers to studies under "No.", to show how many studies were available in each publication. Publications are then assigned a citation number (see Bibliography).

No.	Authors	Publication title	Study design	Setting (Country)	N. of signals reported	Signals, or signals of disproportionate reporting, of adverse reactions to herbal medicines	Citation
1	Fahim SM, Mishuk AU, Cheng N, Hansen R, Calderón AI, Qian J.	Adverse event reporting patterns of concomitant botanical dietary supplements with CYP3A4 interactive & CYP3A4 non-interactive anticancer drugs in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS).	Disproportionality analysis	FAERS (United States)	9	*A. sativum* L., *C. sinensis* (L.) Kuntze, *E. oleracea* Mart, *V. macrocarpon* Aiton, *Z. officinalis* Roscoe in interaction with chemotherapy*	[1]
2	Arnaud M, Salvo F, Ahmed I, Robinson P, Moore N, Begaud B, et al.	A method for the minimization of competition bias in signal detection from spontaneous	Disproportionality analysis	FAERS (United States)	1	*G. biloba* L. and agranulocytosis	[2]

		reporting databases.					
3	Barnes J, van Hunsel F.	*Ginkgo biloba* - Cardiac arrhythmias	Clinical assessment of case reports		1	*G. biloba* L. and cardiac arrhythmias	[3]
4	Woo Y, Hyun MK.	Safety of herbal medicine for elderly patients with chronic disease in the Republic of Korea	Clinical assessment of case reports and disproportionality analysis	KAERS (Republic of Korea)	9	*H. helix* L. and anxiety, bullous dermatitis, lip ulceration, malaise, muscular weakness, peripheral neuropathy, nocturia. *G. biloba* L. and depression *G. biloba* L. and thrombocytopenia	[4]
5	Uppsala Monitoring Centre	Hypericum – hepatic injury	Clinical assessment of case reports	VigiBase (Global)	1	*H. perforatum* L. and hepatic failure	[5]
6	Paal T.	Hypericum perforatum – white blood cell disorders	Clinical assessment of case reports	VigiBase (Global)	1	*H. perforatum* L. and white blood cell disorder	[6]
7, 8, 9	Uppsala Monitoring Centre	Herbal drugs – tooth discolouration	Clinical assessment of case reports	VigiBase (Global)	3	*S. alexandrina* var *alexandrina*, *H. canadensis* L., *C. cardunculus* var. *scolymus* and tooth discolouration	[7]
10	Uppsala Monitoring Centre	Valeriana officinalis - hallucinations	Clinical assessment of case reports	VigiBase (Global)	1	*V. officinalis* L. and sleep related events	[8]

11	Li H, Deng J, Yue Z, Zhang Y, Sun H.	Detecting drug-herbal interaction using a spontaneous reporting system database: An example with benzylpenicillin and qingkailing injection.	Clinical assessment of case reports and disproportionality analysis	Guangdong Provincial Center (People's Republic of China)	1	Qingkailing** in interaction with benzylpenicillin and anaphylactic shock/reaction	[9]
12, 13	Savage R.	Hypericum – unintended pregnancy	Clinical assessment of case reports	VigiBase (Global)	2	*H. perforatum* L. alone or in interaction with oral contraceptives and unintended pregnancy	[10]
14	Napke E.	Echinacea extract – bronchospasm	Clinical assessment of case reports	VigiBase (Global)	1	*E. pallida* (Nutt.) Nutt. or *E. purpurea* (L.) Moench or *Echinacea* spp. and bronchospasm	[11]
15	Uppsala Monitoring Centre	Ginkgo biloba – cerebral haemorrhage	Clinical assessment of case reports	VigiBase (Global)	1	*G. biloba* L. and cerebral haemorrhage	[12]
16	Meyboom R.	Ginkgo biloba – thrombocytopenia	Clinical assessment of case reports	VigiBase (Global)	1	*G. biloba* L. alone or in association with troxerutin and thrombocytopenia	[13]
17	Meyboom R, Farah M.	Ginkgo biloba – thrombocytopenia	Clinical assessment of case reports	VigiBase (Global)	1	*G. biloba* L. alone or in association with troxerutin and thrombocytopenia	[14]

18	De Boer H, Uppsala Monitoring Centre	*Pelargonium sidoides* L./*Pelargonium reniforme* L. – allergic reactions	Clinical assessment of case reports	VigiBase (Global)	1	*P. sidoides* DC. and anaphylactic shock	[15]
19	European Medicines agency	Efavirenz – STOCRIN (CAP), SUSTIVA (CAP). Signal of interaction with Ginkgo biloba	Clinical assessment of case reports	Published case reports (Canada, Australia)	2	*G. biloba* L. in interaction with efavirenz or with the fixed-dose combination efavirenz; emtricitabine; tenofovir and viral load increased	[16]
20	Wechwithan S, Suwankesawong W, Sornsrivichai V, McNeil EB, Jiraphongsa C, Chongsuvivatwong V.	Signal detection for Thai traditional medicine: Examination of national pharmacovigilance data using reporting odds ratio and reported population attributable risk.	Clinical assessment of case reports and disproportionality analysis	Thai Food and Drug Administration adverse drug reaction surveillance database (Thailand)	8	*C. longa* L. and diarrhoea, nausea, vomiting *A. paniculata* (Burm.f.) Wall. ex Nees and anaphylactic shock, urticaria, face oedema *D. scandens (Roxb.) Benth. (B. scandens* (Roxb.) Wight & Arn. ex Miq.) and angioedema *S. exigua* Craib. or *P. cablin* (Blanco)	[17]

						Benth. or *M. fragrans* Houtt. and Stevens-Johnson syndrome	
21	Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, et al.	Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow card scheme': Literature review, descriptive and qualitative analyses, and questionnaire surveys.	Clinical assessment of case reports	Drug Safety Research Unit database (United Kingdom)	1	*H. perforatum* L. and anxiety	[18]
22	Uppsala Monitoring Centre	Ginseng – Hypertension	Clinical assessment of case reports	VigiBase (Global)	1	*P. ginseng* C. A. Mey. or "*ginseng*" not otherwise specified and hypertension	[19]
23	Es Seddiki A, Messaouidi S, Amrani R.	The role of fenugreek in the occurrence of an anomaly of neural tube closure: Warning signal from Morocco.	Clinical assessment of case reports	Anti-poison and pharmacovigilance centre of Rabat (Morocco)	1	*T. foenum-graecum* L. and congenital anomalies	[20]
24	Belamalem S, Benkirane R, Soulaymani A, Talibi I, Ouled Errkhis R, Tebaa A, et al.	Implementing the moroccan database by an automated signal detection method. Drug Safety	Disproportionality analysis	Anti-poison and pharmacovigilance centre of Rabat (Morocco)	1	*T. foenum-graecum* L. and congenital anomalies	[21]

25	Arnaud L, Mertz P, Gavand PE, Martin T, Chasset F, Tebacher-Alt M, et al.	Drug-induced systemic lupus: Revisiting the ever-changing spectrum of the disease using the WHO pharmacovigilance database.	Disproportionality analysis	VigiBase (Global)	1	*A. hippocastanum* L. and systemic lupus erythematosus	[22]
26	Pharmaceuticals and Medical Devices Agency	Summary of investigation results - Gardenia fruit (prescription drug) and preparations containing gardenia fruit (prescription drug)	Clinical assessment of case reports	JADER (Japan)	1	*A. capillaris* Thunb. (*A. scoparia* Waldst. & Kit.); *G. jasminoides* J. Ellis; *Rheum* spp. and mesenteric phlebosclerosis	[23]
27	Pharmaceuticals and Medical Devices Agency	Summary of investigation results - Inchinkoto for ethical use	Clinical assessment of case reports	JADER (Japan)	1	*G. jasminoides* J. Ellis fruit and preparations thereof and mesenteric phlebosclerosis	[24]
28, 29	Paal T.	Teucrium chamaedrys, teucrium scorodonia - Hepatitis, other liver disorders	Clinical assessment of case reports	VigiBase (Global)	2	*T. chamaedrys* L. or *T. scorodonia* L. and hepatitis and hepatic failure	[25]

*Any of the following 26 medicinal products: abiraterone, anastrozole, bortezomib, cetuximab, cisplatin, crizotinib, cyclophosphamide, docetaxel, doxorubicin, erlotinib, etoposide, gemcitabine, ifosfamide, imatinib, irinotecan, lenalidomide, methotrexate, nilotinib, paclitaxel, pazopanib, ruxolitinib, sorafenib, sunitinib, tamoxifen, vemurafenib, vincristine;

**Qingkailing is a preparation containing the following UMC Dictionary ingredients: *Concha margaritifera*, *Gardenia jasminoides, Isatis tinctoria, lonicera japonica,* and baicalin, buffalo horn, cholic acid, hyodeoxycholic acid.

2 Additional information on the methods used to ascertain the presence of adverse reaction terms in the reference documents

We searched the whole US and EU reference documents for the adverse reaction (AR) terms in each signal, and for a set of related ARs. We report our search criteria in the table below, for all the signals of ARs to herbal products. The search criteria were left generic in some cases and, where possible, they include lay terms to extend the reproducibility of the searches to consumer documents.

Table 2s: Adverse Reaction terms of the 44 signals included in the analysis, and related adverse reactions. The term itself and related adverse reactions were used as search criteria in European and American reference documents.

Adverse Reaction Terms	**Related Adverse reactions**
Agranulocytosis	Granulocytes decreased, white blood cell counts decreased, neutropenia
Anaphylactic shock	Anaphylaxis, anaphylactic reactions, hypersensitivity, bronchospasm, angioedema, rash, flushing, face oedema, tongue swelling, mouth swelling, peripheral oedema, pruritus or itching, rhinitis, urticaria, conjunctivitis.
Anxiety	Agitation, restlessness, panic attack.
Bronchospasm	See anaphylactic shock; hypersensitivity
Bullous dermatitis	Dermatitis, hypersensitivity, skin blisters, linear IgA disease, IgA pemphigoid, bullous pemphigoid
Cardiac arrhythmias	QT prolongation, long QT syndrome, torsade de pointes, tachycardia ventricular or atrial, atrial flutter, atrial fibrillation, palpitations, heart beat increased or decreased, bradycardia, bradyarrhythmia, premature ventricular contractions, paroxysmal supraventricular tachycardia, AV blocks (degree: I, II type 1 or 2, III), bundle branch blocks (right or left).
Cerebral haemorrhage	Haemorrhagic stroke, cerebrovascular accident, brain haemorrhages; terms relating to thrombocytopenia (see below)
Congenital anomaly	Any warning against use during pregnancy, generic mentions of congenital disorders or anomalies, and specific major or minor birth defects (spina bifida, meningocele, cleft lip and palate etc.)
Depression	None
Diarrhoea	None
Face oedema	Oedema, facial oedema, allergic reactions, allergy, facial swelling, mouth swelling; see also anaphylactic shock.
Hepatitis and hepatic failure	Liver injury, liver damage, hepatitis, hepatic enzymes increased
Hypertension	Increased blood pressure
Lip ulceration	Ulcerations
Malaise	Nausea, vomiting, weakness
Mesenteric phlebosclerosis	None

Muscular weakness	Weakness
Nausea	None
Nocturia	Micturition disorders, urinary frequency increased at night, hypertension, bed wetting
Peripheral neuropathy	Neuropathy, Guillain Barré syndrome, hypothyroidism
Sleep-related events	Hypersomnia, somnambulism, excessive sleep, circadian rhythm disorders, nightmares, hallucinations, delusions
Stevens-Johnson syndrome	Severe cutaneous adverse drug reactions, toxic epidermal necrolysis or Lyell's syndrome, skin exfoliation or sloughing, mucosal ulceration, erythema multiforme major
Thrombocytopenia	Platelets decreased, anaemia or aplastic anaemia, myelodysplastic syndrome, bone marrow aplasia, bleeding or haemorrhages, concurrent use of anticoagulants (e.g. vitamin K antagonists, salicylates)
Tooth discolouration	Teeth pigmentation, yellowing, or staining
Urticaria	Hives, rash, pruritus or itching, skin irritation
Vomiting	Hyperemesis, vomit
White blood cell disorder	Any decrease in counts of white blood cell, bone marrow aplasia, myelodysplastic syndrome

For signals of "drug-herbal" interactions, we searched the interaction sections of the US or EU product information of the medicinal products involved for any mention of interactions with herbal medicines. We deemed sufficient a mention of a possible interaction between medicinal and herbal products.

3 Signals for which there were no reference documents, or for which information was only available in the US

Table 3s: List of signals for which we were unable to retrieve reference documents in the European Union (EU) or United States (US). Herbal ingredients are named after entries in the UMC Drug Dictionary. Semicolons indicate fixed-dose combinations, and solidi denote "OR" logic.

Herbal ingredients	Adverse reaction terms	US documents	EU documents	Citation
No information available (n= 5)				
Aesculus hippocastanum [a]	Systemic lupus erythematosus	–	–	[22]
Derris scandens	Angioedema	–	–	[17]
Artemisia capillaris; *Gardenia jasminoides*; *Rheum* spp.	Mesenteric phlebosclerosis	–	–	[23]
Teucrium chamaedrys	Hepatitis and hepatic failure [b]	–	–	[25]

Teucrium scorodonia	Hepatitis and hepatic failure [b]	–	–	[25]
Information available in US but not in EU (n= 7)				
Cynara cardunculus	Tooth discolouration	N	–	[7]
Gardenia jasminoides fruit and preparations thereof [c]	Mesenteric phlebosclerosis	N	–	[24]
Hydrastis canadensis	Tooth discolouration	N	–	[7]
Sophora exigua/Pogostemon cablin/*Myristica fragrans* [d]	Stevens-Johnson syndrome	N	–	[17]
Andrographis paniculata	Anaphylactic shock	Y	–	[17]
Andrographis paniculata	Face oedema	Y	–	[17]
Andrographis paniculata	Urticaria	Y	–	[17]

a *= in fixed-dose combination with Convallaria majalis; Drimia maritima; oleandrin; phenopyrazone; yeast;*

b *= includes the MedDRA Preferred Terms: hepatitis, hepatocellular injury, jaundice, alanine aminotransferase increased, aspartate aminotransferase increased, hyperbilirubinaemia, hepatic failure, hepatitis cholestatic;*

c *= in 16 fixed-dose combinations of one or more of the following WHODrug Global active ingredients: Akebia spp., Alisma orientale, Angelica acutiloba, Angelica archangelica, Angelica dahurica, Atractylodes spp., Aucklandia costus, Astragalus spp., Bambusa spp., Bupleurum falcatum, calcium sulfate, Citrus aurantium, Citrus spp., Cimicifuga spp., Cnidium officinale, Coptis spp., Dimocarpus longan, Ephedra spp., Eriobotrya japonica, Forsythia spp., Gardenia jasminoides, Gentiana spp., Glehnia littoralis, Glycyrrhiza spp., Lilium spp., Magnolia spp., Mentha canadensis, Morus alba, Ophiopogon japonicus, Paeonia lactiflora, Paeonia x suffruticosa, Panax ginseng, Phellodendron spp., Plantago asiatica, Platycodon grandiflorus, Polygala tenuifolia, Poria cocos, Prunus spp., Rehmannia glutinosa, Rheum spp., Saposhnikovia divaricata, Schisandra chinensis, Schizonepeta tenuifolia, Scutellaria baicalensis, sodium sulfate, talc, Trichosanthes spp., Zingiber officinale, Ziziphus jujuba;*

d *= refer to M. fragrans and P. cablin, as no preparations of S. exigua were found.*

4 Signals for which there were no US reference documents for healthcare providers, or for which information was only partly available

Table 4s: List of 10 signals for which we able to retrieve reference documents only in the United States, and which of the Botanical Safety Handbook (BSH), Dietary Supplements Fact Sheets (DSFS), included the Adverse Reaction of interest.

Herbal medicinal product	**Adverse Reaction Terms**	**BSH**	**DSFS**	**DSLD Y/total (%)**
Information available in DSFS but not in BSH (n=7)				
Hedera helix	Anxiety	-	N	0/11
	Lip ulceration	-	N	0/11
	Malaise	-	N	0/11
	Muscular weakness	-	N	0/11
	Peripheral neuropathy	-	N	0/11
	Nocturia	-	N	0/11

	Bullous dermatitis	-	Y	0/11
Information available in BSH but not in DSFS (n=3)				
Cynara cardunculus	Tooth discolouration	N	-	0/49
Sophora exigua/Pogostemon cablin/Myristica fragrans	Stevens-Johnson syndrome	N	-	0/14 [a]
Pelargonium sidoides	Anaphylactic shock	Y	-	0/9

a *= refer to M. fragrans and P. cablin, as no preparations of S. exigua were found.*

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