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ORIGINAL RESEARCH ARTICLE

Allergy-Like Immediate Reactions with Herbal Medicines: A Retrospective Study Using Data from VigiBase®

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Abstract

Introduction Herbal medicines are used worldwide and with an increasing popularity in Western countries. Although often perceived as 'naturally safe', herbals may cause severe adverse drug reactions (ADRs), with immediate allergic reactions being particularly life threatening.

Objectives The aim of this study was to analyse immediate allergy-like ADRs to herbals documented in VigiBase®, the WHO international pharmacovigilance database.

Methods The documentation of all suspected ADRs in association with herbal exposure reported to VigiBase® from 1969 to August 2014 was retrieved. Among all reports in which WHO-ART reaction terms were indicative of acute allergic reactions, those classified as 'suspect' with a documented causality assessment and latency time of $\leq$1 day were selected. For the most frequent specific herbal–ADR combinations, the information component (IC) as a measure of disproportionality based on Bayesian statistics was calculated.

Results We identified 757 reports out of 1039 ADRs. Products with mixed herbals (36.0 %) as well as those administered orally (63.2 %) were predominant. The most frequent reactions were urticaria and rash (49.2 %). Anaphylactic reactions accounted for 9.5 %. Disproportionally frequent reporting of mouth edema (IC = 1.81) and anaphylactic reactions (IC = 1.24) to *Phleum pretense* were noted.

Conclusion Our findings indicate that herbal medicines for oral use carry a risk of causing immediate allergy-like ADRs. Studies using the Vigibase® database can identify specific combinations of particular herbs and adverse reactions. Healthcare professionals and patients should be aware of these risks and report any serious adverse experiences.

Key Points

While herbal medicines for oral use are generally regarded as safe, international pharmacovigilance data indicate that many such products carry a risk of causing acute allergy-like adverse reactions.

The recognition of the possibility of such reactions with the use of specific products is needed for timely diagnosis as well as for prevention of problems.

1 Introduction

There is an increased prevalence in the use of herbal medicines among the adult population in many Western countries [1–3]. The most recent 2012 US National Health Interview Survey showed that 18 % of adults used natural

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products including at least one herbal medicine during the past 12 months [3]. Herbal medicines are generally considered harmless since they are natural and thus the general public is unaware that Complementary and Alternative Medicines (CAM) are not tested by regulatory agencies for their safety and efficacy [4, 5]. In most countries, herbal medicines are defined as dietary supplements and as such do not have to meet pre- and postmarketing drug policy regulations [6]. Nevertheless, the use of certain herbal medicines has been associated with the occurrence of severe adverse reactions as a result of the complex chemistry of herbals as well as through their inappropriate use and a lack of quality control [7, 8]. In addition, patients may not disclose self-medication with herbal medicines to their healthcare professionals, who themselves may have limited information about potential adverse reactions and interactions with concomitantly used prescription drugs [9, 10].

In the absence of systematic and comprehensive safety evaluations of herbal medicines, spontaneous reporting systems of adverse drug reactions (ADRs) serve a major function in terms of worldwide safety surveillance and signal detection [11]. Although there have been many case reports of ADRs associated with herbals in the literature, the majority of reports are documented in large pharmacovigilance databases; thus, these valuable resources should be systematically analyzed for ADRs associated with herbals [8, 12, 13]. ADRs to herbals cover a wide range of manifestations that are typically mild and followed by full recovery. Nevertheless, immediate allergic reactions are also often potentially life threatening; thus, these effects represent the most clinically relevant adverse reactions to herbal medicines. Our study of the results of more than 40 years of international pharmacovigilance was conducted with the goal of investigating reporting patterns as well as basic characteristics of immediate allergic adverse reactions associated with herbal medicines.

2 Methods

2.1 Study Settings

The WHO Global Individual Case Safety Report database (VigiBase®), the largest international pharmacovigilance database of spontaneous ADR reports, was the source examined in our study. VigiBase® is maintained by the Uppsala Monitoring Centre (UMC) in association with the World Health Organization's (WHO) international pharmacovigilance program. The UMC is an independent foundation and a center for international service and scientific research which currently collaborates with 122 member countries around the world in the collection and evaluation of spontaneous ADR reports [14]. These centers forward anonymized ADR reports received from various primary reporting sources to the UMC in a standardized format containing structured information on adverse events; that is, patients and drugs involved, including standardized semi-quantitative causality assessments [15].

Vigibase, the UMC's database, currently contains over 11 million case reports (May, 2015). The WHO Adverse Drug Reaction Terminology (WHO-ART) and WHO Drug Dictionary/WHO Herbal Dictionary are used for the coding of clinical information in relation to drug therapy featuring the reported drugs [14]. MedDRA® terminology was introduced to VigiBase in 1994; automated algorithms that convert the codes form those two dictionaries in both directions [16].

Herbal medicine refers to herbs, herbal materials, herbal preparations as well as finished herbal medicines. Herbal medicines are assigned herbal anatomical-therapeutic-chemical (HATC) codes specifying their therapeutic use according to the Guidelines for Herbal ATC classification [17]. HATC classification aggregates herbal medicines according to their medical uses that have been found in the literature, but does not indicate that a given remedy has been proven effective or safe [14]. Herbal pharmacovigilance terminology is used in accordance with WHO guidelines [18].

2.2 Study Design and Selection of Cases

A flowchart of the study design and case selection process is presented in Fig. 1. The aim of our study was to focus on immediate allergic ADRs associated with herbals, as these are more often potentially life threatening and therefore highly relevant clinically. The level of documentation within VigiBase® is heterogeneous, thus it may be difficult to form an exact medical diagnosis based on the available information. With this limitation in mind, case selection criteria were defined through likely indicators of immediate allergic reactions.

Because VigiBase® does not allow for a validation of type 1 immediate hypersensitivity reactions according to comprehensive clinical diagnostic criteria, the cases included have been judiciously referred to as 'allergy-like immediate reactions' in our study. For inclusion in the study population, the following inclusion criteria were used: (1) exposure to manually validated herbal medicines, a category classified by the primary reporter as 'suspect' with regard to the reported ADRs; (2) a documented causality assessment of 'possible,' 'probable' or 'certain' between a herbal product and ADRs; (3) a documented latency time of no more than 1 day from herbal exposure to ADR onset; (4) manual selection of WHO-ART preferred

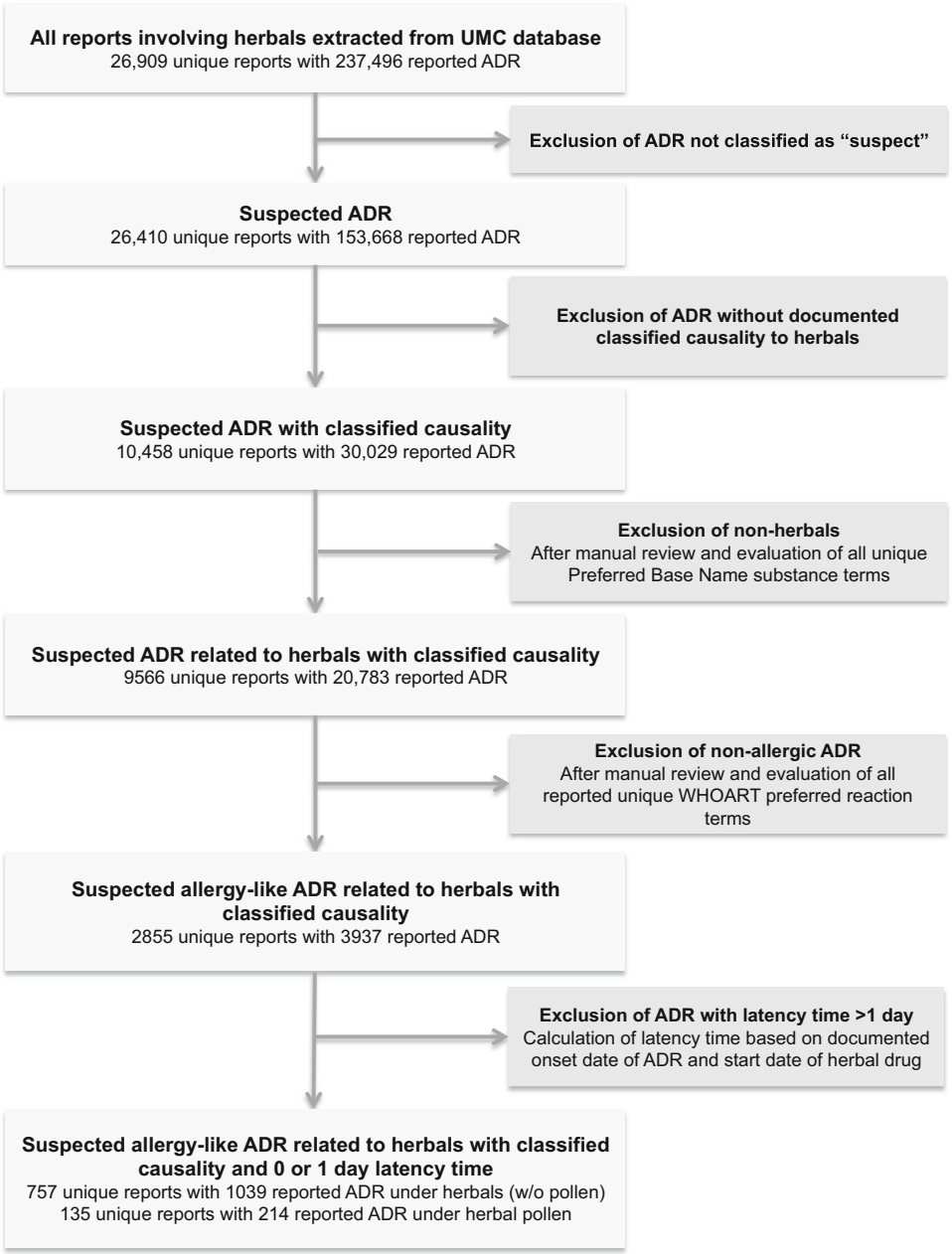

Fig. 1 Flowchart of study design and case selection process. *ADR* adverse drug reactions, *UMC* Uppsala Monitoring Centre, *WHO-ART* World Health Organization Adverse Reactions Terminology

terms indicating an ADR that is a likely symptom of an immediate hypersensitivity reaction.

In contrast, reaction terms that are compatible with but have a low specificity for immediate allergic reactions such as cough, dyspnea, larynx pain, gastrointestinal symptoms or pruritus were on their own not considered sufficient for inclusion. Furthermore, ADRs associated with the HATC term 'herbal pollen not otherwise specified' were excluded from the main analysis because these are likely to refer to desensitization vaccines for the treatment of pollen allergies (ADRs that may have a distinct special relationship to the indication for the suspected herbal medicines). Of note, this HATC term does not include *Phleum pratense* (Timothy grass), although it is also used for desensitization. It is of interest that anaphylaxis has not been reported in clinical trials and reviews on *Phleum pretense* [19, 20], and we therefore explored such a possible association in the main analysis. WHO-ART terms were further divided into asthma-like and allergy-like reaction groups. Asthma-like reactions were defined by the preferred WHO-ART

terms 'asthma,' 'stridor' or 'bronchospasm.' All remaining WHO-ART terms with high specificity for immediate allergic reactions constituted the applicable allergy-like reaction group.

2.3 Statistical Analysis

Descriptive statistics was used to analyze the characteristics of case reports. Unexpected ADRs to herbals were quantitatively analyzed using a measure of disproportionality based on the shrinkage of observed-to-expected ratios expressed as the Information Component (IC) [21]. The IC is computed as the base 2 logarithm of an $(O + 0.5)/(E + 0.5)$ ratio with an observed number of events (O) and expected number of events (E) of reports on the drug–ADR combination. E is given by $(N_A \times N_D)/N$, where N_A is the number of all reports on the ADR, N_D is the number of all reports on the drug, and N is the number of all reports. Credibility intervals for the IC are obtained via Gamma distribution, with IC_α denoting the α percentile of the posterior distribution for the IC. A drug–ADR combination was considered disproportionally reported when IC025 >0 for the whole database. IC025 denotes the lower limits of 95 % credibility intervals for the IC [21, 22]. For the IC analysis we used the dataset of all reports that met our inclusion criteria and calculated the IC for all specific combinations that occurred with a frequency of 10 or more. Data management and analyses were performed using STATA Version 13.1 (StataCorp LP, College Station, TX, USA).

3 Results

The initial dataset extracted from VigiBase® comprised 26,909 unique ADR reports received between 1969 and August 2014 following exposure to herbal medicines. After the application of exclusion criteria, 757 unique reports remained containing 1039 ADRs (i.e., more than one reaction term could be reported per case) related to herbal medicines.

3.1 Case Report Characteristics

The characteristics of the 757 reports are presented in Table 1. Women were overrepresented among included cases (68.6 %), and more than one third of the cases fell into the age category from 18 to 44 years. More than 50 % of all the included reports came from only three countries: Germany (22.3 %), Australia (14.9 %) and Thailand (11.2 %). The most frequent primary reporters were physicians (32.1 %), followed by hospitals (24.7 %) and pharmacists (14.1 %).

Table 1 Case report characteristics ($N = 757$)

Characteristics	*n*	%
Gender		
Female	519	68.6
Male	225	29.7
Not specified	13	1.7
Age group (years)		
<18	109	14.4
18–44	278	36.7
45–64	199	26.3
≥65	117	15.5
Not specified	54	7.1
Reporting country		
Germany	169	22.3
Australia	113	14.9
Thailand	100	13.2
South Korea	49	6.5
Spain	43	5.7
Sweden	39	5.2
Switzerland	37	4.9
Cuba	29	3.8
United Kingdom	17	2.3
Malaysia	16	2.1
New Zealand	15	2.0
Norway	11	1.5
Other (<10 reports per country)	119	15.7
Reporting source		
Physician	243	32.1
Hospital	187	24.7
Pharmacist	107	14.1
Manufacturer	38	5.0
Consumer/non-health-professional	14	1.9
Other/not specified	168	22.2

The chronology of the receipt of those reports is presented in Fig. 2. A pronounced increase in reporting frequency in recent years can be identified, a finding which reflects an overall trend in the database as well.

3.2 Immediate Allergy-Like Reactions

The characteristics of immediate allergy-like reactions to herbal medicines are presented in Table 2. The likelihood of a causal connection in the 1039 reported ADRs has been assessed as 'possible,' 'probable,' and 'certain' in 59.2, 32.2, and 8.6 %, respectively.

Asthma-like reactions accounted for only 4.8 % of all ADRs. The most commonly reported allergy-like immediate adverse reactions associated with herbals were 'rash'

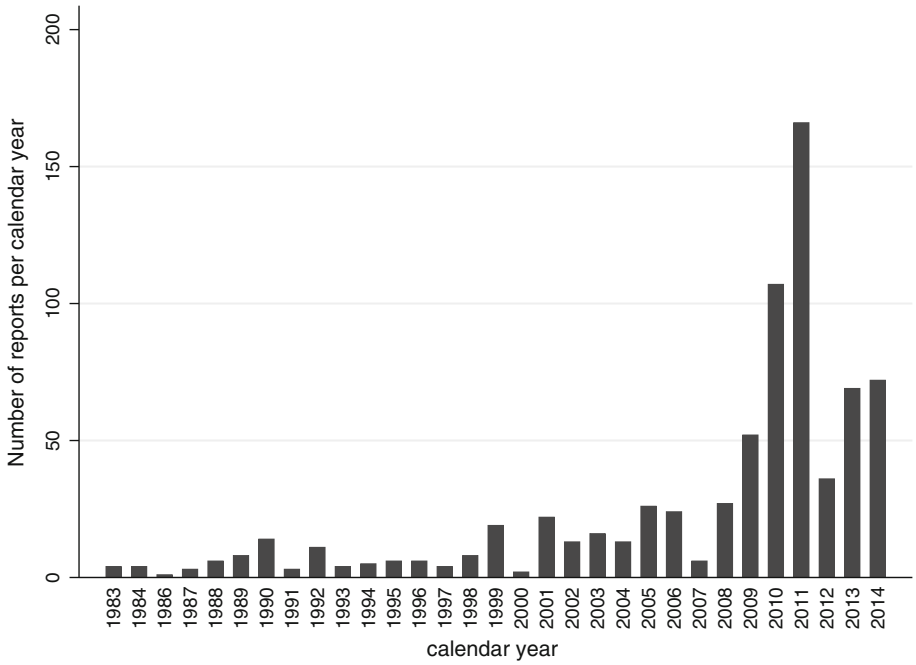

Fig. 2 Number of reports of immediate allergy-like adverse reactions after the use of herbals per year ($N = 757$)

(16.2 %), 'urticaria' (15.3 %) and 'rash erythematous' (13.4 %). Anaphylactic and anaphylactoid reactions accounted altogether for 9.5 % of reported ADRs (anaphylactic reaction 4.5 %, anaphylactic shock 2.8 %, anaphylactoid reaction 2.2 %). Table 2 shows other serious ADRs such as bronchospasm and larynx edema.

Outcome was favorable (i.e., with recovery noted in 77.7 % of all ADRs) and no deaths were reported. It should be noted, however, that no information was available on the outcome for 9.2 %.

3.3 Suspect Herbals

Descriptions of specific herbals associated with the reported ADRs and their route of administration are presented in Table 3. Preparations that contained a mixture of several herbals were the suspected cause in 36 % of all ADRs and therefore by far were the most frequently reported, followed by the single herbals *Phleum pratense* (common name: Timothy grass, 6.5 %), *Andrographis paniculata* (several common names including Kalmegh, 5.0 %), *Echinacea purpurea* (3.8 %) and *Ginkgo biloba* (3.6 %).

Oral administrations accounted for almost two thirds of ADRs, followed by topical/cutaneous and sublingual administrations in 9.0 and 6.4 % of the cases, respectively.

3.4 Disproportionality Analysis

Calculations of IC values for all 16 specific herbal allergy-like reaction combinations that had been reported at least 10 times are presented in Table 4. Accordingly, significantly higher frequencies than expected by chance were found for *Phleum pratense* (Timothy grass) linked to edema of the mouth (IC = 1.81, 95 % CI 0.67–2.86) and to anaphylactic reactions (IC = 1.23, 95 % CI 0.03–2.33).

4 Discussion

Our study consists of an analysis of a series of 757 case reports indicative of allergy-like adverse reactions during the use of herbal medicines as recorded in the VigiBase® database of spontaneous ADR reports representing 42 countries since 1969. Our findings indicate a large number of different herbal medicines causing immediate allergy-like reactions in the population. Among all reports, mixed herbals, *Phleum pratense* and *Andrographis paniculata* were most frequently reported in association with ADRs. *Phleum pratense* has previously not been associated with anaphylaxis [19, 20], although two case reports of anaphylactic reaction after the first dose of grass pollen tablet containing *Phleum pretense* were reported [23]. It is therefore important new information that our study found reports of anaphylaxis related to *Phleum pratense* in VigiBase®, and that the disproportionality analysis even indicated a stronger association compared with other herbals, while evidence on its efficacy for immunotherapy is weak [19]. *Andrographis paniculata* is highly valued in Ayurvedic medicine and is typically used for the treatment of the common cold [24]. In relation to our work, previously reported findings from Thailand investigating the

Table 2 Characteristics of immediate allergy-like reactions after the use of herbal medicines ($N = 757$)

	Causality						Overall	
	Possible		Probable		Certain			
	n	%	*n*	%	*n*	%	*n*	%
Total number of reported ADRs	615	59.2	335	32.2	89	8.6	1039	100
Type of ADRs								
Allergic	584	95.0	319	95.2	86	96.6	989	95.2
Asthma-like[a]	31	5.0	16	4.8	3	3.4	50	4.8
Specification of reported ADRs (WHO-ART preferred term)								
Rash	108	17.6	53	15.8	7	7.9	168	16.2
Urticaria	86	14.0	57	17.0	16	18.0	159	15.3
Rash erythematous	91	14.8	37	11.0	11	12.4	139	13.4
Allergic reaction	42	6.8	13	3.9	3	3.4	58	5.6
Angioedema	27	4.4	21	6.3	5	5.6	53	5.1
Flushing	29	4.7	15	4.5	4	4.5	48	4.6
Anaphylactic reaction	28	4.6	10	3.0	9	10.1	47	4.5
Face edema	34	5.5	10	3.0	2	2.3	46	4.4
Rash maculo-papular	23	3.7	21	6.3			44	4.2
Edema mouth	14	2.3	14	4.2	10	11.2	38	3.7
Edema periorbital	24	3.9	9	2.7	3	3.4	36	3.5
Anaphylactic shock	11	1.8	15	4.5	3	3.4	29	2.8
Bronchospasm	14	2.3	11	3.3	1	1.1	26	2.5
Anaphylactoid reaction	11	1.8	8	2.4	4	4.5	23	2.2
Tongue edema	12	2.0	6	1.8	3	3.4	21	2.0
Asthma	11	1.8	5	1.5	2	2.3	18	1.7
Dermatitis contact	5	0.8	8	2.4	3	3.4	16	1.5
Dermatitis	6	1.0	7	2.1	1	1.1	14	1.4
Edema pharynx	4	0.7	6	1.8	1	1.1	11	1.1
Edema generalized	5	0.8	4	1.2			9	0.9
Eosinophilia	8	1.3					8	0.8
Allergy	6	1.0			1	1.1	7	0.7
Larynx edema	4	0.7	3	0.9			7	0.7
Stridor	5	0.8					5	0.5
Erythema multiforme	3	0.5					3	0.3
Skin reaction localized	2	0.3					2	0.2
Bronchospasm aggravated	1	0.2					1	0.1
Drug hypersensitivity syndrome			1	0.3			1	0.1
Purpura allergic			1	0.3			1	0.1
Urticaria acute	1	0.2					1	0.1
Outcome								
Recovered	431	70.1	296	88.4	80	89.9	807	77.7
Not recovered (yet)	97	15.8	18	5.4	4	4.5	119	11.5
Recovered with sequelae	10	1.6	7	2.1			17	1.6
Died								
Unknown/not specified	77	12.5	14	4.2	5	5.6	96	9.2

ADRs adverse drug reactions, *WHO-ART* World Health Organization Adverse Reactions Terminology

[a] Asthma-like ADRs included WHO-ART preferred terms 'asthma,' 'stridor,' and 'bronchospasm'

safety of *Andrographis paniculata* showed a similar range of hypersensitivity reactions ranging from skin reactions to anaphylaxis [25]. Case reports indicative of hypersensitivity to several other herbals most frequently reported in our study have also been previously published [26–31].

Table 3 Characteristics of suspect herbals associated with immediate allergy-like reactions ($N = 757$)

	Causality						Overall	
	Possible		Probable		Certain			
	n	%	*n*	%	*n*	%	*n*	%
Total number of reported ADRs	615	59.2	335	32.2	89	8.6	1039	100
Herbs reported in association with ADRs								
Mixed herbals	220	35.8	126	37.6	28	31.5	374	36.0
Phleum pratense	16	2.6	25	7.5	27	30.3	68	6.5
Andrographis paniculata	27	4.4	25	7.5			52	5.0
Echinacea purpurea	30	4.9	6	1.8	3	3.4	39	3.8
Ginkgo biloba	29	4.7	6	1.8	2	2.3	37	3.6
Hedera helix	25	4.1	4	1.2	1	1.1	30	2.9
Plantago ovata	6	1.0	9	2.7	4	4.5	19	1.8
Hypericum perforatum	13	2.1	4	1.2	1	1.1	18	1.7
Viscum album	13	2.1	4	1.2	1	1.1	18	1.7
Valeriana officinalis	10	1.6	6	1.8	1	1.1	17	1.6
Cimicifuga racemosa	11	1.8	5	1.5			16	1.5
Mentha x piperita	6	1.0	9	2.7	1	1.1	16	1.5
Other (<15 ADRs per herbal)	209	34.0	106	34.0	20	22.5	335	32.2
Administration route of reported herbal								
Oral	394	64.1	234	69.9	29	32.6	657	63.2
Topical/cutaneous	57	9.3	26	7.8	10	11.2	93	9.0
Sublingual	18	2.9	21	6.3	27	30.3	66	6.4
Intravenous	29	4.7	6	1.8	4	4.5	39	3.8
Subcutaneous	11	1.8	12	3.6	6	6.7	29	2.8
Other (≤10 ADRs per route)	38	6.2	14	4.2	6	6.7	58	5.6
Not specified	68	11.1	22	6.6	7	7.9	97	9.3

ADRs adverse drug reactions

Table 4 Most frequently reported ($N \geq 10$) specific combinations of herbal medicines and allergic reactions with their IC values

Herbal remedy	WHO-ART preferred term	N reports	%	IC	95 % CI
Mixed herbals	Rash	75	7.2	−0.15	(−0.60 to 0.30)
Mixed herbals	Urticaria	58	5.6	−0.44	(−0.93 to 0.04)
Mixed herbals	Rash erythematous	36	3.5	−0.93	(−1.53 to −0.36)
Mixed herbals	Face edema	21	2.0	−0.11	(−0.95 to 0.68)
Mixed herbals	Allergic reaction	20	1.9	−0.52	(−1.35 to 0.26)
Mixed herbals	Rash maculo-papular	20	1.9	−0.12	(−0.98 to 0.70)
Mixed herbals	Edema mouth	19	1.8	0.02	(−0.88 to 0.87)
Mixed herbals	Anaphylactic reaction	15	1.4	−0.63	(−1.59 to 0.26)
Mixed herbals	Angioedema	15	1.4	−0.80	(−1.76 to 0.07)
Mixed herbals	Flushing	15	1.4	−0.66	(−1.62 to 0.22)
Mixed herbals	Anaphylactoid reaction	12	1.2	0.08	(−1.08 to 1.16)
Phleum pratense	Edema mouth	12	1.2	**1.81**	**(0.67 to 2.86)**
Andrographis paniculata	Urticaria	11	1.1	0.01	(−1.11 to 1.01)
Mixed herbals	Edema periorbital	11	1.0	−0.69	(−1.83 to 0.33)
Mixed herbals	Anaphylactic shock	10	1.0	−0.52	(−1.74 to 0.58)
Phleum pratense	Anaphylactic reaction	10	1.0	**1.24**	**(0.03 to 2.33)**

IC025 > 0 are in bold

IC information component, *WHO-ART* World Health Organization Adverse Reactions Terminology

A high proportion of reports concerned women between the age of 18 and 44. The two most frequently reported manifestations of immediate allergy-like reactions were skin reactions and anaphylactic/anaphylactoid reactions, both of which were most frequently observed after oral administration. This finding is surprising since severe ADRs are rarely seen after the oral use of herbals. The occurrence of allergic reactions is rather more likely to be expected after cutaneous and mucosal exposure, which presents a known risk factor for sensitization to allergens [32]. It is reasonable to assume that rather easy to diagnose reactions with a short onset time (e.g., skin manifestations), as well as serious reactions, have more frequently been reported in comparison with other reactions [33]. Oral administration of herbals in females may be most common in the population, an observation which is often made in CAM/herbal use prevalence studies [1–3]. It is therefore expected that this population would also be overrepresented in all included reports. A higher reporting rate of ADRs by females could be another factor contributing to such a pattern [34]. On the other hand, the higher proportion of females experiencing an adverse reaction in our study may confirm results of other studies in which a higher incidence of hypersensitivity reaction in females compared with males was found [35, 36]. Nevertheless, this finding does not allow conclusions to be drawn regarding the role of these characteristics as risk factors, although they are further discussed in the literature.

Asthma-like reactions were found in 4.8 % of the reports. Some commonly used herbals display a wide spectrum of cross-reactivity to other common inhalation or food allergens [7]. Therefore, a preexisting diagnosis of asthma and other atopic diseases may be a risk factor for the development of allergic reactions to herbals [37]. There exists a relevant higher incidence of herbal use among patients with known allergies [38]. For example, herbal medicine was shown to be the third most popular choice among patients suffering from asthma,with a prevalence of 60–70 % in patients with a history of moderate or severe asthma in the UK [39]. These findings imply that in the presence of known atopic diseases, health professionals and patients should use herbals only with great care in order to prevent severe allergic reactions.

Other relevant factors not recorded that could have contributed to the development of allergy-like reactions could be the patient's genetics, nutrition status, concurrent medication, disease states (e.g., food allergies) as well as exercise-induced anaphylaxis [37, 40]. Also, unrecognized herbal–drug interactions could result in a lack of allergy control and the manifestation of allergy symptoms [41].

The strengths of our study design include the international collection of reports from 42 countries over more than four decades as well as the use of standardized HATC drug classification, WHO-ART nomenclature, and formal causality assessment for adverse reactions. At the same time it is important to recognize the special characteristics and the inherent limitations of this data source regarding the interpretation of findings. Most importantly, spontaneous reporting data do not provide information on the actual exposure to herbals in a population nor on the incidence of related ADRs. Therefore, qualitative descriptive analyses and signal detection for previously unknown drug safety issues are the primary strength of spontaneous reporting systems rather than quantitative analyses. Furthermore, the level of documentation in VigiBase® is heterogeneous, as the extracted reports do not contain original detailed free-text descriptions by the primary reporters. Particularly for the earliest reports, formal causality assessment may not be available, thus these reports had to be excluded from our study population. It must also be taken into consideration that a standardized reaction term has many advantages, but it is not the same as a clinical diagnosis based on established clinical diagnostic criteria [42]. In light of those limitations, we used a restrictive study design emphasizing high specificity with regard to the likely diagnosis of immediate allergic reactions and consequently excluded the majority of reports from the extracted original raw dataset. Such a conservative approach implies reduced sensitivity for signal detection, but we believe that overall it improves the interpretability of our findings.

There are several other challenges that pharmacovigilance studies investigating risks associated with herbal medicines face in general. As a result of insufficient herbal product regulations, some ADRs may be attributable to a lack of standardization, contamination, adulteration, plant misidentification/substitution as well as improper use of herbal medicines including their inappropriate labeling rather than the pharmacological/toxicology effects of the herbals themselves [6–8, 43]. Further, innovative preparation methods of traditionally used herbal medicines may alter their pharmacological/toxicological properties and thus lead to toxicity rather than therapeutic use. In the era of market globalization, a base knowledge of the traditional preparation and use of herbals is therefore necessary given the increase in use of these remedies outside of their culture of origin. An estimate of the frequency of ADRs to herbals is not possible based on analyses of spontaneous reporting data, but it must be assumed that our findings represent just the tip of the iceberg regarding safety issues with herbal medicines [10]. Moreover, the particular underreporting of adverse events with herbals by patients as well as healthcare professionals remains high, with health professionals themselves not always being aware of potential safety issues associated with herbal use [9–11, 44, 45].

5 Conclusion

We believe that studies using the WHO-UMC pharmacovigilance database can identify specific associations between particular herbals and adverse reactions; thus, this study has attempted to demonstrate how certain herbal medicines for oral use carry risks for immediate allergy-like ADRs. As the prevalence of herbal use is increasing, healthcare professionals as well as patients need to become better informed about the possible risks associated with these substances. When healthcare professionals record drug histories, they should also actively solicit information from their patients about all self-administered herbal medicines.

In addition, further studies are needed to establish associations and risk factors that are related to herbal use and allergic reactions.

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Compliance with Ethical Standards

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