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REVIEW ARTICLE

HDI Highlighter, The First Intelligent Tool to Screen the Literature on Herb–Drug Interactions

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Abstract
Herbal food supplements are commonly used and can be an important part of patient self-care. Like all other bio-active and therapeutic products, they have a benefit/risk balance. These products are not without adverse effects and potentially interact with other therapies. Educating patients and providing information for health professionals about the risk of herb–drug interactions is key. One of the purposes of the biomedical literature is to inform prescribers. Scientific literature accessible on databases such as PubMed is dense and careful reading is time consuming. We propose a reading aid tool named "HDI highlighter" to help readers to find key information in clinical studies and case reports describing herb–drug interactions. It uses natural language processing algorithms (artificial intelligence) with a pharmaceutical focus. Semantic relation extraction for herb–drug interactions from the biomedical literature are overexpressed using keywords. We have tested it to review 120 published articles over the last 10 years. In these articles, we have shown that case reports often involved long-term or semi-long-term treatments such as cancer or human immunodeficiency virus therapies, antiepileptic drugs, or central nervous system drugs. Similarly, these classes of drugs are more extensively targeted by clinical studies. Herb–drug interactions described in case reports are identified in medicinal, recreational, and alimentary uses. They also usually lack a rigorous description of the herb(s) involved. Typically, clinical studies provide a complete description of protocols and dosages, with a few exceptions explained by patients' needs. Clinical studies on herbs are nevertheless conducted on a limited number of patients. All these limitations make the interpretation of herb–drug interactions complicated, but the HDI highlighter provides a quick overview of the herb–drug interaction literature.

1 Introduction

Herbal drugs are a current hot topic in the supplements industry. The Western population is increasingly in search of a healthy lifestyle using natural complementary and alternative medicines [1]. Natural complementary and alternative medicines are defined as medical products and practices that are not part of standard medical care. The equation is very simple and does not sit well with doctors in favor of an evidence-based medicine approach. People use herbal medicine; some herbal products can be beneficial for certain health disorders (e.g., [2–8]) and patients feel this as such [9]. Consumption of herbal medicines is widespread and increasing in recent years. The world trade in botanicals is US$32.702 billion (2021) [10]. Patients using conventional therapies also use natural products [11, 12]. Like all other bio-active and therapeutic products, they have a benefit-risk balance. These products are not without adverse drug reactions [13–15] and potentially interact with other therapies [16]. An additional complication with these products is their natural origin. They are matrices with a complex chemical composition that is subject to variations, considering biotic and abiotic parameters, preparation/extraction/manufacturing processes, and potency occur without a regulatory establishment oversight. Providing information for health professionals about the risk of HDIs is key. All prescribers must be informed about the precautions and risks associated with natural complementary and alternative medicines to teach patients to behave in a safe manner with all herbal products.

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Key Summary Points

While in the general population natural therapeutic products are still perceived as harmless, health professionals are now aware of the risks of drug interactions.

The scientific literature effectively describes adverse effects due to these combinations.

We describe a tool (HDI highlighter) for a simplified reading of articles describing herb–drug interactions. This tool has been used to review 120 peer-reviewed articles.

The main media for informing health professionals is the scientific biomedical literature. The literature on herb–drug interactions (HDIs) is dense, where herbs are used as phytotherapy products or for food-based consumption. By making a request on the PubMed database with the "herb drug interaction" keywords over the last 10 years, more than 1700 publications are highlighted. If the scientific request covers only the literature review of clinical data (case reports and clinical studies) over the last 10 years, more than 120 articles have been published.

The majority of the HDI literature describes pharmacokinetic (PK) interactions where one (or various) cytochrome P450 (CYP) or P-glycoprotein (or other transporters) are involved. As a result, the pharmacokinetics of conventional drugs is altered and the patient experiences toxicities (when the plasma drug concentration is bigger because of the interaction) or a loss of efficacy of their treatment (when the drug concentration is lower). Case reports lack standardization and the cohort size needed for generalization to a clinical context. Clinical studies ($n > 1$) are generally based on small cohorts when natural products are involved. These clinical studies are often of short duration (often too short to estimate the clinical impact of CYP synthesis induction) and are subject to numerous biases. However, it is still important to consider this literature because it remains the only available validated data. Clinicians need a crucial tool for a quick and efficient interpretation of these articles. We have developed a web tool to help them. The HDI highlighter is an open-source software and can help readers to identify portions of text of interest in a PDF file by highlighting important words or expressions.

2 Literature Search

To carry out this literature review, we used the following methods.

2.1 Sources

The corpus has been extracted from the PubMed database. We have queried on a specific period from 2011 to August 2021 (1814 articles) to identify case reports and clinical studies based on a query containing the terms "herb," "drug," and "interaction." The "Clinical trial" and "Case reports" filters were applied to select only studies conducted in humans. Full-text article PDFs were downloaded (120 articles), and a first sorting was performed to exclude publications with no HDI. For the next step, we used the HDI highlighter for data extraction.

2.2 HDI Highlighter

To allow a quick scan of the articles, we developed a tool called HDI highlighter to highlight fragments of sentences describing the interactions and their clinical impacts. The HDI highlighter interface is shown in Fig. 1. The first step consists of the upload of the PDF file and the process using corresponding buttons, and options to remove pictures and tables from the original PDF (Fig. 1, top left). This feature should be used with a large file size PDF containing a large number of figures to increase processing speed. The main panel contains PDF content highlighted. This content can be switched from extracted and highlighted content to a view to the original PDF using the two tabs above ("Extracted" or "Original"). Below, a button opens a second panel allowing navigation through highlighted terms. In the tabs, categories of terms are shown for each corresponding word or expression. The user can navigate through the text by occurrence using left and right arrows. This panel allows for a fast appreciation of the content based on the number of occurrences of words and expressions. The legend (Fig. 1, on the left) allows the user to hide or show highlighting by category or color. The HDI highlighter is available for download on https://github.com/ancnudde/hdi_highlighter.

The HDI highlighter is based on a set of finite state transducers (or local grammar, see Electronic Supplementary Material), a mathematical model composed of:

- a finite state machine that allows the recognition of strings of characters;
- an output that labels the recognized strings of characters.

Formally, a transducer is defined by a 6-tuple:

$$T = (\Sigma_1, \Sigma_2, Q, I, F, \delta),$$

where Σ_1 is the input alphabet. In our case, this is the set of words in the dictionary used by the HDI highlighter and the semantic and morphosyntactic labels associated with them.Σ_2 is the output alphabet, i.e., the set of semantic

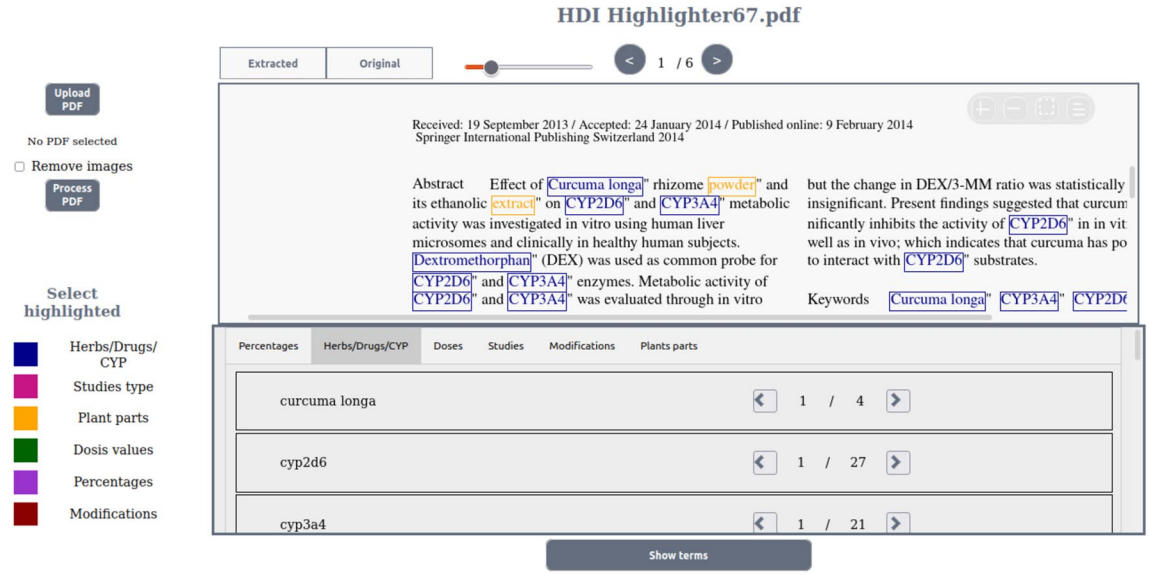

Fig. 1 HDI highlighter interface. The user can upload a PDF file and process it. To handle a large PDF with a large number of figures that might require heavy processing, an option allows the removal of pictures to fasten the process. Words of interest are highlighted in a specific color and can be highlighted or not by clicking on the corresponding legend item. A panel below allows the user to navigate through highlighted terms

labels used to label the sequences recognized by the transducer, Q is the finite set of states, $I \subseteq Q$ is the set of initial states,$F \subseteq Q$ is the set of final states, and δ is the transitions table.

In practice, each transducer describes a linguistic structure corresponding to one of the elements to be recognized. When an element is recognized, a label is assigned to it. This label is then used by our tool to highlight the structure in a specific color (cf. Fig. 1):

- the entities involved in an interaction: herbs, drugs, and pharmacological targets such as CYP isoenzymes, in blue;
- the mentions to type of study held, in pink;
- the herb organs, in yellow;
- the dosages and concentrations, in green;
- the percentages values, in violet; and
- the terms involving a variation in a value, in red.

It is interesting to note that transducers are rule-based models (as opposed to machine learning models). This means that for a word or part of sentence to be recognized, it must be clearly defined in the transducer and every word or part of the sentence defined in the transducer will in turn systematically be highlighted.

The transducers used in our tool are designed using Unitex/Gramlab, a software that provides a graphical user interface to construct these graphs and the linguistic resources needed to define semantical classes. The HDI highlighter is a web app written in HTML/CSS/Javascript and Python and running through a Flask (Python) server.

3 Review of the Findings

In the following paragraphs, we present the results in one section and discuss them further. Tables 1 and 2 summarize the main data of our work.

3.1 Data Extraction

Through a PubMed search with the query "herb drug interaction," we were able to isolate over 10 years 120 publications describing either case reports or clinical studies. Over these articles, 44 were discarded. In these 44 articles, seven were not about HDIs in humans, and eight concerned cases that were unexploitable owing to missing information such as herb identification [17]. The 29 others were discarded because of unavailable access rights. For the rest of the selection, we designed two data sets, one describing 28 case reports with lower statistical validities (because $n = 1$) than the 37 clinical studies.

Table 1 Case reports reviewed from 2011 to 2021

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR1	Boldo/*P. boldus*	300-mg capsules,Nature's Pharma	600 mg for several weeks	Tacrolimus	78-year-old Hispanic man, diabetes mellitus, hypertension, deceased donor renal transplant	Tacrolimus 2 mg; mycophenolate 500 mg	Tacrolimus levels ↗ (<3 ng/mL)	N	D&R tacrolimus levels dose OK	?	[28]
CR2	Cannabis/*C. sativa* + 28 TCM herbs	???	?	Escitalopram	49-year-old man, history of depression for 9 years		Hypomania	?	?	No interpretation	[18]
CR3	Celery/*A. graveo-lens* root extract	Herbal supplement	1000 mg daily for 48 hours	Venlafaxine	52-year-old white woman, past major depressive disorder, hypertension, dyslipidemia	Venlafaxine 75 mg + SJW 600 mg daily for 5 months	Confusion and speech abnormalities for 24 hours	Y	?	?	[35]
CR4	11 TCM herbs	TCM	–	Temozolomide	56-year-old Caucasian woman		Severe liver toxicity, jaundice	?	No toxicity with re-exposition to temozolomide or combination with valaciclovir or levetiracetam	No direct hepatotoxicity, at least 2 herbs (Huang Qi + Huang Qin) with relevant CYP3A4 inh	[19]
CR5	Choke-berry/*A. melanocarpa*	Juice, daily during the last course of trabectedin and in the 2 weeks after	Daily	Trabectedin	56-year-old Caucasian man, no relevant illness, heavy smoker	?	Weakness, difficulty walking, diffuse muscle pain grade 4 pancytopenia	?	D&R after 1 week	Flavonoids, as quercetin = strongly inh CYP3A4	[38]

Table 1 (continued)

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR6	GBE, Horse chestnut/*A. hippocastanum*	Omega-3, fatty acid, vitamins, (GBE) from 2 months	300 mg + 2 months SWJ	Efavirenz	41-year-old man, HIV+ since 1999, excellent adherence and good virologic suppression	Zidovudine, lamivudine,efavirenz	Virological breakthrough		D&R (GBE + horse chestnut): viral load less than 50 copies/mL	Efavirenz = CYP2B6 subs + CYP3A4 (lesser). CYP3A4 subs serum concentrations ↘ after 4 weeks of GBE 240 mg daily, suggesting CYP3A4 ind. No modif. CYP2B6 sub-serum concentrations after 14 days of GBE 240 mg daily Efarirenz + GBE = hepatic clearance of EFV resulting in lower EFV serum concentrations and viral breakthrough	[20]

Table 1 (continued)

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR7	Ginseng/unknown specie	??		Lamotrigine	44-year-old Caucasian man		DRESS syndrome	?	D&R	UGT enzymes for the glucuronidation of lamotrigine were UGT2B7 and UGT1A4 and ginseng was UGT inh with significant inh of UGT1A1 + weak inh of both UGT1A9 and UGT2B7	[33]
CR8	Goji berry/*L. barbarum*	Himala-yan Goji Juice, FreeLife International	60 mL for 4 days	Warfarin	71-year-old Ecuadorean-American woman, hypertension, diabetes mellitus, asthma, arthritis, no smoking, no alcohol, no INR measure	Ezetimibe 10 mg Lisinopril 20 mg Famotidine 40 mg Meclizine 25 mg Alprazolam 0.5 mg Diphenhydramine 50 mg	Ecchymosis epistaxis, one episode of hematochezia, ↗ INR (prothrombin time >120 sec)	N	D&R with symptomatic treatment. No further bleeding	*L. barbarum* significantly inh CYP1A, 2C9, and 3A4 in hepatic cells in vitro	[29]
CR9	Gouqizi/*L. barbarum*	Wine	20 mL, the day before	Warfarin	65-year-old Chinese man	Warfarin	↗ INR, bleeding	N	INR 3.84, D&R = viral load after 1 month: 50 copies/mL in 24 hours	Other cases with the same clinic	[30]

Table 1 (continued)

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR10	Hibiscus/*H. sabdariffa*	Tea		Erlotinib	Woman treated by erlotinib for 5 years	Erlotinib	Severe cutaneous adverse effect	?	D&R = after topical treatments: ciclopiroxolamine + clobetasol + bethametasone: rapid regression 5 days	No explanation	[39]
CR11	Horsetail/E. *arvense*	Food supplement	Daily, 2 months before first case	Zidovudine, lamivudine, efavirenz	49-year-old woman, HIV, adherence OK and virologic suppression	Zidovudine, lamivudine, efavirenz	Detectable viral load	?	D&R = viral load after 1 month: 50 copies/mL	?	[25]
CR12	Horsetail/E. *arvense*	??	?	Emtricitabine, tenofovir, efavirenz	75-year-old man	Emtricitabine, tenofovir, efavirenz	Detectable viral load	?	D&R = viral load after 1 month: 50 copies/mL	?	[25]
CR13	Kratom/*M. speciosa*	?	?	Quetiapine	27-year-old man, Asperger syndrome, bipolar disorder, substance abuse	Quetiapine	Death	Y	?	Combined and/or synergistic reaction to quetiapine and mitragynine (CYP3A4 and/or PgP mechanisms), suppose active metabolite: mitragynine	[36]
CR14	Mauby tree/*C. arborescens.*	Mauby		Warfarin	70-year-old Haitian man, atrial fibrillation, pulmonary hypertension	Warfarin	↗ Levels INR > 8.0	?	D&R	Inh CYP3A4 & PgP	[31]

Table 1 (continued)

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR15	Noni juice/*M. citrifolia*	Tahitian Noni®, original bioactive beverage	Usually90 mL and up to 100 mL twice a day, for 10 years	Phenytoin A	49-year-old man, epilepsy	Phenytoin for more than 10 years	↗ Levels	N	D&R: the patient restarts the noni consumption with the same effect	Noni juice ind P-450 (CYP450) 3A4, 2C8/2C9, and 2D6(5) in vitro. The roles of noni juice and phenytoin are the inducer and substrate of CYP2C9, respectively, and decreased serum phenytoin concentrations	[34]
CR16	Parsley/*P. crispum*	Juice	30 g parsley for 7 days	Sirolimus, mycophenolate mofetil, prednisolone	19-year-old woman, renal transplantation	Prednisolone, tacrolimus, mycophenolate mofetil	↗ Levels	Y	D&R	Apigenin, a flavonoid, inh CYP3A4 and P-gp in vitro	[40]

Table 1 (continued)

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR17	Russian Rhodiola/*R. rosea* golden root		400 mg	Paroxetine	68-year-old woman, recurrent moderate depressive disorder with somatic syndrome (ICD-10 F33.11)	Paroxetine	Vegetative syndrome, restlessness feeling, trembling	N	D&R in 2 days	PD interaction: addition of serotonin syndrome due to temporal correlations and/or PK interaction: potential overdose of paroxetine by inh of CYP2D6 However, the possibility of a discontinuation syndrome (due to the patient not taking the drug regularly) cannot be completely excluded, as the plasma concentration of paroxetine was less than 23 ng/mL	[37]
CR18	SJW/*H. perforatum*	?	?	Warfarin	85-year-old man, hypertension, old infarction, atrial fibrillation, no INR measure	Warfarin for 1 year	Upper gastrointestinal bleeding, Hb: 7.9 g/dl, HTC: 23%, INR: 6.2	?	D&R	It is thought SJW might affect the drug metabolism of warfarin in sensitive individuals by potentiating its effect on the clotting cascade	[24]

Table 1 (continued)

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR19	SJW/*H. perforatum*	NEURAPAS FORTE® (240 mg of SJW, 128 mg of *P. incarnata*, and 112 mg of *V. officinalis*	For 1 month	Dolutegravir	42-year-old man, HIV	Dolutegravir	No effect	?	?	No HDI even if other cases describe HDI where SJW can induce CYP2C19, CYP3A, CYP2E1, and P-gp, with no effects on CYP1A2, CYP2C9, CYP2D6, or UGT	[23]
CR20	Stevi /S. *rebaudiana* + multiple vitamins & herbal supplements	??	?	Simvastatin	69-year-old man	Simvastatin 40 mg daily for 10 years, losartan, linagliptin	Weakness myalgia	?	D&R after treatment	Steviol + stevioside week inh CYP3A4 (in vitro)	[21]
CR21	Sweet clover/*M. officinalis*	Lutein and melilot supplement	?	Coumarin	23-year-old Japanese woman, multiple sclerosis,	Coumarin 10 mg + IFNB-1b	↗ Levels: AST + ALT severe hepatotoxicity	N	D= IFNB-1b +supplements and R: AST and ALT = normal levels	Our patient took a melilot supplement containing coumarin at 10 mg/day. This dose is twice the recommended tolerable daily intake	[32]
CR22	TCM/>10 herbs	–	–	Tacrolimus	8-year-old girl, 28.8 kg	Tacrolimus, nebulizer therapy, cyclophosphamide, methylprednisolone	Refractory nephrotic syndrome	?	D&R: tacrolimus blood concentration ok	Apigenin, a flavonoid, inh CYP3A4 and P-gp	[22]

Table 1 (continued)

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR23	Turmeric/*C. longa*	Infusion	1 tea spoon, 2.5 g/day for 5 days	Oral vitamin K	56-year-old woman, INR had always been OK (INR 2–3)	Fluindione since 1993	INR ↗ to 6.5, no bleeding	N	D&R	Curcumin & bisdemethoxycurcumin prolong prothrombin + activated partial thromboplastin times + inh activated factor X and thrombin synthesis + an antiplatelet effect of curcumin, as well as a prolonged bleeding time (animal studies) + PK interaction: turmeric = inh 2C9 and 3A4 + curcumin = inh P-gp	[26]
CR24	Turmeric/*C. longa*	Powder	15+ spoonfuls daily	Tacrolimus	56-year-old man, history of orthotopic liver transplantation	Tacrolimus	Worsening edema, ↗ creatinine level of 4.2 mg/dL	Y	D&R = tacrolimus was temporarily withheld from the patient's medication regimen; he was discharged on hospital day 4 with reduced edema and a serum creatinine level of 2.9 mg/dL	Curcumin reduced expression of intestinal CYP3A	[27]

Table 1 (continued)

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR25	Multi-herb/*A. lappa Arctiumminus, R. palmatum, R. acetosella U. rubra, N. officinale,C. benedictus, T. pratense,L. digitata*	Herbal supplement, Flor-Essence, Flora Inc. (Lynden, WA, USA)	2–3 ounces, two times between test-dose administration and transplantation	Busulfan	44-year-old man, obesity, stage-III (ISS) IgG kappa multiple myeloma	Busulfan, bortezomib, and melphalan	↗ AUC, ↘ clearance, gastrointestinal toxicities, nausea, vomiting, diarrhea, esophagitis, profound weight loss, dyspnea		D = suggested by timing of herbs intake and absence of other explanation	In vitro inh. Of CYP 1A2, 2C9, 2C19, 2D6, and 3A4 by some ingredients	[41]
CR26	*C. asiatica, F. vesiculo-sus*	?	?	Venlafaxine	35-year-old woman	Slow-release formulation venlafaxine	progressive dyspnea over 3 months, myalgia, dry cough, subacute severe heart failure, class III cardiomyopathy	?	D = venlafaxine was discontinued, improvement shown by tomography 2 weeks later	Moderate-to-strong inh. of CYP2D6 by *C. asiatica* and inh. of CYP450 by *F. vesiculosus*	[42]
CR27	*Yohimbine*	Libido-max	?	Clonidine	46-year-old African-American man, hypertension, end-stage kidney disease, previous cocaine misuse	Clonidine	Severe headache, diaphoresis	?	D = patient stopped Libido-max and had no similar symptoms	Rebound hypertension by interaction between opposite effects of clonidine and yohimbine	[43]

Table 1 (continued)

No.	Case report								Dechallenge	Authors' explanations	References
	English/scientific name	Form	Dose/day	Name	Patient	Treatment/day	Effects	MIS			
CR28	*Berberine*	?	0.2 g 3 cp/day	Tacrolimus	16-year-old child, nephrotic syndrome, edema, proteinuria, diarrhea	Prednisone 60 mg/m^2/day, tacrolimus 40 mg/m^2/day	↗ Tacrolimus C0, ↗ serum creatinine	N	D = reduction in tacrolimus dosage	Patient deficient for CYP3A5 genes, CYP3A4 pathway becomes predominant. Furthermore, patient with homozygous mutated C3435T (T/T) for transporter ABCB1, leading to significantly reduced ABCB1 expression. Competition between the two drugs occurs also at the CYP3A4 pathway, resulting in high tacrolimus concentrations	[44]

The first column assigns a number ID for each analyzed case report. The second set of columns describes herbs and their form and posology. The third column set describes the implicated drugs (by International Non-proprietary Name (INN)). The fourth column set provides a description of the patient's situation and a possible explanation by authors on the clinical history. The last column provides the references

ALT alanine transaminase, *AST* aspartate transaminase, *CYP* cytochrome P450, *D* dechallenge, *DRESS* drug reaction with eosinophilia and systemic symptoms, *GBE* Ginkgo biloba, *HIV* human immunodeficiency virus, *ICD-10* International Classification of Diseases, Tenth Revision, *ind* induction, *inh* inhibition, *INR* international normalized ratio, *PD* pharmacodynamic, *Pgp* P-glycoprotein, *PK* pharmacokinetic, *R* rechallenge, *Ref.* reference, *SJW* St. John's wort, *TCM* traditional Chinese medicine

Table 2 Clinical studies reviewed from 2011 to 2021

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 1	Genistein	Tablets, Western EHSY Shanghai, China	1000 mg 1/day For 14 days	CYP450 3A, P-gp, XO	18 Chinese subjects (M)	M	Randomized 2-phase crossover	↗ CYP3A and possibly P-gp activities, ↘ Midazolam and talinolol C_{max} and AUC values, no significant change in $t_{1/2}$ and T_{max} of midazolam and talinolol	No	Possible effect of genistein on CYP1A2, CYP2A6, and xanthine oxidase	[67]
CS 2	African potato/*H. obtusa*	African potato, 320 mg hypoxoside	4 capsules 1/day For 7 days	Ritonavir/lopinavir	16 subjects (4 M, 12 F)	Healthy, HIV-seronegative, aged 18–60 years	Open-label, 2-period crossover PK drug interaction study	No clinically significant PK changes	No	–	[76]
CS 3	Cancer bush/*S. frutescens*/Trad. Ayurvedic medicine	Capsules, 400 mg dried leaves powder	400, 800, or 1200 mg 2/day For 24 weeks	Isoniazid	Stage 1: 56 subjects (6 M, 50 F) Stage 2: 77 subjects (not known)	Healthy HIV seropositive	Double-blind, randomized, placebo-controlled design with 2 stages	No significant adverse effects	No	Antioxidant/radical quenching properties of *S. frutescens* do not block the action of isoniazid	[55]
CS 4	Curcuma/*C. longa*	Dried ethanolic extract	1.5 g 2/day For 7 days	Dextromethorphan	6 subjects (M)	Healthy aged 18–35 years	2-phase study with 2-week washout period	↘ Dextrorphan and 3-methoxymorphinan, ↗ metabolic ratio of dextrometorphan/dextrorphan, no change in dextrometorphan/3-methoxymorphinan ratio	No	–	[68]
CS 5	Danshen Sanqi/*R. nalviae* + *R. notoginseng*, TCM	T89, Tasly Pharmaceutical Co. Ltd, Tianjin, China)	225mg 2/day For 7 days	Warfarin	23 subjects (22 M, 1 F)	Healthy nonsmoker, BMI from 19.0 to 30.0, aged 18–50 years, [56]	Open-label, multi-dose, single-center, sequential, inpatient study	T89 has no effect on the steady-state pharmacodynamics and pharmacokinetics of warfarin	No	–	[56]

Table 2 (continued)

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 6	Eurycoma/*E. longifolia*	Capsules, 50 mg, water-based, air-dried extract	50 mg 4/day 1 take	Propranolol	14 subjects (M)	Healthy, nonsmoker, aged 19–28 years, BMI 19–24	Placebo-controlled, randomized, single-blinded, 2-treatment crossover design	↘ Propranolol bioavailability and C_{max} ↗ T_{max}, no effect on drug's pharmacodynamics	No	Reduction in bioavailability rather than interference with metabolism	[80]
CS 7	Echinacea /*E. purpurea*	Capsules, *E. purpurea* root extract W064636A; Arkopharma	500 mg every 8 hours For 14 days	Etravirine	15 Caucasian subjects (10 M, 5 F)	HIV+, aged 41–50 years Etravirine 400 mg 1/day for at least 4 weeks 4 patients hepatitis C+	Open-label, fixed-sequence study	No effect	No	Possible CYP3A4 induction (liver) and inhibition (intestinal lumen); possible offset of the induction of hepatic CYP3A4; etravirine = inducer and could mask induction of by echinacea	[77]

Table 2 (continued)

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 8	Echinacea /*E. purpurea*	Capsules, root extract, Arkopharma	500 mg, Every 6 hours, For 14 days	Darunavir/ritonavir	15 subjects (14 M, 1 F)	HIV-infected, aged 43–67 years, BMI 18.7–27.5, darunavir-ritonavir 600/100 mg 2/day for at least 4 weeks, 3 patients hepatitis C+	Open-label, fixed-sequence study	Negligible effect, ↘ C and AUC for individual patients	No	Variability in the effect may imply CYP3A4 inductive/inhibitory potential; ritonavir = CYP3A4 inhibitor, that could mask the influence of echinacea on CYP3A4 activity	[81]
CS 9	Echinacea /*E. purpurea*	*E. purpurea* drops, 95% aerial parts and 5% roots of *E. purpurea*, A. Vogel Echinaforce, Biohorma	20 oral drops 3/day	Docetaxel	10 subjects (8 M, 2 F)	Cancer	Not randomized crossover design. Patients with advanced cancer	No effect on systemic exposure to docetaxel	No	–	[75]
CS 10	Emblic/*P. emblica*	Aqueous extract of edible fruits of *P. emblica* (amla), Brunswick, NJ, USA	Single dose 500-mg extract	Clopidogrel	10 subjects, sex not stated	Stable dose antidiabetic for last 3 months, otherwise healthy	Randomized open label, crossover study	↗ Bleeding and clotting time, values however within the normal reference range	No	–	[73]

Table 2 (continued)

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 11	Fufang Danshen Dripping Pill/*S. miltiorrhiza* + *P. notoginseng*/TCM	Fufang Danshen dripping pill	70 mg 3/day For 7 days	Clopidogrel	63 Chinese subjects, sex not stated	Coronary heart disease, otherwise healthy, aged 10–80 years	Patients randomly divided into four groups	Untargeted metabolomics investigation group with a drug combination is closer to Fufang Danshen Dripping Pill group	No	Effect on glycol metabolism, lipid metabolism, and phospholipid metabolism	[57]
CS 12	Ginkgo/*GBE*	GBE tablet Yangzijiang Pharmaceutical, 40 mg standardized GBE	120 mg 2/day For 14 days	Simvastatin	14 subjects (M)	Healthy, nonsmoker, aged 22.9 ± 2.1 years	Open-label, randomized, 2-period, 2-treatment, balanced, crossover	Concomitant use of the usual therapeutic dose of GBE moderately ↘ simvastatin concentrations but not simvastatin acid	No	GBE mainly affected simvastatin first-pass extraction in the intestine and liver. GBE might enhance CYP3A activity	[82]
CS 13	Ginkgo/GBE	80 mg GBE, Ginexin®; SK Chemical Co.	80 mg 2/day For 7 days	Cilostazol	34 Korean subjects, sex not stated	Healthy	Randomized,double-blind,2-way crossover study with a 2-week washout	No significant difference in any PK parameter, including C_{ss}, C_{max}, or AUCt, between treatments with cilostazol plus GBE or placebo	No	–	[83]
CS 14	Ginkgo/GBE	EGb 761, dry extract from GBE leaves	120 mg or 240 mg 2/day For 8 days	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A	18 subjects (8 M, 10 F)	Healthy, nonsmoker, non-pregnant, aged 18–55 years, BMI 19–29	Open-label, single-center, randomized three-fold crossover study	No CYP1A2, 2C9, and 3A induction	No	–	[69]

Table 2 (continued)

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 15	Ginseng/*P. ginseng*	500-mg capsules, Vitamer Laboratories	500 mg 2/day For 28 days	CYP3A, P-gp	12 subjects (8 M, 4 F)	Healthy, aged 18–50 years	Open label, single-sequence PK study Probe: midazolam and fexofenadine	↘ Midazolam AUC, ↘ $t_{1/2}$, ↘ C_{max}, ↗ CL/F	No	↗ CYP3A activity in the liver and perhaps gastrointestinal	[70]
CS 16	Grapefruit juice/*Citrus* × *paradisi*	Grapefruit juice, double strength	200 mL 3/day For 2 days	Pitavastatin	12 Chinese (12 M)	Healthy, aged 21–25 years	Open-label, single-dose, randomized,2-phase, crossover clinical PK study, Wash-out interval of at least 3 weeks Probe: pitavastatin	↗ Pitavastatin acid and lactone AUC $_{0–48h}$, no change in $t_{1/2}$ elimination influenced by the SLCO1B1 388A>G polymorphism higher plasma concentrations in subjects with the homozygous variant	No	Effect of grapefruit juice on drug transporters expressed in the intestine, pitavastatin is not thought to be metabolized by intestinal CYP3A	[50]
CS 17	Green tea /*C. sinensis*	Teavigo, 300 mg of epigallocatechin-3-gallate	300 mg 10 days	Rosuvastatin	13 Korean subjects (2 M, 11 F)	Healthy, aged 26.8 ± 4.0 years	Open-label, three-treatment, fixed-sequence study	↘ AUC, ↘ C_{max}	No	–	[51]
CS 18	Green tea/*C. sinensis*	Teabag, Twinings green tea	Teabag infused for 5 minutes 2 cups of 150 mL/day For 8 weeks	Ethinyl estradiol, drospirenone = Yasmin®	64 subjects (F)	Healthy, low-dose contraceptive use, no premenopausal status, nonsmokeror excessive alcohol drinking	3-phase study, no more information	MF Templar: ↘ oxidative stress levels	Authors	–	[52]

Table 2 (continued)

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 19	*Hibiscus/H. sabdariffa*	Aqueous beverage, 300 g dried powdered	300 mL One take	Simvastatin	6 subjects (M)	Healthy	Two-period randomized crossover design was employed	↘ Exposure	No	Changes in absorption rather than elimination parameters of the drug	[74]
CS 20	Hops / *H. lupsulus*	59.5 mg extract per capsule	120 mg 2 capsules/day For 2 weeks	CYP2C9, CYP1A2, CYP2D6, CYP3A4/5	16 subjects, aged 40–79 years (F)	Peri- and post-menopausal	Phase I PK drug interactions	No clinically relevant PK interactions	No	–	[71]
CS 21	Huangqi/*R. Astragali*/TCM	Extract granules, 4 g/bag, Sichuan Baili Pharm Co., Ltd, Sichuan, China	4 g 2/day For 7 days	Fexofenadine	14 Chinese subjects (M)	Healthy, aged 25–28 years, BMI 19–25	Randomized, placebo-controlled, 2-period crossover study, 3-week washout	No significant effect on AUC and C_{max}	No	Effect on P-gp by RA extract is more prevalent in the kidney than in the intestine	[58]
CS 22	Keishi-bukuryo-gan/TCM	Keishi-bukuryo-gan (TJ-25), Tsumura & Co., Tokyo, Japan	3.75g 2/day For 7 days	CYP1A2, CYP2D6, CYP3A, XO, NAT2	31 Japanese subjects (F)	Healthy, nonsmoker, with contraceptive use, aged 20–27 years,	Open-label study, each subject served as her own control	↘ CYP1A2 activity, no effect on CYP2D6, CYP3A, XO, or NAT2	No	–	[59]
CS 23	Lavender essential oil/*L. angustifolia*	Silexan® Essential oil capsules, 160 mg	80 mg, 2/day For 28 days	Ethinyl estradiol, Levonorgestrel	24 subjects (F)	pre-menopausal otherwise healthy BMI 18–30	Double-blind, randomized, 2-period crossover study, 2 cycles of 28 days	No interaction	Authors	–	[47]
CS 24	Milk thistle/*S. marianum*	Legalon® 140 mg or MADAUS-GmbH, 175 mg dried extract milk thistle achenes or 140 mg silymarin	1 capsule 3/day For 14 days	CYP1A2, CYP2C9, CYP2D6, CYP3A4/5	12 subjects (M)	Healthy nonsmokers, no CYP2D6 poor metabolizer	Fixed-order, open-label study	CYP1A2, CYP2C9, CYP2D6, and CYP3A4/5 activities unchanged	No	–	[48]

Table 2 (continued)

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 25	Mistletoe/*V. album*	IV or SC	At physician discretion	Immune checkpoint inhibitors	16 subjects (7 M, 9 F)	Patients with cancer, aged 57.8–69.3 years	At the discretion of the physician	No alteration of adverse event rates	No	–	[49]
CS 26	Ojeok-san TCM	Hanpoong Pharm & Foods Co., Ltd.	14.47 g 3/day For 4 days	Celecoxib	20 subjects (M)	Healthy	Open-label, fixed-sequence, two-period, two-treatment crossover study	↘ C_{max} and AUC	No	–	[60]
CS 27	Pomelo pulp/*C. grandis* close relative of grapefruit/*C. paradisi*	250 g of pomelo pulp	250 g, 1 hour before and 10 minutes after cyclosporine One take	Cyclosporine	14 Thai subjects (M)	Healthy, nonsmoker, aged 18–45 years, BMI 18–25	Open-label, single dose, 2-treatment, 2-period, 2-sequence randomized 2×2 crossover study with a 14-day washout period between the 2 study periods	↗ AUC and C_{max}, ↘ T_{max}, unchanged $t_{1/2}$	No	Pomelo pulp slightly increases cyclosporine bioavailability	[53]
CS 28	Resveratrol	Oral dose, Zenith Nutritions, Bangalore, India	500 mg Once daily For 10 days	Chlorzoxazone	12 subjects (M)	Healthy, nonsmoker, no alcohol consumption, aged 24–30 years, BMI 18.15–24.95	Open-label, two period, sequential study	↗ Bioavailability	No	Altered CYP2E1 activity and chlorzoxazone pharmacokinetics mediated by inhibition of CYP2E1	[84]
CS 29	Shiitake/*L. edodes*	High mushroom diet	250 g of mushrooms 3/day One take	Gabapentin	10 Singaporeans subjects (M)	Healthy	No mushrooms or high mushroom diet 1 day prior to administration of a single oral dose of gabapentin 600 mg	↗ Clearance but no clinical impact	No	↗CLR and excretion of gabapentin $AUC_{(last)}$ was not significantly altered, no clinical relevance	[54]

Table 2 (continued)

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 30	SJW/*H. perforatum*	SJW 325 mgNutraceutical Corp. for Solaray, Inc.	325 mg, 3/day For 14 days	Repaglinide	15 subjects (M)	Healthy	2-phase, randomized, crossover study, 4-week washout period between phases	No effect on pharmacokinetics of repaglinide	No	Induction of SJW on hepatic CYP3A4, CYP2C8 is the major contributor to repaglinide metabolism	[78]
CS 31	SJW/*H. perforatum*	Oral, Jarsin®, Cassella-med, GmbH & Co. KG	300 mg, 3/day For 9 days	Ambrisentan	17 Caucasian subjects, 2 Hispanic subjects, 1 Asian subject, (4 F, 13 M)	Healthy, non-smoker, not a regular drug user, 31.3 ± 7.7 years, BMI 23.1 ± 2.7	Open-label, mono-center, 1-sequence, crossover, multiple dose	↘ Exposure with ambrisentan irrespective of the CYP2C19 genotype	No	–	[45]
CS 32	SJW/*H. perforatum*	Dry extract, 240–294 mg Modigen, JemoPharm A/S, Stege, Denmark	240–294 mg 2/day For 21 days	Metformin	20 subjects (M)	Healthy, aged 18–64 years	Open cross-over interaction study, 2 study periods	↗ Glucose-stimulated insulin response, no change in pharmacokinetics	No	–	[85]
CS 33	SJW/H. perforatum	Kira tablet®, Lichtwer Pharma, Berlin, Germany	300 mg 3/day For 30 days	Fentanyl	16 subjects (8 M, 8 F)	Healthy, aged 21–41 years	Randomized, double-blind, parallel-arm design	No effect on the pharmacokinetics and pharmacodynamics or clinical effects	No	Both hepatic CYP3A4 and blood–brain barrier P-gp could be upregulated by SJW but without a clinical impact	[46]

Table 2 (continued)

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 34	Wakame/TCM/*U. pinnatifida*	Fucoidan, Maritech extract, 88.9% fucoidan content, Marinova Pty Ltd	500 mg 2/day For 3 weeks	Letrozole, tamoxifen	20 subjects (F)	Active malignancy	Open label non-crossover study	No changes in steady-state plasma concentrations, no adverse effects, no toxicity	No	–	[61]
CS 35	WooHwangChungSimWo/TCM	Suspension, Kwang-Dong Pharmaceutical Company	4 doses/day One take	Bupropion	14 subjects (M)	Healthy, nonsmoker, no herbal users	Open-label, two-treatment crossover, randomized, 2 phase, 2-week washout	No effect on the pharmacokinetics of bupropion or 4-hydroxybupropion	No	Bioavailability would be low, based on the results of previous studies. Plasma concentrations of borneol and isoborneol lower than their Ki values, so no effect in vivo	[62]
CS 36	Yokukansan/TCM	TJ-54, TSUMURA Yokukansan extract granules, Tsumura & Co.	2.5 g 2/day For 1 week	Caffeine, dextromethorphan	26 Japanese subjects (M)	Healthy, nonsmokers, age 22.7 ± 2.3 years	Open-label study	No significant effect on CYP1A2, CYP3A, CYP2D6, NAT2, or XO	No	–	[63]

Table 2 (continued)

	Herb			Target	Clinical study						References
No.	Name	Form	Dosage	Name	Cohorts	Participant clinical status	Model description	Effect	Firm[a]	Explanation	
CS 37	Zuojin Pill/*R. Coptidis* + *F. Evodiae in* a 6:1 (w/w) ratio/TCM	Zuojin Pill, Hubei Nodse, Pharmaceutical Co., Ltd, China	3 g 2/day For 7 days	Dextromethorphan	18 subjects (9 M, 9 F)	Healthy, 22-26 years, BMI 19–24	Sequential, open-label, 2-period	Moderate inhibition of dextromethorphan, inhibitory influence of CYP2D6 greater in CYP2D6*1/*1 and CYP2D6*1/*10 than CYP2D6 *10/*10 groups	No	Coptisine and berberine cross the intestinal mucosa when Zuojin Pill is taken orally and inhibits CYP2D6	[64]

AUC area under the curve, *BMI* body mass index, *C* concentration, C_{max} maximum concentration, *CYP* cytochrome P450, *F* female, *GBE* Gingko biloba, *HIV* human immunodeficiency virus, *IV* intravenous, *M* male, *P-gp* P-glycoprotein, *PK* pharmacokinetic, *Ref.* reference, *SC* subcutaneous, *SJW* St John's wort, $t_{1/2}$ half-life, *TCM* traditional Chinese medicine, T_{max} time to C_{max}, *Trad.* traditional

[a]Clear implication of the commercial firm in the study

The first column assigns a number to each clinical study. The second column set describes the herbs and their form. The third column set describes the drugs involved. The fourth column set describes the clinical study model, observations, and a possible explanation. The last column provides references for the studies

3.2 Case Reports

We analyzed 28 case reports from 2011 to 2021 (Table 1). Among the analyzed case reports, five described cases (CR 2, 4, 6, 20, 22) in which multiple herbs [18–22] were taken simultaneously, making any conclusion doubtful. This is certainly a problem as many commercial products contain a mixture of herbs in Western countries as in Asian countries. The problem historically exists in traditional Chinese medicine (CR 2, 4, 22) [18, 19, 22], which is a non-negligible part of herbal medicine use and concerns three case reports in our corpus. A second problem with traditional medicine products is the lack of knowledge about the methods of preparation of the extracts consumed. A good practice to propose would be to better describe the natural products consumed by the patients.

All cases involved chronic or semi-chronic diseases, including cancer, human immunodeficiency virus (HIV), epilepsy, psychiatric disorders, coronary heart disease, and transplantation. In 17 cases, the patient was a man, in 12 cases a woman, and one case was unclear about the sex of the patient. Two cases described pediatric adverse drug reactions.

Reported cases relate to therapeutic as well as food and recreational use. Most of the cases concern herbal food supplements in Western countries. Under-reporting [14] is inevitable and an important limitation of spontaneous reporting schemes. It is probably even more important for herbal products, as users typically do not seek professional advice about their use of such products, or report if they experience adverse effects.

Among most represented herbs, two cases described an event related to St John's wort [23, 24] (*Hypericum perforatum*, CR 18, 19), two cases related to horsetail [25] (*Equisetum arvense*, CR 11, 12), and two cases related to turmeric (*Curcuma longa*, CR 23, 24) [26, 27]. In the case of turmeric, two cases were associated with a very high consumption on a daily basis, with 15 g/day and 15 spoonfuls. In many cases, the exact nature of the herbal product is not known or not described. In most cases, we are forced to note that the form of the herb product is not clear. This information is very important and can be illustrated with turmeric. Turmeric is a spice with a spicy woody flavor that is widely used in Indian, African, and Oriental cuisine. The aromas contained in the essential oil are obtained using rhizome powder. However, the powder obviously does not have the same chemical composition as the essential oil. By not specifying whether the patient used a powder or another extractive form (tincture, tea, essential oil), the interpretation of the interaction at a chemical level between molecules remains doubtful.

In HDI case reports, some drug classes are over-represented. These classes include immunosuppressants

(Anatomic Therapeutic Chemical [ATC] class D11, three cases, CR 1, 22, 24) [22, 27, 28], coagulation-related agents (ATC class B, five cases, CR 8, 9, 14, 18, 23), all concerning either warfarin (four cases, CR 8, 9, 14, 18) [24, 29–31] or vitamin K (one case, CR 23) [26], HIV therapies (ATC class J05, three cases, CR 11, 12, 21) [25, 32], central nervous system (ATC class N, CR 2, 3, 7, 13, 15, 17, 26) with antiepileptic drugs (ATC class N03, two cases, CR 7, 15) [33, 34] and psycho-analeptic drugs (five cases, CR 2, 3, 13, 15, 17) [18, 34–37], anticancer drugs (ATC class L01, three cases, CR 4, 5, 10) [19, 38, 39]. This observation confirms that most cases are related to long-term conventional treatments and small therapeutic index drugs.

The observed effects of these interactions are in the majority severe enough to require a consultation and range from ecchymosis, weakness, or myalgia to poor seizure control, viral breakthrough in patients with HIV, or subtherapeutic immunosuppressant levels. This is one of the few cases where information is published concerning patients in therapeutic failure during herbal consumption. We believe that there is probably even greater under-reporting of treatment failure and resistance to sub-therapeutic doses of plasmatic drugs following HDIs.

One case attributed the patient's death to a PK HDI (CR 13). In this case, the interaction is believed to be due to mitragynine, an alkaloid present in kratom (*Mitragyna speciosa*) used recreationally for its opioid-like effects [36]. The leaves can be chewed fresh or dried, smoked, or infused like herbal teas, in CR 13, no information on the form used is mentioned. One case (CR 19) stated no interaction [23], which is surprising given the nature of case reports. The description of this non-case is justified by the author by a possible interaction between a 1-month treatment of St John's wort and dolutegravir as observed in other cases with older antiretroviral agents in which St John's wort induced CYP2C19, CYP3A, CYP2E1, and P-glycoprotein.

In 20 cases, information about the dechallenge of either the herbal product (15 cases) or the drug (five cases, CR 8, CR 21, CR 24, CR 26, CR 28) is provided. In all these cases except one (CR 4), dechallenge resolved the symptoms. In CR 4, a patient taking temozolomide alongside a traditional Chinese medicine comprising 11 herbs experienced severe hepatotoxicity. A re-exposition to either drug alone or in combination with other drugs (valaciclovir, levetiracetam) did not cause any toxicity [19]. In 18 cases, the authors provide possible explanations about their case. In these 18 explanations, all mention a PK mechanism involving bioavailability or metabolic enzyme induction or inhibition. Among these cases, 12 mention CYP isoenzymes (CYP2C9, CYP1A2, CYP2D6, CYP3A4, CYP3A5). In only one case (CR 17), a pharmacodynamic interaction is mentioned with the addition of serotonin syndrome [37].

3.3 Clinical Studies

We analyzed 39 clinical studies from 2011 to 2021 (Table 2). Over these studies, four referred to herbal medicines (phytopharmaceuticals, regulatory speaking) as defined by USA and European status. Among these three, two involved St John's wort (CS 31, Jarsin®, and CS 33, Kira tablets®) [45, 46], one was lavender essential oil (CS 23, Silexan®) [47], and one was milk thistle (CS 24, Legalon®) [48]. Eighteen studies concern food supplements, and one concerns anthroposophic medicine (mistletoe, CS 25) [49].

Four studies (CS 16, CS 18, CS 27, CS 29) described interactions linked with food and not food supplements [50–54]. Products that are not sold with a drug regulatory status are problematic. In this case, firms presenting products as therapeutic (herbal food supplements) are not required to ensure consistency in chemical compositions as they would be for drugs. Furthermore, required quality control largely differs depending on the country of production. Composition of the same product could vary depending on the lot, thus resulting in a variation in clinical effects. In addition to these frontier products, two clinical studies involved the well-known grapefruit juice (*Citrus* × *paradisi Macfad*, CS 16) [50] and pomelo (CS 27) [53]. One concerned green tea (CS 18) [52] and another studied the influence of a high mushroom (shiitake, *Lentinula edodes,* CS 29) [54] diet. Even if this study showed an interaction between a high mushroom diet and gabapentin (600 mg/day, an "intermediate" dosage), interrogations about the relevance of the study conditions can be raised, at least in a broad context. The quantity of shiitake used (250 g at each meal) might be extreme (in Western countries) in relation to most diets and the conclusions might thus be relevant only for specific populations.

Thirteen studies investigated possible interactions involving food herbal supplements: ten clinical studies concerned Ayurvedic (CS 3) [55] and Asian medicines (CS 5, 11, 21, 22, 26, 34, 35, 36, 37) [56–64]. As previously mentioned, these therapies are characterized by the use of combinations of a large number of herbs and are thus too complex to be interpreted in terms of HDIs. Yet, in six of these ten studies (CS 3, 5, 21, 34, 35, 36), no interactions were highlighted by authors.

The main classes of drugs involved in these studies are long-term treatments for case reports and medicines specific to women. For the last point, this could be owing to the fact that most herbal therapy users are women [65]. The first observation here is that studies tend to focus on chronic diseases where the risk is obviously greater. This can be linked to the fact that an important part of observed interactions also involves these classes of medicines. As previously shown, most case reports concern cases of interactions with anticancer drugs, antiepileptic drugs, psycho-analeptics,

coagulation medicines, and HIV therapies. Notably, patients undergoing chemotherapy are known to be large consumers of herbal products [66]. In nine of these studies, drugs are used as a probe with the goal to evaluate metabolic enzyme induction or inhibition as a primary endpoint (CS 1, 4, 14, 15, 20, 22, 24, 36, 37) [48, 59, 63, 64, 67–71]. Probes are used as specific substrates of a given isoenzyme. They allow the study of changes in activity of these enzymes by keeping track of their metabolization. Despite not being clinically interpretable because of the complexity of the interpretation of PK data, they provide interesting theoretical information. Tools such as the DDI predictor [72] allow the extension of these data to other drugs using known relations. The studied enzymes mainly consist of CYP450. Another extensively studied interaction target is P-glycoprotein (CS 1, 15) [67, 70]. Two studies also measured more specific activities of N-acetyltransferase 2 and xanthine oxidase (CS 22, 36) [59, 63].

Over these studies, 32 aimed to highlight only PK mechanisms such as area under the curve, half-life, or clearance. Only five studies considered clinical effects rather than only PK parameters (CS 3, 10, 25, 33, 34) [46, 49, 55, 61, 73]. With such a limited number of studies describing clinical effects, interpretation is limited. Cohorts of patients are typically limited in size, with around 20 patients per cohort. Such a cohort is typically sufficient for bioequivalence studies but would fail to describe inter-individual variations. This raises questions about the use of this information in the context of phytovigilance where a large range of reactions is awaited. The smallest number of patients in a cohort was six (CS 19) [74], while the largest observed cohort comprised 133 participants (CS 3) [55]. In 29 studies, selected patients were required to be healthy. In other cases, the patient status was correlated with their treatment as in studies concerning anticancer therapies (three studies, CS 9, 25, 34) [49, 61, 75], HIV treatments (three studies, CS 2, 3, 8) [55, 76, 77], diabetes mellitus (one study, CS 30) [78], or coronary heart diseases (one study, CS 11) [57]. Cohorts were well balanced in terms of the sex ratio in only four studies (CS 14, 25, 33, 37) [46, 49, 64, 69]. In other cases, patients were from only one sex, usually only male (CS 1, 6, 12, 16, 19, 21, 24, 26, 27, 28, 29, 30, 32, 35, 36) but sometimes only female (CS 18, 20, 22, 23, 34) [47, 52, 59, 61, 71], or largely imbalanced. Men are over-represented in cohorts of herbal clinical studies in the last 10 years where women are known to be under-represented [79]. This conflicts with the fact that women are known to be larger consumers of herbal products [28, 35]. Studies conducted only in female individuals made sense considering that in four of these studies the tested treatment involved contraceptives (CS 18, 20, 23) [47, 52, 71] or anti-hormonal therapy after breast cancer (CS 34) [61].

Among these clinical studies, two were conducted by the supplements industry (CS 18, 23) [47, 52]. One of the studies stated the absence of an interaction between Silexan® and the contraceptive pill (ethinylestradiol, drospirenone) [CS 23] [47]. The other study stated the superiority of MS-Templar, a supplement containing, among others, classic green tea. This study showed a largely more efficient activity of the product compared with green tea alone (CS 18) [52]. In both cases, studies were favorable to interests of the supplements industry. If the absence of an interaction is not surprising, as it is the case in the majority of interaction studies, the large superiority of the supplement in the second study raises more questions about its objectivity.

In all studies, the type of intervention is well stated. In the majority of cases, the treatment schedule is well defined and coherent with real-use cases. One justified exception concerns long-term or semi-long-term therapies such as anticancer treatments where the physicians adapt the treatment to the patient's needs (CS 9, 25) [49, 75].

In most of these studies, no significant HDIs are highlighted. One possible explanation is that the dosage used in these studies is congruent with the rational use of herbal medicines. In these cases, interactions can be expected to be scarce. With a more pessimistic point of view, the quality of studies could be highlighted. In HDI clinical studies, a lower number of participants are recruited than in drug clinical studies, the supplements industry is sometimes implicated, or a very short herb treatment duration is established to allow an observable interaction.

An important problem in natural products that are not phyto-pharmaceuticals is the possible discrepancies between labeled and actual content, as stated in CS 7 [77]. The lack of regulation and control of natural products can lead to differences in composition and thus to unexpected consequences.

4 Conclusions

This review of clinical studies and case reports from the last 10 years was carried out using the primary screening tool HDI highlighter. This tool is freely available to help the rapid interpretation of the literature from PDF publications. This review provides an overview of the features of the case reports and clinical studies describing HDIs. It highlights the overall poor quality or lack of generalizable information available to describe these interactions in the literature. Among the main causes of this problem, we identify the lack of information and description of products used by patients and their dosages in case reports, and the limited size of the cohorts in clinical studies. The focus on enzyme activity modulation as a primary endpoint, although pharmacologically relevant, also contributes to the lack of clinical interpretability of these studies. Inferring possible

clinical outcomes from PK parameters is a difficult task and such predictions are not expected to be reliable.

The quality of products used is also questionable owing to the regulatory status of food herbal supplements and food. Among all analyzed studies, only four are focused on herbs with a drug status, which is the status that ensures the most reliable quality control. Conclusions are harder to draw for case reports as the products are usually not clearly identified. However, given the much larger number of supplements available compared with medicines, the conclusion is likely to remain the same.

In most cases, herbal supplements or medicine industry involvement in studies does not appear to influence the conclusions. Yet, in the very small number of articles written by the supplements industry, all draw beneficial conclusions for their products, and one stated a surprisingly high efficiency of their product compared with raw alternatives. Such an implication should be kept in mind.

In general, clinical studies concerning HDIs are much less robust than clinical studies on drugs. This makes the information search and evidence-based decision-making challenging for health practitioners.

In terms of risks, few articles show the presence of significant interactions. Yet, some herbs stand out in terms of risk: St John's wort, horsetail, and turmeric led to multiple case reports. Traditional Asian medicine is also a source of HDIs, but their interpretation is harder as it usually involves a complex mix of herbs.

Currently, the tool developed is based on a symbolic (rule-based) approach. Future versions will incorporate machine learning models to ensure better coverage. We will also consider labeling the type of interaction as well as its gravity ranking.

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