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REVIEW

Critical evaluation of causality assessment of herb–drug interactions in patients

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The aim of this review was to assess the severity of adverse drug reactions (ADRs) due to herb–drug interactions (HDI) in patients taking herbs and prescribed medications based on published evidence. Electronic databases of PubMed, the Cochrane Library, Medline and Scopus were searched for randomized or nonrandomized clinical studies, case–control and case reports of HDI. The data were extracted and the causal relationship of ADRs as consequences of HDI assessed using Horn's drug interaction probability scale or Roussel Uclaf Causality Assessment Method scoring systems. The mechanism of interaction was ascertained using Stockley's herbal medicine interaction companion. Forty-nine case reports and two observational studies with 15 cases of ADRs were recorded. The majority of the patients were diagnosed with cardiovascular diseases (30.60%), cancer (22.45%) and renal transplants (16.32%) receiving mostly warfarin, alkylating agents and cyclosporine, respectively. HDI occurred in patients resulting in clinical ADRs with different severity. Patients may poorly respond to therapeutic agents or develop toxicity due to severe HDI, which in either scenario may increase the cost of treatment and/or lead to or prolong patient hospitalization. It is warranted to increase patient awareness of the potential interaction between herbs and prescribed medicines and their consequences to curb HDI as a potential health problem.

Introduction

The risk of herb–drug interaction (HDI) is increasingly recognized as a public health problem often accompanied by life-threatening adverse drug events, prolonged hospitalization and loss of life [1]. With a rise in global burden of noncommunicable diseases [2–5], pain syndromes, anxiety, depression and aging [6, 7], co-usage of prescribed medications and herbal products will persistently be a potential health problem in both developed and developing nations. For instance, cases of acute rejection episodes have been reported in heart, renal or liver transplant patients stabilized on immunosuppressives including cyclosporine and tacrolimus due to concomitant intake of St John's wort (SJW) known to induce drug metabolizing enzymes [8, 9]. In two case reports, patients with a history of generalized anxiety disorder and mild traumatic brain injury experienced serotonin syndrome and hypomania after addition of SJW or *Ginkgo biloba* to either a buspirone or fluoxetine regimen [10, 11]. Patients' deliberate refusal to disclose their use of herbal medicines to clinicians have led to underreporting of clinically relevant HDI cases. In addition, underestimation of the consequences of HDI due to lack of a standardized probability scoring system has contributed to wrong classification of the causality of adverse drug reactions (ADRs). Different experimental models have been used to understand the mechanism of such interactions [12–15].

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In most instances, *in vitro* and animal studies are conducted to evaluate the effect of herbal extracts and phytochemical constituents on pharmacokinetic and pharmacodynamic properties of probe drugs [16–22]. However, preclinical investigations often do not correlate with findings in human subjects [23–27]. Clinical studies in patients adopting a population pharmacokinetic approach is considered as the gold standard to determine the clinical consequences of potential interaction of herbal medicines with prescribed medications [28]. Nevertheless, pharmacokinetic interaction studies are often conducted in healthy subjects [29, 30]. Incidences of ADRs are rarely reported in these types of studies due to limited number of co-administered drugs, small sample size, lack of an appropriate placebo arm and the recruitment of healthy young subjects. Only a few cases recorded HDI-linked ADRs and the causality of adverse effect was assessed using an appropriate classification tool [31, 32].

Few studies have adapted the Naranjo tool to classify the severity of HDI [33, 34]. The Naranjo tool was designed to evaluate ADRs due to a single agent, and it is thus less useful for the categorization of HDI linked ADRs [35]. Fugh-Berman and Ernst developed a 10-point scoring system to assess the reliability scale of HDI [36]. Later, Horn and colleagues proposed a specific tool for causality assessment of drug–drug interactions by adopting the Naranjo scale as a guide. The Horn's drug interaction probability scale (DIPS) consists of 10 questions each with three response options to which a score is assigned [37]. In 1985, the French pharmaceutical company Roussel Uclaf organized a consensus meeting for experts in hepatology to define terminologies used in drug induced liver injuries (DILI) assessment and qualitative criteria based on the French causality assessment method (CAM). The meeting outcomes included additional criteria and assigned weight to each criterion leading to the Roussel Uclaf Causality Assessment Method (RUCAM). RUCAM is regarded as a well-established tool for qualitative assessment of causality in cases of suspected herb-induced liver injury (HILI) and DILI [38–40]. Nevertheless, only a few HDI studies have applied the Horn's DIPS and RUCAM scores to ascertain the causal relationship of ADRs. In addition, for studies where one or both classification systems were used, the mechanism of HDI was either unclear or not reported. Stockley's herbal medicine interaction companion contains arrays of herbal medicines with documented literature of interaction studies conducted *in vitro*, in animal models and healthy subjects [41]. Observational and survey control studies have adopted this companion to flag herbal medicines with potential to cause adverse effect due to interaction with prescribed medications. Such information could be useful in educating both clinicians and patients about the consequences of consuming herbal medicines with prescribed medications based on established reports. This review, therefore, aims to conduct causality assessment on HDI in clinical trials, case–controls studies, and case reports in in/out-patients from January 2001 to August 2017 using Horn's DIPS for general HDI and RUCAM for HILI specific injuries, respectively. In addition, the mechanism of HDI was evaluated by using Stockley's herbal medicines interaction companion.

Methods

Databases of *PubMed*, the *Cochrane Library*, *Medline* and *Scopus* were searched from January 2001 to August 2017. A combination of the following keywords were used for title, abstract and keywords fields: herbal drugs, herbal supplements, phytochemicals, drug interactions, herb–drug interactions, side effect and adverse-effects. Preliminary assessment was conducted on abstracts retrieved from the databases to identify publications that met the pre-specified criteria. Articles describing randomized or nonrandomized clinical studies, case–control and case reports in both in- and out-patients where conventional medications and herbal medicines were co-administered met the inclusion criteria. The review excluded all HDI studies conducted in healthy subjects, *in vitro* and *in vivo* models and other sources of natural products. Reference lists from eligible publications were another source for articles included in this review. Full text articles of abstracts meeting the eligibility criteria were extracted, validated and summarized (Table 1). Two independent reviewers (C.A. and M.M.) conducted causality assessment on validated data using the Horn's DIPS for general ADRs or RUCAM for HILI. The Stockley's herbal medicine interaction companion was consulted in cases where the mechanism of interaction was not reported.

The results of this review are divided into two parts: 1) characteristics of studies, and 2) tabularized description of studies, probability score and mechanism of interactions.

Results

The initial electronic database search identified 5113 articles, of which 1963 were screened after removal of duplications. In total 5035 publications were excluded based on titles and abstracts. On application of the review inclusion criteria to the 78 full-text papers, a further 24 articles were excluded. Five additional papers were discarded because full text of two studies were not available, two papers in German and one paper in Turkish could not be translated into English. Thus, 49 full text articles consisting of 47 case reports publications and two observational studies were included in this review. One publication presented three different reports and hence, 49 case reports were reviewed. The majority of the case reports described patients between 51–69 years (n = 12, 24.49%) and older than 70 years (n = 11, 22.45%), respectively. Fifteen of the patients (30.60%) had a history of cardiovascular conditions such as hypertension, dyslipidaemia, myocardial infarction, atrial fibrillation and cardiomyopathy. Thirteen patients (86.67%) with a history of cardiovascular conditions were on warfarin treatment. Eleven cases (22.45%) were cancer patients of whom the majority were on alkylating agents (busulfan, temozolomide and trabectedin) and/or kinase inhibitors (imatinib and gefitinib). There were eight case reports of patients with renal transplant (16.33%) of which five patients (62.5%) received cyclosporine as immunosuppressive agent. Three HIV positive patients received a protease inhibitor (lopinavir), an integrase inhibitor (raltegravir) or a non-

Table 1

Summary of observational studies included

Description	Levy *et al.*, 2017	Jeong *et al.*, 2012
Study design, population and duration	Cross-sectional study of 947 patients hospitalized in 12 departments of a tertiary academic medical Centre in Haifa, Israel from 2009 to 2014.	A prospective study of 313 inpatients (87 male and 226 female) hospitalized in two Oriental Hospitals of Daejeon University, Daejeon, Korea from August 2008 to October 2010
Inclusion criteria	Intake of herbal medicine at least 1 week prior to hospitalization. Patients at 18 years and above who were able to communicate and provide verbal informed consent.	Intake of herbal medicine at least 10 days during hospitalization.
Exclusion criteria	Not mentioned	A life expectancy of <12 months (by judgment of the patient's doctor); current or previous liver diseases including carrier status of hepatitis virus, renal disease, or autoimmune disease; and abnormal baseline results on liver or renal function tests on hospitalization.
Sex	Male: 152 (33%) Female: 306 (67%)	Male 87 (27.8%) Female 226 (72.2%)
Mean age	61.3 years	51 years
Herb users with different comorbidities	458 (100%)	313 (100%)
Metabolic	243 (53%)	
Circulatory system	237 (52%)	87 (27.8%)
Haemato-oncological	95 (21%)	77 (24.6%)
Musculoskeletal system		66 (21.1%)
Neurologic	38 (8%)	40 (12.8%)
Digestive system	39 (8.5%)	17 (5.4%)
Endocrine	132 (29%)	
Respiratory	39 (8.5%)	
Renal	37 (8%)	
Rheumatological	37 (8%)	
Pregnancy	30 (7%)	
Psychiatric	29 (6%)	
Ophthalmological	21 (5%)	
Urological	17 (4%)	
Hepatobiliary	10 (2%)	
HIV		23 (7.3)
Others		3 (1.0)
Mode of causality assessment	DIPS	RUCAM score
Cases of ADR	Total = 17 Herbs/pure compounds = 7 Other supplements = 10	Total = 6 Herb/pure compounds = 6 Other supplements = 0

ADRs classified by RUCAM score for liver injury; no provision of patient history and ADRs classified by Horn's DIPS score for other injuries. ADR = adverse drug reaction; HIV = human immunodeficiency virus; DIPS = drug interaction probability scale; RUCAM = Roussel Uclaf Causality Assessment Method

nucleoside reverse transcriptase inhibitor (efavirenz). There were eight patients (16.33%) with central nervous system diseases such as depression, schizophrenia, anxiety disorders and seizures. The patients with central nervous system disorders received anticonvulsants (lamotrigine and phenytoin), atypical antipsychotics (clozapine), a selective serotonin reuptake inhibitor (sertraline) or a norepinephrine reuptake inhibitor (venlafaxine). Concomitant intake of

Table 2

Case reports of herb–drug interactions in individual patients

Patient description [reference]	Herb supplement Latin name (common use)	Affected drug	Concomitant medications	Signs or symptoms of possible interaction	Plausible mode of interaction	Probability scale [37]
58-year-old man with a history of phalangeal fracture [42]	*Ginkgo biloba* (improve cognitive function)	Sodium aescinate	Cefuroxime	Elevated serum creatinine and blood, urea and nitrogen (BUN) levels	CYP2C9 and 3A4 inhibition	Probable (5)
56-year-old man with a history of orthotopic liver transplantation [43]	*Curcuma longa* (anti-inflammatory and liver protection)	Tacrolimus	Steroids, IV immunoglobulin, rituximab, sofosbuvir/ribavirin	Abdominal distention, scrotal and peripheral oedema, increased creatinine	CYP3A4/5 inhibition	Probable (7)
50-year-old Caucasian man with monophasic synovial sarcoma [44]	Diosmin (blood disorders)	Trabectedin	Epirubicin, ifosfamide	Rhabdomyolysis, increase serum myoglobin, creatinine phosphokinase and liver function	CYP3A4 inhibition	Probable (5)
52-year-old white, woman, with a history of major depressive disorder, hypertension and dyslipidaemia [45]	Celery root (menopause)	Venlafaxine	SJW	Confusion and speech abnormalities	CYP2D6 inhibition	Possible (4)
49-year-old man without a family history had partial seizures with a secondarily generalization since he was age 27 years. [46]	Noni juice (Tahitian Noni Original Bioactive Beverage)	Phenytoin	Lamotrigine, lorazepam, clobazam	Low phenytoin level in blood	CYP2C9 induction	Highly probable (9)
44-year-old white man generalized tonic–clonicseizure disorder [47]	Ginseng (improve mental and physical performance)	Lamotrigine	Deer antler velvet, sildenafil, hydrocortisone cream	DRESS syndrome (pruritic rash on more than 50% of his body, eosinophilia, myalgias, and elevated liver enzymes)	UGT2B7 inhibition	Probable (5)
35-year-old woman with a history of depression [48]	*Centella asiatica* and *Fucus vesiculosus*(rash, eczema, psoriasis and other skin infections)	Venlafaxine	None	Progressive dyspnoea over the previous, New York Heart Association(NYHA) functional class III, myalgia, and dry cough	CYP2D6 slow metabolizer or CYP2D6 inhibition by *Centella asiatica*	Possible (3)
56-year-old woman Caucasian patient diagnosed witha temporal–parietal glioblastoma WHO IV [49]	*Bu Zhong Yi Qi Wan* (promotes physical strength)	Temozolomide	Dexamethasone, pantoprazol, levetiracetam, mirtazapine, valaciclovir	Grade II thrombopenia and elevated liver enzymes	Unknown	Probable (5)
78-year-old Hispanic, man, renal transplant patient [50]	*Pneumus boldus*(mild dyspepsia and spastic gastrointestinal complaints)	Tacrolimus	mycophenolate, metoprolol, simvastatin, tamsulosin, aspirin, lisinopril, amlodipine, calcium carbonate, omeprazole, and insulin	Asymptomatic	Unknown	Probable (6)
44-year-old obese man (body mass index: 53 kg m^{-2}) with stage-III (ISS) IgG-κ multiple myeloma [51]	Flor-Essence (anticancer)	Busulfan	Bortezomib, melphalan	GI toxicities, including Grade 3 nausea,vomiting, diarrhoea and oesophagitis	Unknown	Possible (2)

(*continues*)

Table 2

(Continued)

Patient description [reference]	Herb supplement Latin name (common use)	Affected drug	Concomitant medications	Signs or symptoms of possible interaction	Plausible mode of interaction	Probability scale [37]
82-year-old woman with a history of hypertension, hypothyroidism, gastritis, atrial fibrillation [52]	*Artemisia absinthium* (sore throat)	Warfarin	Nebivolol, valsartan hydrochlorothiazide, levothyroxine and esomeprazole	abdominal pain and black, tarry stool	Unknown	Possible (4)
56-year-old Caucasian man with a history of progressive abdominal pain due to liposarcoma with a retroperitoneum mass (5 × 8 cm) [53]	Chokeberry juice (anticancer)	Trabectedin	Peg-granulocyte colony stimulating factor	Rhabdomyolysis, G4 pancytopenia, elevated liver enzymes	CYP3A4 inhibition	Possible (4)
16-year-old child with nephrotic syndrome [54]	Berberine (diarrhoea)	Tacrolimus	Prednisone	Renal toxicity	CYP3A4/5 inhibition	Possible (4)
52-year-old woman with a history of severe psoriasis [55]	Red clover (menopausal flushing)	Methotrexate	Not mentioned	Severe vomiting and epigastric pain	Probably OAT3 inhibition	Possible (4)
23-year-old Japanese woman with multiple sclerosis [56]	Lutein and melilot supplements (indigestion and other GI tract problems)	Interferon β-1b	Not mentioned	Jaundiced palms, elevated alanine transaminase, periventricular and juxtacortical hyperintense signal lesions	Unknown	Probable (5)
41-year-old woman with disorganized schizophrenia [57]	SJW (depression)	Clozapine	Not mentioned	Increased disorganization and tension	CYP3A4 induction	Probable (6)
56-year-old white Caucasian man with a history of HIV+ [58]	Ginseng-based oral lozenges (sexual disability)	Raltegravir plus lopinavir/ritonavir	Aspirin, esomeprazole, trimethoprim/ sulfamethoxazole	Generalized pruritus, scratching lesions, increased transaminase, visible jaundiced skin and mucous membranes	CYP3A4 inhibition	Probable (6)
71-year-old Ecuadorean-American woman with a history of complete left knee arthroplasty [33]	Himalayan goji juice (cleanse body)	Warfarin	Ezetimibe, lisinopril, famotidine, meclizine, alprazolam, and diphenhydramine	Ecchymosis, epistaxis, and one episode of haematochezia, elevated INR	CYP2C9 inhibition	Probable (7)
41-year-old man diagnosed with HIV [59]	*Ginkgo biloba* (improve cognitive function)	Efavirenz	Zidovudine, lamivudine	Increased viral load at 1350 copies ml^{-1}	CYP3A4 induction	Probable (6)
61-year-old man with a T3N1M0 (stage IIIA) squamous cell carcinoma of the lung [60]	Echinacea (common cold and flu)	Etoposide	Cisplatin, omeprazole, enalapril, hydrocodone/ paracetamol, prochlorperazine, ondansetron, vitamins B12, E, D, B17 and C	Seizure-like activity, grade 4 thrombocytopenia	Unknown	Possible (2)
85-year-old man with a history of hypertension, old anterior wall myocardial infarctio nand atrial fibrillation [61]	SJW (depression)	Warfarin	Not mentioned	Upper gastrointestinal bleeding, increased INR	Possibly additive clotting effect	Probable (6)

(*continues*)

Table 2

(Continued)

Patient description [reference]	Herb supplement Latin name (common use)	Affected drug	Concomitant medications	Signs or symptoms of possible interaction	Plausible mode of interaction	Probability scale [37]
46-year-old African American woman with a history of stage 1 sarcoidosis, uterine fibroids, anaemia, cardiomyopathy and depression [62]	Cranberry juice (constipation)	Warfarin	Not mentioned	Increased INR	Unknown	Highly probable (10)
71-year-old man with aortic valve and mitral valve replacement [63]	*Sheng Mai-yin* (improvement of peripheral circulation)	Warfarin	Not mentioned	Consciousness disturbance – right hemiplegia and active pupils, increased INR	CYP2C9 induction, downregulates plasminogen inhibitor 1 (PAI-1), tissue factor pathway inhibitor, coagulation factorXIII, A1, and, coagulation factor II (thrombin) receptor (F2R).	Probable (8)
71-year-old Caucasian man with a history of atrial flutter, hypertension, hyperlipidemia, diabetes mellitus, erectile dysfunction and hypothyroidism [64]	Bee pollen granules (general wellbeing)	Warfarin	Hydrochlorothiazide, lisinopril, levothyroxine, simvastatin, glyburide, metformin, vardenafil, aspirin, multivitamin and amlodipine	Elevated INR	CYP2C9 inhibition	Probable (5)
58-year-old Mexican man with a history of type 2 diabetes mellitus, osteoarthritis, hyperlipidaemia, hypertension, and degenerative disc disease of the spine [65]	Prickly pear cactus (diabetes)	Glipizide	Metformin, rosuvastatin, fenofibrate, aspirin, lisinopril, gabapentin, tramado1, nabumetone and nitroglycerin	Hypoglycaemic	Unknown	Probable (8)
26-year-old man with chronic myeloid leukaemia [34]	*Panax ginseng* (improve mental and physical performance)	Imatinib	Not mentioned	Right upper quadrant pain, elevated liver enzymes	CYP3A4 and P-glycoprotein inhibition	Probable (5)
79-year-old man with atrial fibrillation and metastatic bladder carcinoma [66]	Grifron-Pro Maitake D – fraction (immunoinstimulant)	Warfarin	diltiazem, hydromorphone, tamsulosin, prednisolone ophthalmic suspension, simvastatin and eszopiclone	Elevated INR	Unknown	Possible (4)
59-year-old black man with hyperlipidaemia [67]	SJW (insomnia)	Rosuvastatin	Not mentioned	Increased total and low-density lipoprotein cholesterol	CYP2C9 and CYP2C19 induction via PXR activation	Possible (3)
53-year-old Sri Lankan woman with unipolar depression [68]	Arthiritis QR, Cholesterol QR, *Triphala churna*, *Yogaraja Guggulu*, Mentat, *Rumalaya*, Decoction-1, Decoction-2 (backache)	Sertraline	Not mentioned	Moderate and severe depression	Unknown	Probable (6)

(*continues*)

Table 2

(Continued)

Patient description [reference]	Herb supplement Latin name (common use)	Affected drug	Concomitant medications	Signs or symptoms of possible interaction	Plausible mode of interaction	Probability scale [37]
40-year-old man with generalized anxiety disorder and dream disorders [69]	*Valeriana officinalis* L. and *Passiflora incarnata* L. (anxiety and insomnia)	Lorazepam	Not mentioned	Handshaking, dizziness, throbbing and muscular fatigue	Synergistic effect only	Possible (3)
52-year-old woman with essential hypertension and a minor ischemic stroke [70]	Nattokinase (stroke)	Aspirin	Not mentioned	Vertigo and unsteady gait, high blood pressure, cerebral microbleed	Unknown	Doubtful (0)
47-year-old man with HIV-1 infection [71]	Efamol tablets, rheum frangula tablets and colayur syrup (laxative intestinal cleaners)	Lopinavir, ritonavir	Stavudine, lamivudine and tenofovir	Diarrhoea, toxic lopinavir plasma level	CYP3A4 and CYP2D6 inhibition	Probable (8)
36-year old woman with stage IV adenocarcinoma of lung [72]	Ginseng, *Fomes fomentarius, Inonotus obliquus, Phellinus linteus* (improve mental and physical performance)	Gefitinib	Not mentioned	Increased shortness of breath	CYP3A4/5 induction	Probable (5)
61-year-old man with a history of primary hypercholesterolemia [73]	Green tea (fat and weight loss)	Simvastatin	Amlodipine	Elevated liver enzymes, increase simvastatin lactone levels	Unknown	Probable (7)
80 year-old Chinese woman with a history of diabetes mellitus, hypertension, cerebrovascular accident and atrial fibrillation [74]	*Lycium barbarum* L or goji berry (promote longevity)	Warfarin	Nifedipine, glibenclamide, metformin, lorazepam	Increased INR,	Probably CYP2C9 inhibition and/or additive anticoagulation	Highly probable (9)
77-year-old Japanese man with a history of hypertension and hyperuricemia [75]	Arejin and Daiokanzo-to (chronic allergic rhinitis and constipation)	Enalapril	Nifedipine, famotidine, brotizolam and terazosin	Mild anaemia, liver dysfunction, mildly elevated creatine kinase (CK) level, and severehypokalaemia and hypochloraemia.	Probably via inhibition of renal 11-beta-hydroxysteroid dehydrogenase	Probable (7)
70-year-old woman with history of a mechanical mitral valve placement and an episode of atrial fibrillation [76]	*Matricaria chamomilla* (pedal oedema)	Warfarin	Amiodarone, digoxin, synthroid, lendronate, metoprolol and a calcium–vitamin D supplement	Elevated INR, dyspnoeic on exertion, bilateralpedal oedema and ecchymoses in her perineal area, across her lower abdomen and over her left hip	Probably synergistic anticoagulation	Possible (3)
55-year-old Indian woman with a node-positive 4-cm grade 3 invasive ductal carcinoma [77]	Betel quid (CNS stimulant)	Doxorubicin, cyclophosphamide, paclitaxel	Docetaxel, 5-fluorouracil and methotrexate	Grade IV mucositis, dysuria, mouth pain, and furunculosis.	Sensitization of normal tissues to the cytotoxic chemotherapy	Probable (5)
57-year-old man with prosthetic mitral valve due to rheumatic heart disease [78]	*Commiphora molmol* (acute bronchitis)	Warfarin	Not mentioned	Decreased INR	Unknown	Possible (3)

(*continues*)

Table 2

(Continued)

Patient description [reference]	Herb supplement Latin name (common use)	Affected drug	Concomitant medications	Signs or symptoms of possible interaction	Plausible mode of interaction	Probability scale [37]
48-year-old woman with a cadaveric renal allograft [79]	Thüringen 9- Kräutertee (not indicated)	Cyclosporine	Mycophenolate mofetil, pravastatin, valsartan and hydrochlorothiazide	Decreased cyclosporine level, rhabdomyolysis	Unknown	Possible (4)
37-year-old Armenian man with a cadaveric renal transplant [79]	Chamomile Tea (dyspepsia, nausea, vomiting)	Cyclosporine	Azathioprineand Mycophenolate mofetil	Decreased cyclosporine level	Unknown	Probable (7)
33-year-old man with a cadaveric renal transplant [79]	Wild fruit tea drink (not indicated)	Cyclosporine	Mycophenolate mofetil	Increased cyclosporine level	Unknown	Possible (4)
55-year-old man with a history of cerebrovascular accident following coronary artery bypass and seizure disorder [80]	Ginkgo supplement (improve cognitive function)	Valproic acid and phenytoin	Not mentioned	Seizure disorder leading to death while swimming	Indirect inhibition of glutamate decarboxylase and glycine activities and CYP2C19 induction	Probable (7)
35-year-old woman with a left thigh haemangioma [81]	*Aloe vera* (leg pain)	Sevoflurane	Propofol, fentanyl, and rocuronium, Cefazolin, morphine	Perioperative bleeding	Probably additive inhibition of cyclooxygenase activity	Possible (3)
57-year-old kidney transplant [82]	SJW (depression)	Cyclosporine	Prednisolone	Decrease cyclosporine concentration	CYP3A4 and P-gp induction	Highly probable (9)
61-year-old man with atrial fibrillation and chronic rheumatic heart disease [83]	*Quilinggao* (to quench *internal heat*)	Warfarin	Digoxin, simvastatin, furosemide and potassium chloride	gum bleeding and epistaxis, elevated INR	Inhibition of platelet function	Probable (5)
28-year-old woman a recipient of a live-donor allograft due to end-stage renal disease attributed to hypertensive nephrosclerosis [84]	Rice fermented with red yeast, beta-sitosterol, danshen root *(Salvia mitorriza)*, and garlic bulb *(Allium sativum)*(to lower cholesterol)	Cyclosporine and/ or diltiazem	azathioprine, prednisone, enalapril and famotidine	Increased serum creatine phosphokinase rhabdomyolysis	Unknown	Possible (3)
61-year-old Chinese woman with a history of recurring atrial fibrillation, hypertension, hypercholesterolaemia and tricuspid regurgitation [85]	*L. barbarum* L. (blurred vision)	Warfarin	Benazepril, atenolol, digoxin and fluvastatin	Elevated INR	Probably CYP2C9 inhibition and/or additive anticoagulation	Probable (6)
67-year-old Caucasian woman with a history of hypertension [86]	Boldo-fenugreek (to *help liver* and stimulate digestion)	Warfarin	Metoprolol	Increased bleeding time	Inhibition of thromboxane A2	Probable (5)

CYP, Cytochrome P450; GI, gastrointestinal; HIV, human immunodeficiency virus; INR, international normalized ratio; IV, intravenous; PXR, pregnane X receptor; SJW, St John's wort; UGT, uridine-5′-diphospho-glucuronosyltransferase

Table 3

Case reports of herb-drug interactions in observational studies

Authors [Ref]	Patient	Herbal medicine/ product	Reported ADRs	Mode of interaction	Prescribed drugs (Score)
Jeong *et al.*, [31][a]	**Case 1**: 42-year-old man diagnosed with cerebral infarction	Product A	Cholestatic injury	Unknown	Cefuroxime (6) Paracetamol (6) diclofenac (6)
	Case 2: 54-year-old man with cerebral infarction.	Product B	Hepatocellular injury	Unknown	Sarpogrelate (0) Actobacillus (0)
	Case 3: 40-year-old man with Bell's palsy	Product C	Hepatocellular injury	Unknown	Prednisolone (3)
	Case 4: 61-year -old man with subdural hematoma	Product D	Hepatocellular injury	Unknown	Paracetamol (7) diclofenac (7) aspirin (7) clopidogrel (7) rebamipide (5)
	Case 5: 57-year-old woman with cerebral infarction	Product E	Hepatocellular injury	Unknown	Roxoprofen (6) baclofen (6) cimetidine (6)
	Case 6: 71-year-old woman with cerebral infarction	Product	Hepatocellular injury	Unknown	Amoxicillin (4) serratiopeptidase (4)
Levy *et al.*, [32][b]	**Case 1**	Green tea	Lowered digoxin level	Unknown	Digoxin (3)
	Case 2	Turmeric	GIT bleeding	Additive antiplatelet effect	Clopidogrel (5)
	Case 3	Sage	CO_2 narcosis Respiratory failure	Unknown	Methadone (3)
	Case 4	Sage/peppermint oil	Rhabdomyolysis	CYP3A4 inhibition	Simvastatin (3)
	Case 5	Flaxseed	Anaemia Rectal bleeding	Synergistic effect	Aspirin (5)
	Case 6	Blond Psyllium	Orthostatic hypotension	Unknown	3 antihypertensive drugs (3)
	Case 7	Flaxseed	Melena INR 4.18	Additive anticoagulation	Warfarin (6)
	Case 8	Chamomile	Melena INR 4.18	Probably CYP2C9 inhibition or additive anticoagulation	Warfarin (3)
	Case 9	Sage	Melena INR 4.18	Probably CYP2C9 inhibition or additive anticoagulation	Warfarin (6)

[a]ADRs classified by RUCAM score for liver injury;
[b]No provision of patient history and ADRs classified by DIPS score for other injuries.
ADR = adverse drug reaction; GIT = gastrointestinal tract; INR = international normalized ratio; Product A = *Pinellia ternata Breitenbach, Atractylodes japonica koidzumi, Citrus unshiu Markovich, Gastrodia elata Blume, Poria cocos Wolf, Glycyrrhiza glabra Linne, Zingiber officinale Rosco*; Product B = *Pueraria lobata Ohwil, Scutellaria baicalensis Georgi, Angelica tenuissima Nakai, Raphanus sativus Linne, Platycodon grandiflorum A. De candole, Angelica dahurica Bentham et Hooker.*; Product C = *Astragalus membranaceus Bunge, Rehmannia glutinosa Liboschitz var. purpurea Makino, Angelica gigas Nakai, Paeonia lactiflora Pallas, Poria cocos Wolf, Atractylodes japonica koidzumi, Panax ginseng C. A. Meyer, Acorus gramineus Solander, Ostericum Koreanum Maxim, Pinellia ternata Breitenbach, Gastrodia elata Blume, Aconitum koreanum Raymond, Glycyrrhiza glabra Linne.*; Product D = *Scutellaria baicalensis Georgi, Atractylodes lancea D. C, Atracylodes chinensis Koidzumi, Ostericum Koreanum Maxim, Aralia continentalis Kitagawa, Saposhnikovia divaricata Schiskin, Cnidium officinale Makino, Angelica dahurica Bentham et Hooker, Liriope platyphylla Wang et Tang, Vitex rotundifolia Linne fil. Chrysanthemum indicum Linne, Asiasarum sieboldi F. Maekawa, Glycyrrhiza glabra Linne.*; Product E = *Agastache rugosaO.Kuntze, Perilla frutescens var. acuta Kudo, Angelica dahurica Bentham et Hooker, Areca catechu Linne, Polyporium bellati Polyporaceae, Magnolia ovobata Thunberg, Atractylodes japonica koidzumi, trus unshiu Markovich, Pinellia ternate Breitenbach, Platycodon grandiflorum A. Decandole, Arisaema amurense, Maximowicz Saussurea lappaClarke, Glycyrrhiz aglabra Linne.*; Product F = *Lindera strichnifolia Villars, ractylodes lancea D.C, Atracylodes chinensis Koidzumi, Ephedra sinica Stapf, Angelica dahurica Bentham et Hooker, Platycodon grandiflorum A. Decandole, Citrus aurantium Linne, Cinnamomum cassia Blume, Glycyrrhiza glabra Linne*

SJW and *Panax ginseng* were recorded in patients treated with warfarin, cyclosporine or kinase inhibitors (gefitinib and imatinib). HDI cases reported to be probable and highly probable were 25 (51.02%) and four (8.16%), respectively. Eighteen cases (36.73%) were classified as possible whilst two cases (4.08%) were identified to be doubtful. The predominant ADRs were elevated liver enzymes, INR, GIT disturbances and rhabdomyolysis. The detailed descriptions and causality scales of the 49 cases included in this review are presented in Table 2.

The majority of patients in the two observational studies were aged between 51–61 years. Female patients (532 patients, 69.0%) constituted the majority. Most of the patients had a history of metabolic, cardiovascular, endocrine or haemato-oncological complications (Table 1). In the study by Jeong *et al.*, six cases of ADRs were reported [31]. Four ADRs were reported in patients with a history of cerebral infarction taking herbal concoctions with NSAIDs (aspirin and diclofenac), P2Y12 inhibitor (clopidogrel) and analgesic (paracetamol) experiencing probable HDI (Table 3). Levy *et al.*, reported nine cases of ADRs as a consequences of herbal medicine intake [32]. The majority of the cases in this study were due to interaction between warfarin and sage or flaxseed (Table 3).

Discussion

Concomitant intake of herbal medicines and prescribed medications is a common practice, especially in patients with hypertension, diabetes, cancer, seizures and depression. This is problematic particularly for drugs exhibiting a narrow therapeutic index. Incidences of underreporting and non-standardized causality estimation of HDI in patients have resulted in life-threatening ADRs, hospitalization and fatality in some cases [87–89]. Intensification of monitoring and critical appraisal procedures to identify the severity of ADRs linked to concomitant consumption of herbs and prescribed medicines is critical in averting untoward occurrences.

The WHO Collaborating Centre for International Drug Monitoring-Uppsala Monitoring Centre (WHO-UMC) has the mandate to co-ordinate global ADRs data and search this data to identify signals of new ADRs to notify the pharmacovigilance centres of member countries and other organizations concerned with drug safety. In a study conducted by WHO-UMC the majority of HDI-linked ADRs reported were from developed countries, including USA and Europe with South Africa as the only contributory developing country [90] and this re-affirms the concern of underreporting of HDIs in developing countries. Adverse reactions related to HDIs have been documented in observational studies and case reports [70, 71, 83, 84, 91]. Nonetheless, few review studies have been conducted to estimate the severity of the ADRs due to HDI in patients. Hence, this review adapted the DIPS and RUCAM scores to estimate the severity of ADRs, whilst the Stockley's herbal medicines interaction companion was consulted in assessing the mechanism of interactions.

The majority of cases recorded in this study showed that patients taking warfarin and/or statins (atorvastatin, simvastatin and rosuvastatin) for the management of cardiovascular complications reported clinically significant interactions after combination with herbal products including sage, flaxseed, SJW, cranberry, goji juice, green tea and chamomile. Warfarin is a racemic mixture of R and S stereoisomers with S-warfarin being a 3–5 times more potent inhibitor of the vitamin K epoxide reductase complex than the R isomer. Warfarin is used for the management of atrial fibrillation and heart valve replacement. Metabolism of S-warfarin is predominantly mediated by CYP2C9. Herbal medicines altering the activity of CYP2C9 may cause under-anticoagulation or bleeding episodes. Potential interaction of warfarin and active constituents of sage, flaxseed, goji juice, cranberry and chamomile led to ADRs such as ecchymosis, epistaxis, haematuria, hemiplegia and elevated INR [33, 63, 74, 76, 85]. The active constituents of SJW namely hyperforin, flavonols, flavonol glycosides, biflavones, napthodianthrones, acylphloroglucinols and phenylpropranes are known to reduce plasma concentration of warfarin via induction of CYP3A4 and CYP2C9. However, one case study reported SJW to cause sudden upper GIT bleeding in a sensitive patient [61]. This interaction might have been caused by active constituents of SJW potentiating the clotting effect of warfarin. In addition, the Chinese herbal product Sheg Mai-yin is used to improve peripheral circulation due to its effect on oxidative damage in heart, brain and other tissues. Sheg Mai-yin contains red ginseng, liriope and *Schisandra chinesis*. A case of intracranial haematoma has been reported in a patient with a history of aortic valve and mitral valve replacement receiving warfarin and Sheg Mai-yin [63]. Red ginseng enhances the production of interleukin-1β, which increases the production of tissue plasminogen activators responsible for suppression of thrombin formation during blood coagulation and fibrinolysis processes [92]. Furthermore, the saponin-related active constituents of red ginseng, namely ginsenosides Rg1 and Rg5, downregulate plasminogen inhibitor 1, tissue factor pathway inhibitor, coagulation factors XIII, A1 and coagulation factor II (thrombin) receptor (FR2), which may lead to increase INR [93].

Besides anticoagulants, patients with cardiovascular complications (coronary artery disease) often take statins, including atorvastatin, rosuvastatin, simvastatin and others to lower low-density lipoprotein and total cholesterol levels. However, many patients on statins complain of muscle pain, which affects quality of life and adherence to treatment. Statin-induced muscle intolerance could be elicited by its co-usage with herbal supplements and other prescribed medications. For example, a patient receiving amlodipine (10 mg day^{-1}) and simvastatin (10 mg day^{-1}) complained of intense leg muscle cramps and pain after ingestion of green tea [73]. This was attributed to a 2-fold increase plasma levels of simvastatin lactone due to inhibitory effect of green tea on CYP3A4 [94, 95]. However, further studies need to be conducted to ascertain other potential mechanisms for statin intolerance due to green tea intake.

In organ transplant patients, tacrolimus and cyclosporine A are principal immunosuppressive agents commonly administered to protect and reduce episodes of organ rejection. Both drugs have a narrow therapeutic index and are metabolized primarily by CYP3A4/5. Herbal medicines that alter the activities of CYP3A4 are likely to affect the protective effect of tacrolimus and cyclosporine in transplant patients.

Cases of treatment failure or toxicity have been reported in patients consuming tacrolimus, azathioprine and cyclosporine with herbal preparations such as turmeric or chamomile tea [43, 50, 79, 82]. The active phytoconstituents of the herbal medicines inhibit CYP3A4 and P-glycoprotein to reduce elimination of the immunosuppressive agents [96–100]. Tacrolimus and cyclosporine bind to immunophilins to block calcineurin's mediated T-lymphocyte activation. In general, increased plasma levels of calcineurins have been reported to trigger calcineurin-induced vasoconstriction and release of endothelin-1 (a potent vasoconstrictor), decrease production of nitric oxide and increase expression of transforming growth factor β1 in renal transplantation patients [101]. Thus, the active ingredients of turmeric and chamomile induced nephrotoxicity in patients taking tacrolimus and/or cyclosporine via CYP3A4 inhibition. For probe drugs such as azathioprine, metabolic transformation of parent compound to the active moiety 6-mercaptopurine by glutathione S transferase (GST) and subsequent inactivation to 6-methylmercaptopurine by thiopurine methyltransferase (TPMT) is necessary [102]. Herbal medicines capable of altering the activity of GST and/or TPMT could potentially induce clinically significant ADRs.

Other immunocompromised patients, including those with HIV infections, often take herbs for various reasons, and as immune boosters. A number of antiretroviral medications including protease inhibitors (lopinavir and ritonavir) and non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine) with narrow therapeutic indices and elimination via hepatic metabolism are susceptible to HDI. HIV patients experienced signs of toxicity and detectable levels of viral load while taking raltegravir plus lopinavir/ritonavir [58] or efavirenz [59] with ginseng and *G. biloba,* respectively. The mechanism of ginseng–raltegravir interaction is unknown, as several conflicting outcomes have been reported on the influence of various active ingredients of ginseng on CYP450 enzymes [103–105]. However, one study reported ginseng-mediated hepatotoxicity in a chronic myeloid leukaemia patient on imatinib due to inhibition of CYP3A4 [34]. The inhibitory effect of ginseng on CYP3A4 was thus probably accountable for the observed adverse effect of raltegravir. For *G. biloba*, a unique active ingredient, bilobalide, has been demonstrated to induce CYP2B6 mRNA in animal models, although such a result was irreproducible in human subjects [106, 107]. In a patient taking efavirenz and ginkgo, it is speculated that a breakthrough in viral load occurred because of a decrease in plasma levels of EFV as consequence of the inductive effect of active ingredients in *G. biloba*.

The current review study also recorded a significant number of HDI cases in patients with depression and seizure disorders. Antidepression medications, including valafaxine and sertraline, are eliminated primarily by hepatic metabolism. Patients taking these medications with herbal drugs including QR and Mentat for arthritis and celery root for menopause developed episodes of worsening depression [45, 68]. In addition, cases of seizure induction occurred in a patient taking either phenytoin or valproic acid after consuming *G. biloba* supplement. In one recorded case, seizure induction led to the demise of a patient while swimming. The autopsy results confirmed a decreased plasma levels of both phenytoin and valproic due to inductive effect of *G. biloba* on CYP2C19 [80]. Another study in 18 healthy Chinese subjects showed significant reduction in plasma concentration of omeprazole as a probe substrate of CYP2C19 in the presence of *G. biloba* compared to the controls [108]. Furthermore, Ginkgo contains a potent neurotoxin, 4′-0-methoxypyridoxine, which indirectly inhibits glutamate decarboxylase and glycine activities leading to seizure induction [109]. The effect of 4′-0-methoxypyridoxine on inhibitory neurotransmitters is predicted as the most likely cause of seizure induction leading to his demise since CYP2C19 would have accounted only for a minor proportion of phenytoin and valproic acid elimination.

Finally, the consumption of herbal medicines is a well-known practice among cancer patients [110–113]. Currently, imatinib is the main drug for the treatment of chronic myeloid leukaemia. It is a first- generation inhibitor of *bcr-abl* tyrosine kinase enzyme. Imatinib is primarily metabolized by CYP3A4, and hence, any herbal medicine that alters the activity of CYP3A4, may affect the activity of imatinib. Concomitant intake of imatinib and an energy drink containing *P. ginseng* led to aberrant liver enzyme levels in a patient [34]. Previous study showed that ginseng increases plasma concentrations of prescribed medications via CYP3A4 inhibition [105]. Thus, the reduced activity of CYP3A4 in the presence of *P. ginseng* precipitated imatinib-induced hepatotoxicity characterized by late-stage acute lobular hepatitis [105]. Other chemotherapeuticals such as cisplatin, etoposide and trabectedin have been reported to interact with herbal medicines, including *Echinacea purpurea* [60] and chokeberry juice (*Aronia melanocarpa*) [53] in patients presenting with different types of cancer. Chokeberry contains concentrated flavonoids – procyanidin B5, cyaniding-3-arabinoside and quercetin – which strongly inhibit CYP3A4 activity in the liver [114]. Thus, reduced activity of CYP3A4 due to chokeberry intake caused trabectedin-induced rhabdomyolysis in this patient [53]. Conversely, echinacea has a mild inhibitory effect on CYP3A4 activity, which is likely to potentiate the myelosuppressive effect of etoposide and could elicit neutropenia and thrombocytopenia in patients.

Conclusion

Patients taking herbal medicines containing *G. biloba*, *P. ginseng*, SJW, green tea and others affecting the pharmacokinetic and pharmacodynamic properties of prescribed medications are at risk of experiencing different degrees of HDI. Few case reports of potential HDI have been documented in the literature despite the detrimental consequences of such interactions. In addition, even in cases where HDI were reported in patients, inadequate provision of information hindered the utilization of the data to draw clinically meaningful conclusions. Generally, these challenges could be attributed to a number of reasons including: (i) inability to re-challenge patients with the herbs involved to confirm the causal relationship of the interaction for ethical reasons; (ii) lack of analytical capacity to measure the plasma levels of the affected drug; (iii) difficulty in identification of the phytochemical responsible for the interaction; (iv) nonexistence of adequate genetic information especially

for high-risk drugs, such as clopidogrel, warfarin, codeine, tamoxifen or terbinafine; (v) lack of standardized HDI-specific causality assessment tool; and (vi) lack of motivation of clinicians to publish HDI case reports. Critical assessment of the causality of ADRs using the recommended scoring systems reported in this study will strengthen the applicability of HDI data in clinical practice. In addition, mechanistic investigations in healthy subjects and *in vitro* liver models as a follow-up study on herbs recorded to elicit clinically significant HDI in patients. Thus, we recommend a bench-to-bed-side approach to understand the causal relationship of HDI linked ADRs and the potential mechanism of observed interactions. This approach will inform drug regulatory agencies and pharmaceutical companies about the need to update information in package inserts of medicines to avoid untoward adverse events, based on available data. In conclusion, causality assessment and subsequent mechanistic studies of herbs with clinically relevant HDI must be publicized to alert both clinicians and patients about the need to avoid co-usage of certain herbal medicines with specific prescribed medications.

Competing Interests

There are no competing interests to declare.

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