Herb-drug interactions: A review and study based on assessment of clinical case reports in literature

K.J. Gohil, J.A. Patel*

Department of Pharmacology, Maliba Pharmacy College, Gopal Vidyanagar, Tarsadi, Bardoli, Surat, *Department of Pharmacology, Institute of Pharmacy, Nirma University of Science and Technology, Ahmedabad, India

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Correspondence to:
Jagruti A. Patel,
E-mail: jagrutiap@gmail.com

ABSTRACT

Objective: To conduct a systematic review of literature on interactions between conventional drugs and various herbs.

Materials and Methods: We carried out a literature survey to assess published herb-drug interaction information in clinical case reports and case series to check the report reliabilities.

Results: From 133 cases of suspected interactions, 67% cases were classified as possible interactions, 27% cases were unable to be evaluated and only 6% of the cases were well-documented. St. John's wort was the most common herb involved (37 cases) in drug interactions. Warfarin was the most common drug (34 cases) interacting with various herbs.

Conclusion: Herb-drug interactions are a stark reality today. Hence, proper reporting of cases, careful vigilance, evidence-based appraisal and constantly updated reviews of such herb-drug interactions are very important to promote systematic research.

KEY WORDS: Case series, clinical assessment, clinical case reports, herb-drug interactions

Introduction

Millions of people today use herbal therapies along with prescription and nonprescription medications. Although considered natural, many of these herbal therapies can interact with other medications, causing either potentially dangerous side effects and / or reduced benefits from the medications. Currently, there is very little information published on herb-drug interactions whilst the use of herbs is progressively growing across the world.

The size of the worldwide market of herbal medicines is estimated to be around US $80 billion to US $100 billion and this market is expected to reach US $2500 billion by the year 2010.[1-2] In the West, the demand for herbal drugs has reached a new high in recent years. Since 1999, the global market for herbal supplements exceeded US $ 15 billion, with a US $ 7 billion market in Europe, US $ 2.4 billion in Japan, US $ 2.7 in the rest of Asia and US $ 3 billion in North America.[3] The results of a nationwide survey indicated a marked increase in the number of individuals using alternative therapies between 1990 and 1997 estimating total out-of-pocket expenditures for alternative therapies at $27 billion.[4]

India is very rich in natural resources and the knowledge of traditional medicine and the use of plants as a source of medicine is an innate and very important component of the healthcare system. The Indian system of medicine has identified 1,500 medicinal plants of which 500 are commonly used.[2] It is estimated that there are over 7800 medicinal drug-manufacturing units in India, which are estimated to consume about 2000 tons of herbs annually.[5] According to a recent estimate of the World Health Organization (WHO), 70-80% of the world population especially in developing countries, relies on traditional medicine, mostly plant drugs for their primary healthcare needs.[2,6]

As the use of herbs is getting popular, interactions between herbs and allopathic drugs need to be addressed and reviewed properly. Certain herbal supplements can cause potentially dangerous side effects when taken with prescription drugs. The use of alternative therapy is mostly not supervised by physicians or alternative therapy practitioners resulting in increased harm to patients, especially if they are using herbal and prescription medicines that have latent interactions. These interactions can go unnoticed until a patient is hurt or a serious life-threatening event has occurred.

Despite the urgent need for information, very little is known about herb-drug interactions unfortunately as experimental data in this field is limited and case reports and case series are rare.[7-8]

Objective

The aim of our present study was to conduct a review of literature on interactions between conventional drugs and various herbs based on descriptions of the clinical consequences, case series and case reports. In addition, we

also wanted to assess the quality of the data generated for the study of herb-drug interactions.

Materials and Methods

A literature survey was carried out to compile information about herb-drug interactions. As per the guidelines for the use of electronic and internet media,[9-10] a high quality and reliable medical information from the internet was retrieved only from the Health-on-Net (HON) conduct-certified and accredited websites like Entrez PubMed [Medline], CAM-PubMed, Allied and complementary medicine database, Natural medicine comprehensive database, Embase and Cochrane library. The databases were searched from 1986-2006 using the search terms "herb-drug interactions, side effects, herb toxicities, adverse drug reactions, herbal medicine, herbal medicinal, prescriptions, case reports, case series, clinical trials and clinical assessments". Non-English language citations were excluded. An extensive review of the literature identified reported herb-drug interactions with clinical significance, many of which were in the form of case reports and limited clinical observations. The nature of the findings and probability of interactions were then abstracted and compiled in a final report [Table 1]. The probability of interactions was evaluated on a 10 point scoring scale reported earlier,[8] where each of the case reports received one point for inclusion of any of the following ten evaluating parameters:

- Adequate patient history.
- Concurrent diseases, conditions.
- Documentation of concomitant medications.
- Adequate description of interactions.
- Exclusion of obvious alternative explanations.
- Complete chronology.
- Reasonable time sequence of drug administration to adverse event.
- Adequate description of adverse event.
- Cessation of event on stopping the drug.
- Recurrence of event with a re-challenge.

This probability scale, though not validated, served only as a guide to assess whether the reports of herb-drug interactions contained reliable information or not. The sum total of all these parameters was calculated and referred to as report reliability scores as per the criteria mentioned below. This report reliability score was further validated by a third party, *i.e.*, two independent raters unaware of the study protocol.

a. A score of 0-3 suggested that the case contains insufficient information (unable to be evaluated).
b. A score of 4-7 implied some evidence for an interaction (possible) and
c. A score of 8-10 indicated a well-documented report with reliable evidence for interaction (likely).

Results

The search of all listed sources produced 133 cases of suspected interactions. All interactions were tabulated and categorized by herb, drug, other medications, signs or symptoms of interaction, mechanism and report reliability scores [Table 1]. 67% of the cases (89/133) were classified as possible interactions, 27% (36/133) were considered to contain insufficient information to evaluate the probability of an interaction (Unable to be evaluated) and 6% (08/133) as well-documented (likely) interactions. St. John's wort was the herb most commonly implicated in interactions with various drugs (37 cases) namely digoxin (13 cases), clopidogrel (06 cases), indinavir (08 cases), irinotecan (05 cases), antipsychotics (04 cases) and tacrolimus (01 case). Other herbs most commonly implicated in herb-drug interactions were ginkgo biloba (27 cases), kava-kava (08 cases), ginger (06 cases) and Panax ginseng (05 cases). The anticoagulant drug, warfarin was found to be the most common drug interacting with various herbs (34 cases) of which 22 cases were classified as 'unable to be evaluated' interactions, 10 cases were 'possible' interactions and 2 cases were classified as 'well-documented' or 'likely' interactions.

Discussion

The results of our search point towards the fact that herb-drug interactions certainly do occur and are much more common than we would like to believe, contrary to the popular belief that Nature is always safe. In many cases, mechanisms and causality are uncertain or unpredictable; in addition, inadequate information and under-reporting make it very difficult to determine whether herb-drug interactions have occurred or not. In the past, very few case reports related to herb-drug interactions were reported and many reactions could only be explained theoretically. Recently, however, there are several reported cases of possible herb-drug interactions with the increased use of herbal medications.[11-14]

An earlier survey of literature for reports of herb-drug interactions presented 108 cases of suspected interactions out of which 68.5% were reported as unable to be evaluated, 18.5% as possible and 13% as well documented cases.[8] In this study, 133 new cases of suspected herb-drug interactions were identified of which 27% cases (36/133) were unable to be evaluated, 67% cases (89/133) were described as possible and only 06% cases (08/133) emerged as well documented interactions.

In the present study, St. John's Wort was the most common herb implicated in various drug interactions and warfarin was the most common drug interacting with various herbs.[8,15-18] A previous study reported 85 interaction cases of St. John's Wort of which 54 cases were with the drug cyclosporin. Other drug categories mentioned were oral contraceptives (12 cases), antidepressants (09 cases), warfarin (07 cases) and one case each with theophylline, phenprocoumon and loperamide interacting with St. John's Wort.[8] The present study identified 37 cases of interactions for St. John's Wort with digoxin (13 cases), clopidogrel (06 cases), indinavir (08 cases), irinotecan (05), antipsychotics (03), tacrolimus (01 case) and with an anesthetic (01 case). This makes St. John's Wort a somewhat risky proposition when combined with drugs in the categories mentioned above.

As with conventional medicines, herbal medicines interact with drugs in two general ways: pharmacokinetically and pharmacodynamically.[14] Pharmacokinetic interactions result in alterations of the drug's or natural medicine's absorption, distribution, metabolism or elimination. These interactions affect drug action by quantitative alterations, either increasing or decreasing the amount of drug available to have an effect.

Table 1

Assessment of clinical case reports on herb-drug interactions

Case No.	*Patient- description*	*Herb*	*Drug*	*Other medications*	*Symptom(s) of interaction*	*Mechanism*	*Report-reliability score*
1-13.	St. John's Wort used by 13 volunteers for two weeks.[32]	St. John's Wort *Hypericum perforatum* (Depression)	Digoxin	None	Reduction in serum digoxin level by 18-25%	Induction of P-glycoprotein by St. John's Wort	Possible 0+1+1+1+1+0+ 1+1+0+0=6
14-21.	In 8 healthy volunteers, 14 days' course.[34]	St. John's Wort *Hypericum perforatum* (Depression)	Indinavir	None	A 57% reduction of Indinavir area-under-the-curve (AUC)	Induction of cytochrome P450 (Cyp450)	Possible 0+1+1+1+1+1+ 1+0+0+0=6
22-27.	Case series 06 healthy volunteers.[35]	St. John's Wort *Hypericum perforatum* (Depression)	Clopidogrel (Plavix)	None	Decline in platelet aggregation	Induction of Cyp450	Possible 1+1+1+0+0+ 0+0+1+0+0=4
28	20 year-old college student with major depressive episode.[50]	St. John's Wort *Hypericum perforatum* (Depression)	Clonazepam	Lithium	Extreme agitation, irritability, pressured speech, anxiety	Not known	Possible 1+1+1+0+0+0 +0+1+0+0=4
29	A 51 year-old female with history of psychotic mania.[50]	St. John's Wort *Hypericum perforatum* (Depression)	Haloperidol	Lithium	Bizarre behavior, Excessive motor activity and disorganized speech.	Not known	Possible 1+1+1+0+0+0 +0+1+0+0=4
30	Not known.[107]	St. John's Wort *Hypericum perforatum* (Depression)	Olanzapine	None	Olanzapine level is increased by 300%	Inhibition of CYP1A2	Unevaluable 0+1+0+1+0+0 +0+1+0+0=3
31	21 year-old woman undergone surgery.[108]	St. John's Wort *Hypericum perforatum* (Depression)	Sevoflurane, nitrous oxide	Propofol, Fentanyl and Diclofenac	Delay in recovery from anesthesia	Not known	Possible 1+1+1+1+1+0 +1+0+0+0=6
32	A kidney transplant patient.[109]	St. John's Wort *Hypericum perforatum* (Depression)	Tacrolimus	None	Lower blood levels of drug	Induction of CYP3A4 system	Possible 1+1+0+0+1+0+0+ 1+1+1+0=6
33-37.	Five cancer patients: two men, three women with a median age of 58 years[110]	St John's Wort *Hypericum perforatum* (Depression)	Irinotecan	None	Reduction in serum irinotecan level results in decreased side effects of drug	Induction of Cyp450	Possible 1+1+0+0+1+0+0+ 1+1+1+0=6
38	33 year-old woman with bilateral subdural hematomas[20,55]	Ginkgo biloba	Acetaminophen	Ergotamine caffeine	Increased bleeding time up to 15 min	Herb has antiplatelet Activity	Likely 1+1+1+1+0+1 +1+1+1+0=8
39	No information[57]	Ginkgo biloba (Circulatory disorders)	Ibuprofen	None	Fatal intracerebral hemorrhage	Herb has Antiplatelet activity	Unevaluable 0+1+0+1+1+0+0 +0+0+0=3
40-61.	Case series n=22 Healthy subjects.[77]	Ginkgo biloba	Nifedipine	None.	Increase in mean plasma level of Nifedipine	Inhibition of CYP3A4	Possible 0+1+1+1+1 +0+0+1+1+0=6

Table 1 contd...

Case No.	*Patient- description*	*Herb*	*Drug*	*Other medications*	*Symptom(s) of interaction*	*Mechanism*	*Report-reliability score*
62-63.	Two elderly epilepsy patients[111]	Ginkgo biloba (Circulatory disorders)	Sodium valproate	None	3 to 4 seizures within 2 weeks	Not known	Likely 1+1+0+1+1+1 +1+1+1+0=8
64	34 year-old male undergoing laparoscopic cholecystectomy[112-113]	Ginkgo biloba	No medication stated	None.	Increase in postoperative bleeding	Inhibit platelet Activating factor	Possible 1+1+0+1+1+0+ 0+1+0+0=5
65	One man-no other information[65,78]	Green tea *Camellia sinensis*	Warfarin	None	Thickening of blood	Herb has antagonistic Effect	Possible 0+1+0+1+1+0 +1+0+1+0=5
66	A 44 year-old man with a mechanical heart valve[65,78]	Green tea *Camellia sinensis*	Warfarin	None	Decreased INR to 1.37 from 3.79	Herb has antagonistic effect due to presence of vitamin K in herb	Possible 1+1+0+1+0+0 +1+1+0+0+0=5
67	A 72 year-old lady[65]	Coenzyme Q (ubiquinone or ubidecare-none)	Warfarin	None	Decreased response to warfarin	Herb possesses procoagulant property	Possible 1+1+0+1+0+0 0+1+1+0=5
68	A 68 year-old male with history of pulmonary and cerebro vascular disease[65]	Coenzyme Q (ubiquinone or ubidecare-none	Warfarin	None	Decreased INR to 1.31 from 2-3	Herb possesses procoagulant property	Likely 1+1+0+1+1+1 +1+1+1+0=8
69	A 67 year-old female with atrial fibrillation[76]	Boldo *Peumus boldus* Fenugreek	Warfarin	Metoprolol	INR increased	Not known	Possible 1+1+1+0+0+0+1 +0+0+0=4
70	No information[79]	Quilinggao (Chinese herbal product containing Cinchona species.)	Warfarin	None	Bleeding episode	Synergism	Unevaluable 0+1+0+1+0+0 +0+1+0+0=3
71	No information provided[80]	*Lycium barbarum* (Chinese herbal tea)	Warfarin	None	Interfere with the effect of warfarin	Not known	Unevaluable 0
72	No information[81-82]	Saw palmetto *Serenoa repens*	Warfarin	None.	Increased INR	Not known	Unevaluable 2
73	A 36 year-old male with depression[86]	Ayahusca *Banisteriopsis caapi*	Fluoxetine	None	Tremors, shivering, sweating, severe nausea and vomiting	Not known	Unevaluable 1+1+0+0+0+0+ 0+0+0+0=2
74-75.	55 year-old female and another 49 year-old patient. No other information[87]	Celery *Apium graveolens*	Thyroxin	None	Decreased T4	Not known	Possible 1+1+0+0+0+0+ 1+1+0+0=4
76	60 year-old male with hypertension and CHF.[88]	Fennel fruit *Foeniculam vulgar*	Enalapril	None.	Patient was free from cough after chewing fennel	Not known	Possible 1+1+1+1+1+1 +0+0+0+0=6

Table 1 contd...

Case No.	Patient- description	Herb	Drug	Other medications	Symptom(s) of interaction	Mechanism	Report-reliability score
77	57 year-old male with type 2 diabetes[89]	Prickly pear *Opuntia streptacantha*	Oral hypoglycemic agent	None	Mean fasting glucose level increased up to 205 mg/dl	Not known	Possible 1+1+1+1+0+0 +1+1+0=0=6
78	Healthy volunteers[90]	Garlic *Allium sativum* (Hypercholesterolemia)	Saquinavir	None	Significantly reduced plasma Saquinavir concentration	Unknown	Unevaluable 0+1+1+0+1+0+0 +0+0+0=3
79-84.	Six Danish rheumatoid arthritis patients[91]	Ginger *Zingiber officinale*	NSAIDS	None	No symptomatic relief	Not known	Possible 0+1+1+1+0+0+1 +1+0+0=5
85	No information[92]	Licorice Glycyrrhiza glabra	Laxative	None	Potassium loss	Additive effect	Unevaluable 0+1+0+1+0+ 0+0+0+0+0=2
86	No information[93]	Licorice *Glycyrrhiza glabra*	Sennoside	None	Myoclonus due to metabolic alkalosis	Not known	Unevaluable 2
87	No information[94]	Soybeans Glycine max	Warfarin	None	Decline in INR reduced anticoagulation	Not known	Possible 0+1+0+1+1+1 = 4
88	A 59 year-old Caucasian female received a cadaveric renal transplant 16 years before this admission[95]	Alfalfa *Medicago sativa*	Immunosuppressants. Azathioprin Cyclosporin	None	She began to reject the transplanted kidney.	Not known	Possible 1+1+1+1+1+1 +0+1+0+0=7
89-90.	Two Patients of epilepsy no other information[96]	Shankhapushpi *Evolvulus alsinoides*	Phenytoin	None	Loss of seizure control	Not known	Possible 0+1+1+1+0+0+1 +1+0+0=5
91	A 47 year-old man[64]	Ginseng *Panax ginseng*	Warfarin	Diltiazem Nitroglycerin Salsalate	INR declined to 1.5	Not known	Possible 1+1+1+0+0+0+ 1+1+1+0=6
92	A post-menopausal woman[114]	Ginseng (Topical) *Panax ginseng*	Hormone therapy	None	Mastalgia and vaginal bleeding	Herb shows Estrogen-like Effect	Possible 0+1+1+1+0+0+0 1+0+0=4
93	A 39 yearr-old female experienced menometrorrhagia[115]	Ginseng *Panax ginseng*	Caffeine and nicotine	None	Sinus tachycardia	Not known	Possible 1+1+0+1+1+1+ 1+0+1+0=7
94	A patient with depression[116]	Ginseng *Panax ginseng*	Lithium	Amitriptyline	Maniac episode	Not known	Possible 1++1+1+0+0+1 +0+0+0+0=4
95	A woman with major depression.[117]	Ginseng *Panax ginseng*	Clomipramine	Haloperidol	Maniac episode	Not known	Possible 1+1+1+0+0+0
96-99	Case series (*n*=4)[60]	Kava *Piper methysticum*	Levodopa	None	Dyskinesia	Not known	Unevaluable 0+0+0+1+0+ 0+1+1+0+0=3
100	A 29 year-old man[118]	Kava *Piper methysticum*	Gaurana (caffeine)	Gingko	Myoglobinuria Rhabdomyolysis Severe muscle pain, dark urine and elevated creatine kinase	Not known	Possible 1+0+1+1+0+0+ 0+1+0+0=4

Table 1 contd...

Case No.	Patient- description	Herb	Drug	Other medications	Symptom(s) of interaction	Mechanism	Report-reliability score
101	A 81 year-old female suffering from hepatitis.[119]	Kava *Piper methysticum*	Hydrochlorthiazide	Nifedipine	Fatal liver failure.	Probably no Interaction But adverse effect of kava	Unevaluable 1+1+0+0+0+0+1 +0+0+0=3
102	A 47 year-old female with developing hepatic encephalopathy.[119]	Kava *Piper methysticum*	Amino acid complex	Ornithine, liquid mineral supplement	Discolored feces, pathologic urine, anorexia.	Probably no Interaction But adverse effect of kava	Unevaluable 1+0+1+0+0+0+ 0+1+0+0=3
103	A 28 year-old man with anxiety and history of 3 episodes of acute dystonic reactions.[60,120]	Kava *Piper methysticum*	Promethazine Fluspirilen injections Biperiden	None	Acute attack of involuntary neck extension with forceful upward deviation of his eyes, 90 min after the intake of the first dose of 100 mg kava extract (Laitan).	Supposed dopamine antagonism	Possible 1+1+1+1+0+0+ +0+1+1+0=6
104	A woman in Mexico(121)	Papain	Warfarin	None	Skin, urinary, GIT bleeding Prolonged Prothrombin time.	Synergism	Possible 1+1+0+0+0+0+0 +1+1+0+0=4
105-106	Two patients topical use of ointment containing Birch bark oil, no other information.[75]	BIRCH *Betula pendua* *Betula alba* leaves or bark (Methylsalicylate main content)	Warfarin	None	GI bleeding and a doubled Prothrombin time.	Potentiation	Unevaluable 0+1+0+0+0+0 +0+0+1+0=2
107	22 year-old Caucasian woman with arthritis applied topical pain relieving gel to her knees daily for 8 days.[122]	BIRCH *Betula pendua* *Betula alba* Leaves or barks (Methylsalicylate main content)	Warfarin	None	Elevated INR up to 12.2 and 6.1 respectively resulting in multiple bruising.	Interfering with vitamin K Metabolism or Displacement from Protein binding site	Possible 1+1+0+0+1+0 +1+1+0+0=5
108	No information[123]	Cannabis	Cisplatin.	None	Lethal ischemic stroke.	Not known	Unevaluable 1
109	A patient with congestive heart failure.[124]	*Cannabis sativa* Ephedra	Caffeine	None	Patient died after 6 weeks.	Not known	Unevaluable 1+1+0+0+0+1 = 3
110	40 year-old lady on statin therapy[125]	Grape fruit juice	Simvastatin	None	Muscle weakness in her lower extremities due to statin induced Rhabdomyolysis.	Inhibition of CYP450	Possible 1+1+0+1+0+ 1+1+1+0+0=6
111	A man with depression, maintained on HIV protease inhibitor[125]	Grape fruit juice	Fluoxetine and trazodone	Indinavir, stavudin	Serotonin syndrome.	Inhibition of CYP450	Likely 1+1+1+0+1+ 1+1+1+1+0=8

Table 1 contd...

Case No.	Patient- description	Herb	Drug	Other medications	Symptom(s) of interaction	Mechanism	Report-reliability score
112	A diabetic woman[126]	Grape fruit juice	Quinine	None	Torses de pointes, convulsive Syncope with Polydipsia.	Flavonoid naringen increases quinine availability	Likely 1+1+1+0+1+ 1+1+1+1+0=8
113-117.	5 different cases, no other information[127]	Cranberry juice	Warfarin	None	Increase the activity of warfarin.	Inhibit breakdown of warfarin in body	Unevaluable 0+1+0+0+0 +0+0+1+0 +0=2
118	A man in 70's after a chest infection and with a poor appetite[128]	Cranberry juice	Warfarin	Cefalexin Digoxin Phenytoin	Patient died of GIT and pericardial hemorrhage.	Not described	Possible. 1+1+1+0+1 +1+1+10+0 = 7
119-130	12 different cases of interactions[129]	Cranberry juice	Warfarin	Not described	-	Not described	Unevaluable 0
131	A patient No other information[130]	Cranberry juice	Warfarin	None	High INR Major bleeding.	Not described	Possible. 0+0+0+1+0+1 +0+1+1+0=4
132.	70-year-old women with mechanical mitral valve and previous episode of atrial fibrillation.[131]	Chamomile *(Matricaria chamomilla*)	Warfarin	Amiodarone Digoxin Synthroid Alendronate Metoprolol Calcium-vitamin D supplement.	High INR (7.9) Major bleeding.	Coumarin constituent of herb resulting in supra therapeutic anticoagulation.	Likely 1+1+1+1+1+1 +1+1+0+0 = 09
133	77 year-old man with history of hypertension and hyperuricemia.[132]	Two Chinese herbal medicines, both containing glycyrrhizin.	Enalapril	None	Marked metabolic alkalosis with severe hypokalemia. Pseudoaldosteronism.	Interaction of rennin angiotensin system with the herb.	Likely 1+1+0+1+ 1+1+1+1 +1+0 = 08

The interfering drug may act as an inducer, inhibitor and / or substrate of the cytochrome P450 enzyme that is responsible for the metabolism of the respective drugs. This is the most important mechanism for interactions between herbal therapies and antiretroviral drugs.[19] St. John wort, widely prescribed for various psychopathologic conditions involving depression and anxiety[20] is reported to lower serum concentrations of cyclosporine,[8,21-27] theophyllin,[28] warfarin,[29-30] oral contraceptives,[30] digoxin,[31-33] indinavir[34] and clopidogrel[35] by inducing CYP450 (CYP 3A4, CYP 2C9 and CYP1A2).[8,36-39] On the other hand, the same herb has also been reported to inhibit the CYP 3A4 isoform.[40] Another mechanism stated for St. John's wort, responsible for affecting clearance of many drugs is that it increases expression of duodenal P-glycoprotein (PgP), an ATP-dependent drug efflux transporter known to pump drugs out of the cell and thus decrease the intracellular concentration of drugs.[8,41-43] Caution is warranted when using St. John's wort with several medications like barbiturates, carbamazepine, dextromethorphan, fenfluramine, fexofenadine, narcotics, nortriptyline, phenytoin, photosensitizing drugs, reserpine and simvastatin during pregnancy and lactation for the risk of potential interactions.[44]

Pharmacodynamic interactions affect a drug's action in a qualitative way, either through enhancing effects (synergistic or additive actions) or antagonizing effects. The interactions reported in this category include those of St. John's wort with various antidepressants namely paroxetine, sertraline, nefazodone, venlafaxine, clonazepam and interactions of haloperidol[45-49] with loperamide[50] and kava-kava with alprazolam.[51] Cases of serotonin syndrome (serotonin-amplifying effect) with St. John's wort have also been studied.[52]

Ginkgo biloba, the secondmost common herb involved in drug interactions is reported to have potent drug interactions with fluoxetine, buspirone, insulin, monoamine oxidase inhibitors (MAOIs) and with drugs metabolized by cytochrome P450 3A4, P450 3A5, P450 1A2 and P450 2D6 enzymes. Hence, Ginkgo biloba should be used with caution during pregnancy and lactation.[53] This antioxidant herb is mainly promoted for use in improving cognitive function (brain booster) and blood flow.[20,54] It is reported to inhibit platelet aggregation activity resulting in spontaneous bleeding when used simultaneously with aspirin,[20,54] acetaminophen,[20,54-55] trazodone,[56] ibuprofen[57] and warfarin.[53-54,58] Twenty-seven cases of ginkgo interactions were noted with acetaminophen, ibuprofen, nifedipine and sodium valproate in the present study, extending the list in a previous study where the herb was reported to interact with trazodone, warfarin, aspirin and thiazide diuretics.[8] *CYP2C9* is the CYP- 450 isoenzyme responsible for the metabolism of the more potent warfarin enantiomer, (S)-warfarin. Recently, a study conducted to ascertain the influence of Ginkgo biloba on *CYP2C9*, stated that Ginkgo biloba extract inhibits human liver microsomal *CYP2C9* enzyme *in vitro* but not *in vivo*.[59]

Kava kava is shown to have additive effects with central nervous system depressants and caution is advised with regards to its simultaneous use with benzodiazepines, barbiturates, antipsychotics and alcohol.[20,51] In addition, patients with Parkinson's disease are also discouraged from using kava products.[20,60] In this report, eight new cases of kava-kava were listed with various drugs including levodopa,[60] caffeine,[118] hydrochlorthiazide,[119] amino acid complex,[119] promethazine and biperiden.[120]

Millions of people regularly take blood-thinning medications such as warfarin and over-the-counter drugs like aspirin and similar medications. These medications are very commonly prescribed for patients with high risk of blood clotting such as those with artificial heart valves, deep vein thrombosis or arterial fibrillation. The risk grows many fold when such patients take herbs possessing antiplatelet or anticoagulant activities and fail to report the use of herbs to their doctors. There are reports of potential herb-drug interactions with analgesic drugs, particularly aspirin, which have the potential to interact with herbal supplements that are known to possess antiplatelet activity as well as those containing coumarin components, thus enhancing the risk of bleeding.[61,62] In the present study, warfarin was found to interact with at least 19 types of different herbs with a total of 34 cases of interactions adding to the list of 18 interactions previously reported.[8] There is a reasonable documentation of interactions between coumarin anticoagulants like warfarin with various herbs,[63] apart from St John's Wort, ginkgo biloba,[20,55,65] panax ginseng,[20,64-65] coenzyme-Q,[65] siberian ginseng,[66] danshen,[67-69] dong quai,[70-72] garlic,[73] devil's claw,[74] birch,[75] boldo, fenugreek,[76] green tea,[65,78] quilinggao, a Chinese herbal product,[79] Chinese herbal tea (*Lycium barbarum*),[80] saw palmetto,[81-82] papain,[121] cranberry juice[127-130] and chamomile.[131] Taking much needed precautions such as regular monitoring of weekly prothrombin time (PT test) and International normalized ratio (INR) can prove to be helpful in avoiding risk due to these interactions.

Addition of herbal medicine to multiple drug therapy holds the potential for herb-drug interactions,[43,83-84] although it is also suggested that some of the adverse drug effects and drug interactions reported for herbal products could be caused by impurities as allergens, pollen and spores or batch-to-batch variability.[20] This is because unlike conventional drugs, herbal drug products are not regulated for their purity and potency.[20,21,85]

The present study also reports isolated cases of some herbs involved in interactions with various drugs such as ayahusca with fluoxetine,[86] celery with thyroxin,[87] fennel with enalapril,[88] prickly pear with an oral hypoglycemic agent,[89] garlic with saquinavir,[90] ginger with nonsteroidal anti-inflammatory drugs (NSAIDS),[91] licorice with a laxative,[92-93] soya bean with warfarin,[94] alfalfa with immunosuppresants,[95] shankhapushpi with phenytoin[96] and chamomile with enalapril.[131] In most cases, the mechanism is unknown or just plain additive effects between the herbs and drugs responsible for the respective toxicity.

In an earlier report, concern was raised about herb-drug interactions with anesthesia and it was suggested that herbal therapies be discontinued at least two to three weeks prior to surgeries requiring anesthesia.[97-98] Grapefruit juice too is reported to interact with number of drugs. Since the first report in 1989 as a result of using the juice as part of placebo preparation in a drug trial,[99-102] the list has expanded tremendously. At present, grapefruit juice is reported to interact with number of anticancer agents including erlotinib, recently approved by the Canadian health authority as a monotherapy for locally advanced, small cell lung cancer.[103]

A broad concern is raised for a variety of potential interactions based on their pharmacological actions when case reports are not available. Examples are 1) laxative herbs (Aloe, licorice, senna, cascara) with potassium-wasting medications and with the drugs that act on the heart due to the risk of additional loss of potassium,[11,14,104-105] 2) herbs and drugs with similar actions like bitter melon and gymnema with other antidiabetic medications due to the risk of excessive hypoglycemia and 3) herbs like valerian, kava kava, ginger, goldenseal, chamomile with centrally acting agents due to the risk of increased sedation. Also worthy of mention are interactions of caffeine-containing herbs (Guarana, green tea) with other drugs that also affect the central nervous system[11,14,104] and of herbs containing a coumarin component (black cohosh, chamomile, bilberry leaf) with warfarin due to the risk of hemorrhage.[14] Recently, reports have emerged that the ayurvedic herbal medicine gugulipid or "guggul" may have unwanted interactions with many prescription medications.[106] The herb is an Ayurvedic medicine taken to help lower cholesterol and stimulate thyroid function. It may interfere with drugs used for treating AIDS and cancer, specifically, gugulipid could interfere with drugs such as azathioprine, various other anticancer agents and cholesterol-lowering statins. The authors suggested that guggulsterone interacts with drugs by binding to a protein called pregnane X receptor (PXR). PXRs induce the body to "turn on" a gene that encodes another protein that breaks down various drugs. Thus, the drug levels in the body are lowered. However, there are no case reports pertaining to interactions of guggul with any medication.

Inadequate reporting makes it very difficult to determine whether a particular herb-drug interaction has occurred. Proper

documentation is necessary with all relevant information, clear description of adverse event and careful exploration of alternative explanations along with consideration for a reasonable re-challenge whenever possible.

Although, one or two reports may not warrant an absolute contraindication to combinations of herbal and prescription therapies, precautions do need to be exercised by taking the medical history of patients during counseling sessions to obtain this information. The onus lies on healthcare professionals who can monitor the use of herbal medicines, especially if the patients are taking them with prescription medications. An open-minded approach during patients' visits is to counsel the patients with enough information about signs and symptoms of herb-drug interactions so that they are able to recognize an adverse event if it occurs. It seems only rational that the administration of herb and drug, if taken together, should be at least 1 to 2 hours or several hours apart from each other. It is advisable to avoid using the herb and drug combinations altogether; which are contraindicated or reported frequently for interactions with the specific drug. Despite widespread use, herb-drug interactions are a stark reality today. The number of cases reported for the emerging herb-drug interactions are already on the rise. In fact, the actual number of cases may be higher due to under-reporting There are many plant compounds, which are still unfamiliar and new drugs are produced every day. Unfortunately, the herb-drug interaction remains an unknown area. It is now known that millions of patients take herbal and conventional medicines concomitantly, often without the knowledge of their physicians. Considering our present lack of understanding of herb-drug interactions, proper reporting of such cases, careful vigilance, evidence-based appraisal and constantly updated reviews of such information are very important to promote understanding in this area.

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