Review Article

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Understanding the relevance of herb–drug interaction studies with special focus on interplays: a prerequisite for integrative medicine

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Abstract

Integrative medicine refers to the blending of conventional and evidence-based complementary medicines and therapies with the aim of using the most appropriate of either or both modalities for ultimate patient benefits. One of the major hurdles for the same is the chances of potential herb–drug interactions (HDIs). These HDIs could be beneficial or harmful, or even fatal; therefore, a thorough understanding of the eventualities of HDIs is essential so that a successful integration of the modern and complementary alternative systems of medicine could be achieved. Here, we summarize all the important points related to HDIs, including types, tools/methods for study, and prediction of the HDIs, along with a special focus on interplays between drug metabolizing enzymes and transporters. In addition, this article covers future perspective, with a focus on background endogenous players of interplays and approaches to predict the drug–disease–herb interactions so as to fetch the desired effects of these interactions.

Keywords: Ayurveda, drug metabolizing enzymes–transporter interplays, herb–drug–disease interactions, integrative medicine

Introduction

Modern system of medicine has emerged as the primary choice for the treatment of nearly all types of health-related issues, although, it is mainly based on the nonholistic/bug killing/target-based approach, which ultimately leads to future side effects (notable in case of chronic disorders such as cancer, diabetes, arthritis, etc).[1–3] However, patients with such chronic illnesses directly/indirectly undergo combinational/multimodal therapy with or without the knowledge of physicians, leading to potential herb–drug interactions (HDIs).[1] The MD Anderson Cancer Centre, in USA, reported that 52% of their cancer patients had used at least one form of complementary and alternative medicine (CAM), and 77% of those were using herbs.[4] While, according to the World Health Organization (WHO) and other reviews >80% world's population uses CAM for their health care needs and particularly in western countries CAM has become increasingly popular over the last few decades.[5–8] However, concomitant usage of herbs and conventional medicines globally could be much higher as healthcare professionals often do not ask about herbal remedies when prescribing and patients do not volunteer that they are taking them.[1,9–11] Indeed, such a scenario of concomitant usage of herbs/CAM and conventional medicines brings with it the potential problem of HDIs and this issue has emerged as a major hurdle/problem in our journey toward integrative medicine (IM).[1,12,13] IM refers to the blending of conventional and evidence-based complementary medicines and therapies with the aim of using the most appropriate of either or both modalities for efficient patient care.[14] In short, IM uses all appropriate, evidence-based therapies to achieve health.[15] For example, *Withania somnifera*, have been widely accepted as a novel complementary therapy for integrative oncology care.[16] *W somnifera* not only helps in controlling the tumor growth but also exerts antioxidant, anti-inflammatory, immunemodulating, and antistress properties that help in combating the cancer and associated complications. It has also been found that, *W somnifera* enhances the effectiveness of radiation therapy and chemotherapy while potentially mitigating their undesirable side effects.[16–18] Similar experiences were also observed by Patil et al and Borse et al for *Asparagus racemosus* and/or *Tinospora cordifolia accepted as novel complementary therapy for integrative oncology care*.[18–22] IM/care practices are getting increased day by day throughout the world. For instance, IM is being practiced at BSDT's Ayurvedic Hospital & Research Centre, India, The Osher Center for Integrative Medicine, Arizona Center for Integrative Medicine, and many other places in the world.[23–26] However, integrative management of the disease is far bigger challenge in spite of high scientific efforts proceeding globally mainly because of the potential risk associated with HDIs.[27–33] Hence, the focus needs to be shifted on potential interactions between herbs and pharmaceuticals because of the growing popularity of herbal medicines/CAM. Here, it must be highlighted that the probability of HDIs can be much higher than drug–drug interactions, since most herbal medicines (even single-herb products) contain mixtures of pharmacologically active

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constituents compared to conventional/modern medicines.[1,34] These HDIs could be beneficial or harmful, or even fatal; therefore, a thorough understanding of the eventualities of HDIs is essential so that a successful integration of the modern and complementary alternative systems of medicine could be achieved. Here, in the present review, we summarize all the important points related to HDIs, including types, tools/methods for study, and prediction of the HDI, along with a special focus on interplays between drug metabolizing enzymes (DMEs) and transporters. The interplays between 2 or more things may affect the functioning of each other. Indeed, interplay between DMEs and transporters hold potential to not only alter the pharmacokinetics (PK)–pharmacodynamics (PD) of herb/drug but also their safety profile. In this context, this article also covers future perspective, with a focus on background endogenous players of interplays and approaches to predict the drug–disease–herb interactions so as to fetch the desired effects of these interactions.

Methodology

Both online and offline literature searches were carried out to compile this review. We searched Medline, PubMed, the Cochrane library, ResearchGate, and Google Scholar, for mainly original research articles published between 1970 and 2017 for HDIs studies with focus on role of interplays in it. The main search terms which were used alone or in combination with each other includes but may not be limited to HDI, phytopharmaceuticals–drug–metabolite interactions, drug–herb–disease–metabolite–phytochemical interactions, types, mechanism, tools and techniques, databases, novel approaches, integrative approaches, regulatory guidelines or requirements, mechanistic PK–PD interactions, substrate overlap, enzyme–transporter interplays, cytokines–hormones–neurotransmitter–enzymes–transporter (CHNET) interplays, personalized medicine, and IM, We identified full-text articles without imposing any language restrictions. Reference lists of original studies, narrative reviews, and previous systematic reviews and meta-analyses were also searched carefully. Letters were sent to experts in the field requesting additional information on ongoing or unpublished data. Conference proceedings, dissertation abstracts, and reference lists from included and relevant articles were also searched.

Herb–drug interactions?

It has become clear that both conventional and herbal medicines are often used concomitantly[35–37] and this can lead to clinically relevant HDIs.[38] The HDI can be seen commonly and these may be beneficial, harmful, or even fatal. Usually the HDI either causes some beneficial or unsuspecting effects. The latter may turn into adverse effects, which may be fatal.[39] A systematic approach is required for minimizing the untoward consequences and to reap out the potential benefits of these interactions.

Mechanisms of HDIs

Indeed, a single herb contains multiple phytoconstituents that may be biologically active and capable of modulating physiological actions, similar to therapeutic drugs, through complex synergistic and/or antagonistic effects.[39] HDIs are mediated by pharmacodynamic and/or pharmacokinetic mechanisms. Pharmacokinetic interactions are much more difficult to anticipate than pharmacodynamic interactions.[40,41] Most commonly reported HDIs are pharmacokinetic interactions, especially those resulting from the functional modulation of DMEs mainly cytochromes (CYPs); drug transporters such as P-gp; and protein binding. While, pharmacodynamic interaction involves antagonism, addition/summation, synergism, and even sometimes modulation of drug targets. However, there could be some other type of interactions, that is, multiple/complex HDIs which may lead to pharmacokinetic as well as pharmacodynamic interactions and may or may not be mediated through interplays involving alteration of CHNET.[41–43]Figure 1 gives the overview of HDIs, and Figure 2 describes the mechanisms of HDIs.

Pharmacokinetic HDIs. Pharmacokinetic HDIs may occur at any step of absorption, distribution, metabolism, and excretion (ADME), which have been explained section wise. Table 1 covers some representative examples.

Absorption interactions. Any herb which affects the normal gastrointestinal tract environment will be responsible for the changes in the expected absorption pattern of the drug and will lead to HDI (see Fig. 1 absorption box). For example, any herbal laxative or bulk-forming agent will speed up the intestinal transit, and thus may interfere with the intestinal absorption. The most popular laxative herbs are anthranoid-containing herbs such as senna (*Cassia senna* and *C angustifolia*) and cascara sagrada (*Rhamnus purshiana*).[43,85] In addition, in the presence of the drugs belonging to the class of antacids, systemic antiulcer agents, which will increase the pH of stomach, the absorption of weak acidic herbal extracts/formulations may get affected and vice versa.[43,85]

Distribution interactions. These interactions may occur with drugs having higher plasma protein-binding property (>95%), less Vd (volume of distribution), and narrow therapeutic window (NTW).[86] For instance, warfarin a well known anticoagulant remains 98% plasma protein bound with less Vd of 0.11 to 0.18 L/kg and NTW of 1 to 2 which varies with respect to polymorphism of cytochrome P450 (CYP450) enzymes.[30,87,88] Some known examples of agents that interact with warfarin include vitamin K, some types of tea and green leafy vegetables. *Agrimonia eupatoria* has been reported to interfere with the efficacy of anticoagulants.[89] These agents interact with warfarin by either increasing or decreasing its effectiveness and thus, leading to prolonged bleeding or increasing the risk of blood clotting, respectively.[90–92] Hence, patients on warfarin need to be extremely cautious while taking herbs concomitantly as HDIs pose immense risk which could be even fatal. For instance, PK–PD of warfarin in healthy subjects is insignificantly affected at recommended doses of ginkgo and ginger.[91] Echinacea, significantly reduces plasma concentrations of S-warfarin.[93] St John's wort decreases the anticoagulant effect of warfarin,[90] whereas *Allium sativum* increases the bleeding risk.[90]

Metabolism interactions. Metabolism is the biochemical modification of xenobiotics by living organisms, usually through specialized enzymatic systems to eliminate the same.[94] The rate of metabolism determines the duration and intensity of a drug's pharmacological action. A large number of phytochemicals that gain access to the systemic circulation tend to be lipophilic, and consequently are difficult to excrete; thus, the body renders them hydrophilic through metabolism to facilitate their excretion.[95] This is done in 2 phases, phase I involves CYP450 isoenzyme system, which oxidizes, reduces, or hydrolyzes the drug/xenobiotic, whereas phase II involves conjugation reactions such

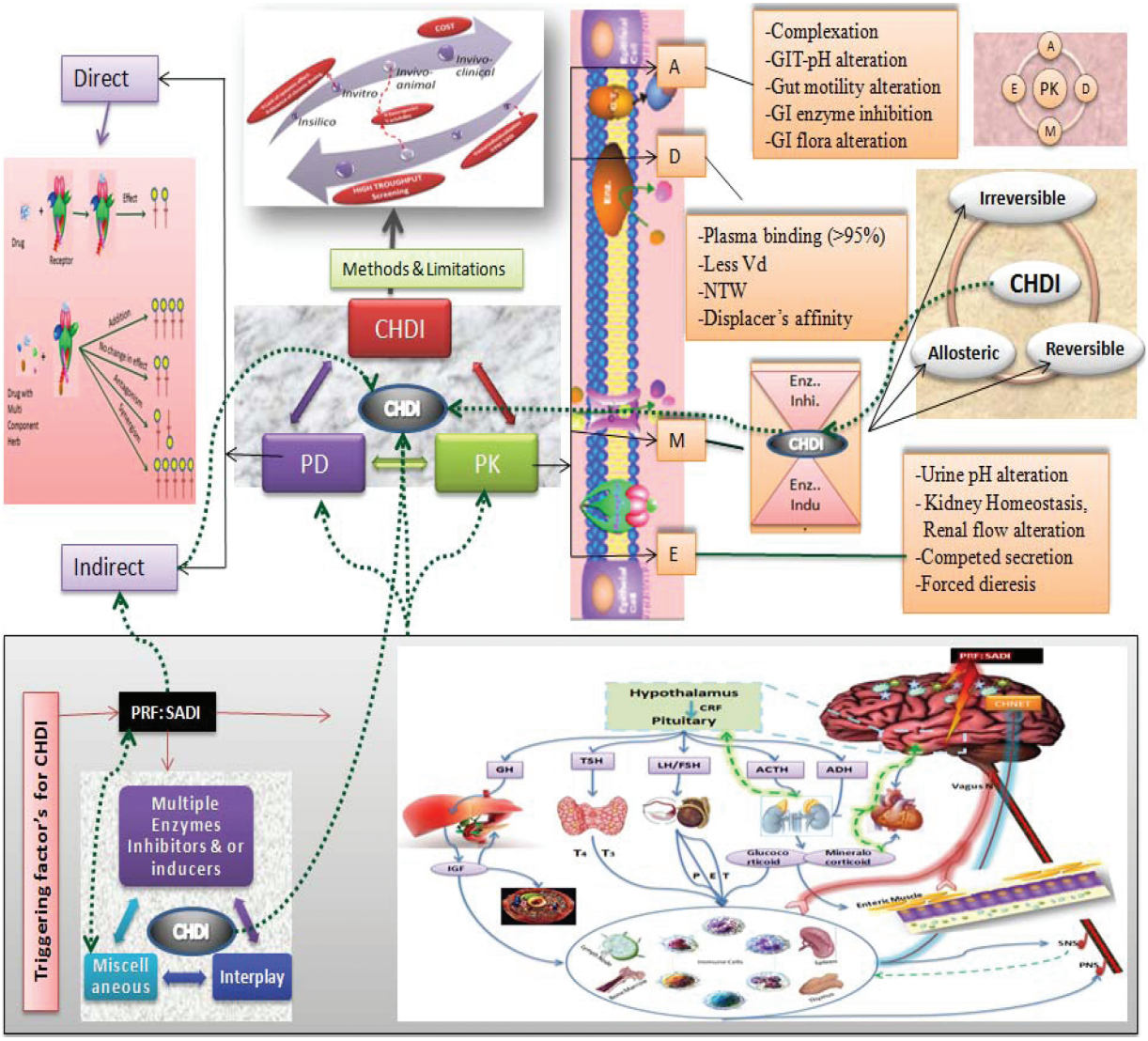

Figure 1. Overview of herb-drug interaction: herb-drug interactions (HDI) have direct and/or indirect effect on pharmacokinetics (PK)-pharmacodynamics (PD) of drug and/or herb which may lead to complex HDI (CHDI). Type and intensity of HDI depends upon the properties of the herb and drug under consideration along with indirect role of PRF:SADI (Patient-related factors: sex, age, disease/disorder, and individualization). Note: Straight line indicates main types and/or main effect, whereas dotted line indicates background interaction/effect. GIT = gastrointestinal tract, NTW = narrow therapeutic window.

as glucuronidation, acetylation, and sulfation reactions that increase water solubility of drug with a polar moiety glucuronate, acetate, and sulfate, respectively.[96]Table 2 covers important metabolizing enzymes with their functional role.[97] Many DMEs shows polymorphic nature and intensity of the same varies with respect to patient-related factors: sex, age, disease/disorder, and individualization (PRF:SADI).[101] Phytochemicals/xenobiotics can modulate the hepatic and extrahepatic expression of DMEs resulting in marked changes in the metabolism of drugs that leads to HDIs.[95,102] Considering these facts Food and Drug Administration (USFDA) asks for the data of drug interactions.[103] The significance of the individual CYP enzyme in human drug metabolism varies, with CYP3A, CYP2D, and CYP2C being responsible for the metabolism of 50%, 25%, and 20%, respectively, of most of the pharmaceuticals/xenobiotics.[102] Herbal ingredients can alter metabolizing enzymes through induction and/or inhibition.[104] Induction of CYPs by herbal products usually requires several days; however, induction of the enzyme(s) may lead to decreased drug plasma levels (through increased drug metabolism), and subsequently to reduced drug effects.[38,95,105] Conversely, the inhibition of CYPs is often immediate and may lead to increased drug plasma levels (through decreased drug metabolism), resulting in an enhanced drug effect, that may result in significant adverse reactions or toxicities.[95,105,106] In case of prodrugs, opposite may happen, for both induction and inhibition.[95,105] Many clinical adverse events have been reported to be associated with CYP-mediated HDIs.[107,108] Metabolic pharmacokinetic HDIs occur by various mechanisms (Fig. 3).

Mutual competitive inhibition may occur between herbal constituent and a drug, as both are often metabolized by the same CYP isoform. For example, diallyl sulfide from garlic is a competitive inhibitor of CYP2E1.[108] Noncompetitive inhibition is caused by the binding of herbal constituents containing electrophilic groups (eg, imidazole or hydrazine group) to the heme portion of CYPs. For example, piperine inhibits CYP1A

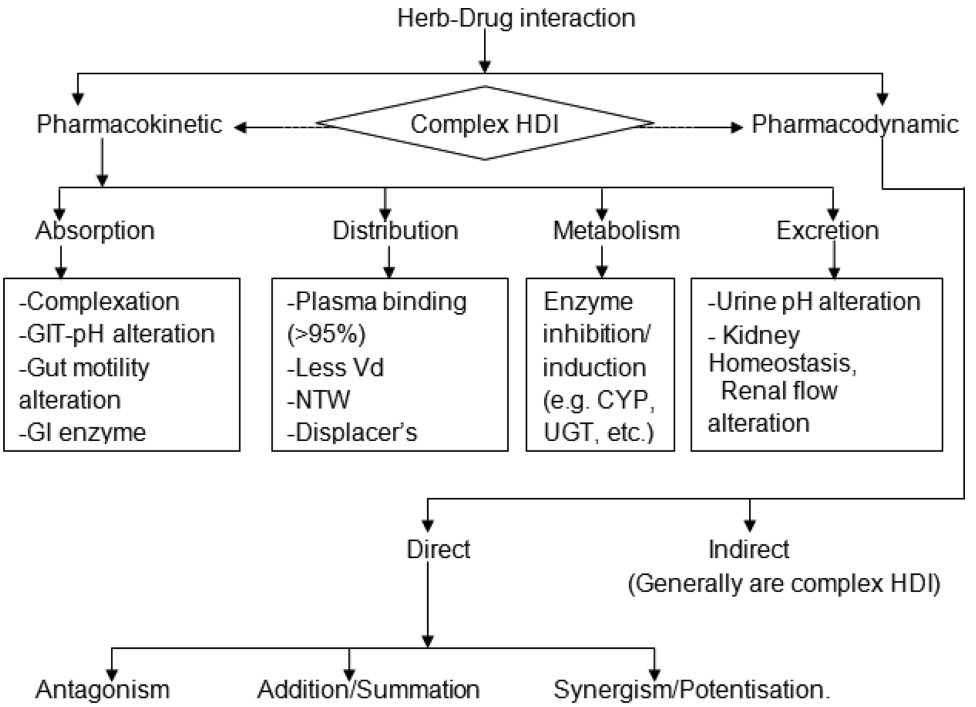

Figure 2. Mechanism of herb-drug interactions. CYP = cytochrome, GIT = gastrointestinal tract, Vd = volume of distribution, UGT = UDP-glucuronosyltransferase.

Table 1

Pharmacokinetic–pharmacodynamic HDIs

Pharmacokinetic HDI Sr. No.	Herb	Process and/or protein involved	Significance	Ref
1.	*Hypericum perforatum* (St John's wort)	Absorption: Increases expression of efflux protein (P-gp)/MDRI. And also CYP3A2 and CYP2A4	Reduces the plasma levels of coadministered cyclosporine, amitriptyline, digoxin, indinavir, nevirapine, oral contraceptives, warfarin, phenprocoumon, theophylline, or simvastatin	44,45
2.		Metabolism: induction of CYP1A1,1A2, 3A4, and P-gp	Decreases bioavailability (by altering metabolism) of digoxin, theophylline, cyclosporin, and phenprocoumon	10,45
3.	*Plantago ovata*	Absorption: high mucilage alters absorption	Plant decreases absorption of carbamazepine in healthy volunteers	46
4.	*Rheum palmatum*	Absorption: alters GI motility and diarrhea	Decreases absorption of digoxin	46,47
5.	*Sophora flavescens*	Metabolism: increased CYP3A1 genomic expression and induces hepatic and intestinal Pgp which leads to AUC and CL/F And these results were not observed in the ethyl acetate fraction of	Concomitant oral administration of sophora extract resulted in a dose-dependent decrease of plasma indinavir concentrations, with 55%–83% decrease in AUC0-∞ and 38%–78% reduction in Cmax. The CL (clearance)/F (fraction of dose available in the systemic circulation) increased up to 7.4-fold in *Sophora*-treated rats.	48
6.	*Salvia miltiorrhiza*	Distribution: interfere with warfarin protein binding	Moderately inhibits warfarin action.	49
7.	*Hypericum perforatum, Glycine max Merr, Camellia sinensis, Echinacea purpurea*	Metabolism: inhibit the drug metabolizing enzymes through which the warfarin get metabolized	Inhibit the action of Warfarin	10,50
8.	*Vaccinium macrocarpon, Angelica sinensis, Matricaria recutita, Harpagophytum procumbens,Trifolium pretense*	Metabolism: Induces the drug metabolizing enzymes through which the warfarin get metabolized	Potentiate the action of warfarin	
9.	*Hypericum perforatum*	Metabolism: induction of CYP1A1,1A2, 3A4, and P-gp	Increases metabolism of theophylline and cylcosporine	
10.	*Pueraria lobata*	Elimination: MRP inhibition or substrate for OATP	Decreases elimination of methotrexate	51
11.	*Glycyrrhiza uralensis*	Elimination: BCRP and MRP inhibition; substrate for OATP		

(*continued*)

Table 1

(continued).

Sr. No.	Herb	Process and/or protein involved	Significance	Ref
Pharmacokinetic HDI				
12.	*Piper nigrum linn*	Metabolism: Inhibition of CYP1A1, CYP1A2, and CYP2D6	Increases the oral absorption of theophylline, phenytoin, and propranolol, and slows down elimination of later 2	52
13.	Grape fruit juice	Absorption: P-gp inhibition	Increases the bioavailability of Ca-channel blocker felodipine and may other drugs including antihistaminics, anitpsycotics, and statins.	53–55
14.			Inhibition of vinblastine efflux when given grape fruit juice in Coca-2	53,55
15.	Angelica (*Angelica dahurica*)	Metabolism and clearance: risky	Xanthotoxin; osthol; bergapten present in plant along with other constituents interact with tolbutamide: prolonged half-life and reduced the clearance	56
16.	Garlic	Metabolism: risky	Decrease the plasma concentrations of saquinavir, but not ritonavir	10,57–59
17.	*Shankhpushpi (Ayurvedic fomulatioon)*	Metabolism- (PK–PD): Risky	On multiple doses co-administration of *Shankhpushpi* not only reduced the antiepileptic activity of phenytoin but also lowered plasma concentration. *Shankhpushpi* itself shows antiepileptic activity compared to placebo and is worth further investigation.	10,60
Pharmacodynamic HDIs				
18.	coffee and tea; xanthines	Additive:	Could counteract the action of sedatives or produce excessive stimulation with stimulant drugs	61,62
19.	Ma Huang; ephedrine-like alkaloids	Additive: MAO	Increase the actions of MAOI and adrenergic agonists such as clonidine, and decrease the actions of bethanidine and guanethidine	63
20.	Garlic, ginkgo, ginger, and ginseng	Additive	Potentiate the effect of warfarin, resulting in longer bleeding time	10,64
21.	*Hypericum perforatum*	Absorption: Increases expression of efflux protein (P-gp)	When combined with oral contraceptives, loperamide, or it caused intermenstrual bleeding, delirium, etc	50
22.		Absorption: risky/harmful	Drug absorption by cell membrane will decreased/ inhibited and may lead to serotonergic syndrome in the elderly	65–68
23.		Antagonism: risky	Decreases anticoagulant activity of warfarin	69
24.	*Gymnema sylvestre (Gurmur)*	Additive	Reduces carbohydrate absorption in GIT hence insulin requirement.	70,71
25.	Arecoline	Antagonism	Reduces the effect of antiparkinsonism drugs such as flupenthixol, phenothiazine, and anticholinargics such as procyclidine	52
26.	Soya milk	Potentiasaton: indirect/complex HDI	When given with warfarin INR decrease by 69.56%	72
27.	Cranberry	Potentiasaton: indirect/complex HDI	Increases area under the INR–time curve by 30% when administered with warfarin when compared with warfarin alone. Cranberry did not alter S- or R-warfarin pharmacokinetics or plasma protein binding	73
28.	*Piper methysticum*	Antagonism:	Interact with L-dopa by dopamine antagonism	10
29.	*Piper nigrum* or *Piper longum* or *Zingiber officinale*	Antagonism:	Phytoconstituent Trikatu interacts with diclofenac and decrease its bioavailability and anti-inflammatory actions	10
30.	*Glycyrrhiza glabra*	No change	No change in sedative effect of midazolam	10
31.	*Allium sativum*	Synergistic: risky	Enhances anticoagulant effect of warfarin and fluindione	74
32.		Additive: beneficial	Increases in antidiabetic effect of chlorpropamide	39,75
33.	*Ginkgo biloba*	Synergistic: beneficial	Increases efficiency of haloperidol	39,76,77
34.			Raised blood pressure when combined with a thiazide diuretic and coma when combined with trazodone	
35.		Synergistic: risky/harmful	Ginkgo inhibits platelet aggregation: increases prothrombin time, partial thromboplastin time, when given with warfarin in patient having cardiovascular disorder and produces left parietal hemorrhage	78
36.	*Piper methysticum* (Kava)	Direct: modulate level of neurotransmitters and neurotransmission	Resulted in coma when used with alprazolam	79
37.	*Panax quinquefolius* (Ginseng)	Direct: modulate level of neurotransmitters and neurotransmission	Induced mania when used concomitantly with phenelzine	80,81
38.	*Salvia miltiorrhiza*	Additive: risky/harmful	Increased INR* gives additive anticoagulation effect due to coumarin content in danshen	10,82,83
39.	Curry containing *Allium sativum*, (garlic) and *Momordica charantia* (Karela),	Synergistic: risky/harmful	Along with chlorpropamide therapy enhances hypoglycemic response	84

BCRP = breast cancer resistance protein, MAO = monoamino oxidase, MAOI = monoamino oxidase inhibitor, GIT = gastrointestinal tract, HDI = herb drug interaction, INR = international normalized ratio (related to blood clotting time), OATP = organic anion transporting polypeptide, PD = pharmacodynamics, PK = pharmacokinetics.

Table 2

Main enzymes/proteins involved in HDIs (Data obtained from[98–100])

Sr No	Tth No	Target; (synonyms)	Target information			PDB structure's
			Biochemical class	Drugs approved.	Function	
1.	R01445	CP450 2A5 (Cyp2a5, CP450-15-COH, CP450-IIA3.2)	Hydroxylase		Exhibits a high coumarin 7-hydroxylase activity	2HI4
2.	R01443	CYP2A6 (CYP2A3, coumarin 7-hydroxylase)	Hydroxylase		As above and can act in the hydroxylation of the anticancer drugs cyclophosphamide and ifosphamide. Competent in the metabolic activation of aflatoxin B1. Constitutes the major nicotine C-oxidase. Possesses low phenacetin O-deethylation activity	
3.	R00242	CYP1B1	Oxidoreductases acting on paired donors		CYP1B1 are a group of heme-thiolate monooxygenases. In liver microsomes, this enzyme is involved in an NADPH-dependent electron transport pathway. It oxidizes a variety of structurally unrelated compounds, including steroids and fatty acids.	
4.	R01442	CYP450 2B2 (CP450 PB4, CP450E)			Same as 4; R00242	
5.	R01444	CYP2B6			Same as above, ie, 4; R00242	
6.	S00475	Cytochrome P450 2D6 (CYP2D6, CYP2DL1, CYPIID6, debrisoquine 4-hydroxylase, P450-DB1)	Oxidoreductases acting on paired donors	A: Glutethimide (for insomnia)	Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants.	2F9Q
7.	S00418	CYP3A4; albendazole monooxygenase/sulfoxidase, CYP3A3, HLp, NF-25, nifedipine oxidase, P450-PCN1	Oxidoreductases acting on paired donors	A: Clotrimazole (for fungal disease)		1TQN; 1W0E; 1W0F; 1W0G; 2J0D; 2V0M
8.		CYP 2C9				1R9O, 1OG2
9.		CP450 19 (aromatase, P-450AROM)	Oxidoreductases acting on paired donors	A: Anastrozole, exemestane letrozole, ttestolactone aminoglutethimide (for cancer)	Catalyzes the formation of aromatic c18 estrogens from c19 androgens.	1TQA; 3EQM
10.	R00561	UGT	Glycosyltransferases		Udpgt is of major importance in the conjugation and subsequent elimination of potentially toxic xenobiotics and endogenous compounds.	2O6L
11.		SLUTs	Sulfotransferases		Known to catalyze the sulfate conjugation	1T8U, 1AQU, 3ETS

A = approved, CYP450 = cytochrome P450, PDB = Protein Data Bank, TTD = Therapeutic Target Database, UGT = UDP-glucuronosyltransferase important phase-II enzyme.

and CYP2A by noncompetitive mechanism.[109] Hyperforin present in St John's wort is also a potent noncompetitive inhibitor of CYP2D6.[110] The mechanism-based inhibition of CYP is due to the formation of a complex between herbal metabolite with CYP under consideration. For example, diallyl sulfone derived from diallyl sulfide is a suicide inhibitor of CYP2E1 by forming a complex via an epoxide metabolite,[111] leading to autocatalytic destruction of CYP2E1.[112] Therefore, the drugs that get metabolized by CYP2E1 are needed to be taken/monitored cautiously while concomitant administration with garlic.[112,113]

It is evident that, the formation of reactive metabolite of drug/xenobiotic is associated with toxicity.[113] Toxicity mediated by herbal metabolites mostly happens *via* multiple pathways such as cytotoxicity, oncogene activation, and hypersensitivity reactions.[113] For instance, CYP1A1/2-mediated bioactivation of aristolochic acid present in *Aristolochia* spp. produces nitrenium ion that activates H-ras oncogene and finally results in carcinogenesis.[114] Similarly, Germander (*Teucrium chamaedrys*), which is a folk medicine was used as antiseptic and adjuvant to slim diet.[114] In 1991 Germander has been found to be hepatotoxic and fatal.[115] The furan ring of diterpenoids present in the Germander gets metabolized by CYP3A4 to form reactive epoxide radicals.[114] These epoxide radicals react with CYP3A and epoxide hydroxylase which, further causes mitochondrial permeability transition, caspase activation, and apoptosis of hepatocytes.[114,115]

Elimination interactions. The sources of drug elimination from the body are urine, feces, sweat, tears, semen, menstrual discharge, etc. The main players in drug or xenobiotic elimination are cell transporter protein/enzymes such as P-gp, organic anion transporting polypeptide (OATP), organic anion transporter, OCTP, breast cancer resistance protein, and others in this process. However, these may get affected by concomitant administration of herb and drug resulting in HDIs.[43] Furthermore, some herbs are known diuretic, which can affect the excretion of medicinal drugs.[116] The nephrotoxic drug induces kidney damage resulting in slow rate of elimination leading to an accumulation of herbs and drugs in the body. Important examples of drugs that damage the kidneys include gentamicin, amphotericin B, methotrexate, and tobramycin. Hence, a close monitoring is required to avoid the unwanted HDIs. Furthermore, in case of elimination interactions the role of transporters needs to be focused as transporters govern the transport of xenobiotics in and out of the cells.

Although less well-recognized than DMEs, membrane transporters can have important effects on PK–PD of the drugs/herbs. However, in contrast to DMEs, which are largely concentrated in the liver and intestine, transporters are present with varying abundance in all tissues in the body and play an important role in drug absorption, distribution, tissue-specific drug targeting, and elimination (Fig. 4).[10,101,117]

A number of transporter-based interactions have been documented in recent years.[118–120] To date, most of the identified

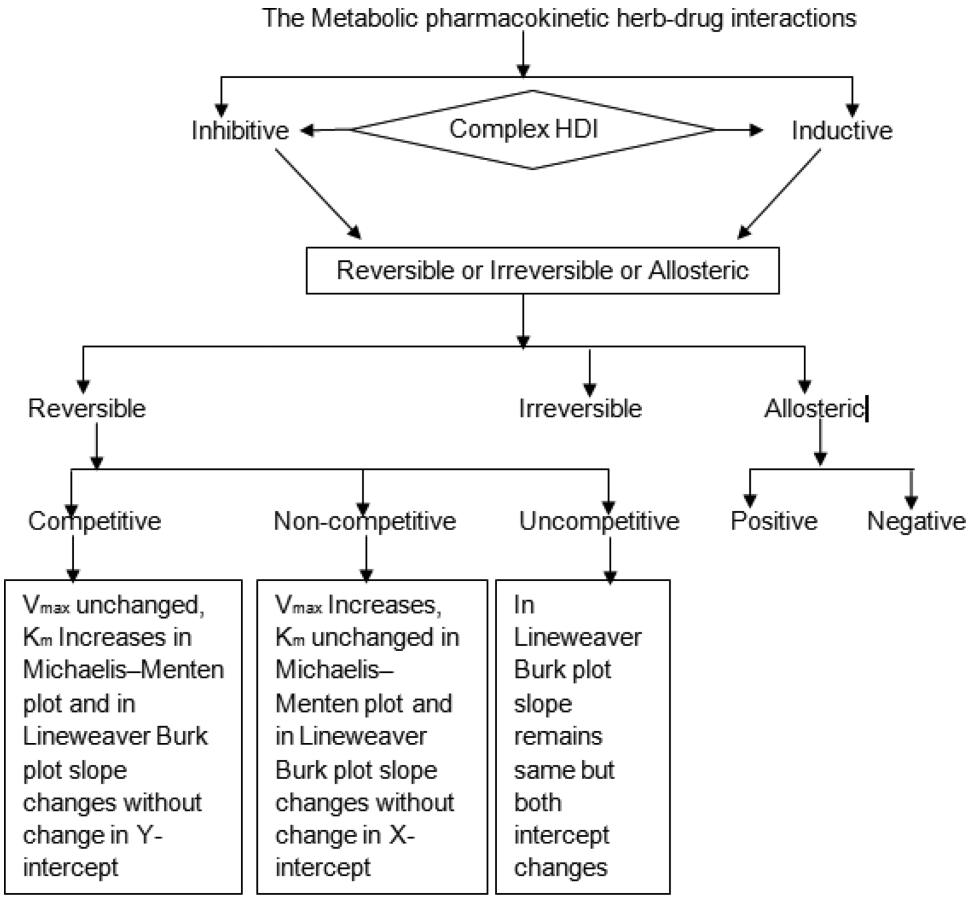

Figure 3. The metabolic pharmacokinetic herb-drug interactions. V_{max} = maximum reaction velocity in enzyme kinetics, K_m = the substrate concentration required to produce half V_{max} in enzyme kinetics.

transporters belong to 1 of the 2 super families: ATP-binding cassette, that is, P-gp and solute carrier. Transporters and DMEs show substrate specific interplay (due to substrate overlapping) and may affect each other's functional efficacy. P-gp is a plasma membrane–bound drug efflux protein found primarily in drug-eliminating organs and presumably functions as a detoxifying transporter,[121] because, P-gp actively extrudes xenobiotics from the body.[121,122] In the small intestine, P-gp is localized to the apical membrane of the intestinal epithelial cells, having a role of effluxing the compounds back into the intestinal lumen.[122] Pharmacokinetic studies of paclitaxel, and digoxin, in mdr1a knockout mice have revealed the importance of intestinal P-gp in limiting the oral bioavailability of these drugs.[123] Phytochemicals are also known to interact with the ATP-dependent transporter proteins such as the intestinal P-gp and other multidrug resistance proteins that facilitate the efflux of the drugs.[124–126] It has been shown that various drugs (eg, quinidine, verapamil, and itraconazole) increase plasma levels of digoxin by inhibiting

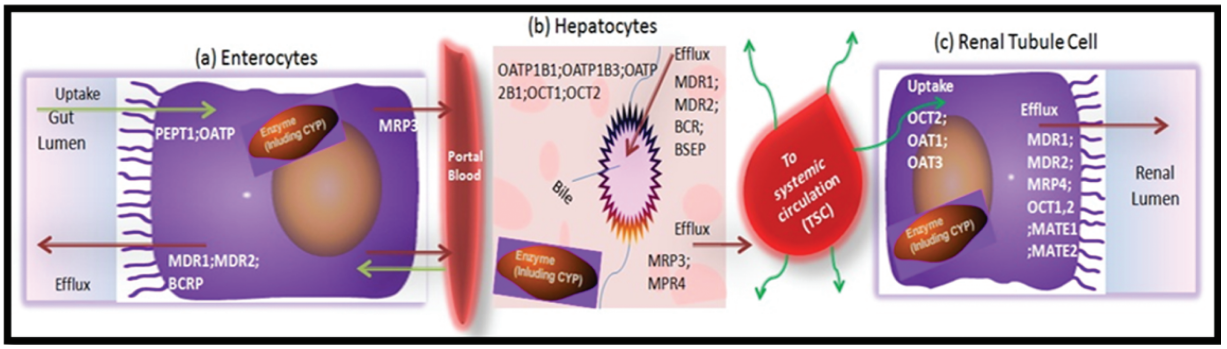

Figure 4. Illustration of examples of efflux and uptake transporters in the gut wall (A), liver (B), and kidneys (C) that may be involved in a drug's absorption, distribution, metabolism, and excretion. BCRP = breast cancer resistance protein, , MATE = multidrug and toxic compound extrusion protein, MDR1 = multidrug resistance 1(P-glycoprotein (P-gp)), MRP = multidrug resistance associated protein, OAT = organic anion transporter, OATP = organic anion transporting polypeptide, OCT = organic cation transporter,PEPT1 = peptide transporter 1.

the efflux transporter P-gp at the intestinal level. Plasma levels of many β-Hydroxy β-methylglutaryl-CoA reductase inhibitors including rosuvastatin, pravastatin, and pitavastatin, are increased by co-administration of inhibitors of hepatic uptake transporters (eg, OATP1B1), such as cyclosporine, rifampin, and flavonoids (a commonly found herbal constituents, such as quercetin, curcumin, etc) are competitive inhibitor of OATP1B1/1B3.[127] In this purview, Tucker et al[42] has discussed various key points to improve the ability to predict HDIs at the transporter level.

Multiple/complex HDIs: importance of interplay(s) in context to HDIs. The HDIs related to ADME and transporters have been discussed separately, but, in some cases drug interactions may occur by combination of these mechanisms called multiple/complex HDI and such scenarios include but are not limited to[102]:

(1) Concurrent inhibition and induction of 1 enzyme or concurrent inhibition of enzyme and transporter by a drug and/or herb
(2) Increased inhibition of drug elimination by the use of more than 1 inhibitor of the same enzyme that metabolizes the drug and/or herb
(3) Increased inhibition of drug elimination by use of inhibitors of more than 1 enzyme that metabolizes the drug and/or herb
(4) Inhibition by a drug and its metabolite(s), both of which inhibit the enzyme that metabolizes the substrate drug and/or herb
(5) Inhibition of an enzyme other than the genetic polymorphic enzyme in poor metabolizers taking substrate that is metabolized by both enzymes
(6) Use of enzyme/transporter inhibitors in subjects with varying degrees of impairment of xenobiotics eliminating organs (eg, liver or kidney).

However, when multiple mechanisms are involved in HDIs then interplays may happen. In general, as interplays increase, complexity of HDIs is also increased. Figure 5 explains the different ways of multiple/complex HDIs. The size of the quadrant reflects its probable contribution in it.

Interplay is said to happen when 2 or more things have an effect on each other. As discussed above there are many factors that affect ADME of drug leading/contributing to HDIs. When these confounding factors and/or players of ADME affect each other and/or show substrate overlapping this leads to interplay. The most studied and common interplays are enzyme-transporter interplay(s).

DMEs-transporter interplays

In early 1900 the concept of interplay started to fertilize in the laboratory of University of California, San Francisco resulting from the efforts by Benet and his coworkers.[128] Benet and his coworkers first studied the effects of a high-fat meal on cyclosporine pharmacokinetics in healthy subjects,[128] which led them to believe that the unusual effects resulting from a high-fat meal, that is, no change in the absorption rate but a significant increase in the extent of absorption[128,129] and an increase in the clearance of cyclosporine,[130] could be explained by a lipid effect in the liver.[131] They were first to note and publish the striking overlap of substrate specificity and the tissue distribution for CYP3A and Pgp. They proposed that CYP3A and P-gp played complementary roles in ADME of the drug by biotransformation and counter transport, particularly in the villi of the small intestine. Shortly following publication of this coordinated protective mechanism,[132] Schuetz et al[133] demonstrated that modulators and substrates of P-gp and CYP3A coordinately upregulated these proteins in human colon carcinoma cells and that P-gp was a major determinant of rifampicin-inducible expression of CYP3A in mice and humans.[134] Similar studies to those described above for cyclosporine were also reported for tacrolimus and sirolimus.[135–137] Herbal medicines are often administered orally and they can attain moderate to high concentrations in the gut lumen (the primary site of absorption for most orally administered drugs) and liver, and may exert a significant effect on enterocytes and hepatocytes. Both P-gp and CYP3A4 are abundantly expressed in the villus tip of enterocytes and hepatocytes. The interplay of both intestinal P-gp and CYP3A4 has a strong effect on the bioavailability of most orally administered drugs including cyclosporine, midazolam, talinolol, statins, HIV protease inhibitors, and verapamil.[138] Many studies have suggested that both CYP3A4 and P-gp have cosubstrates

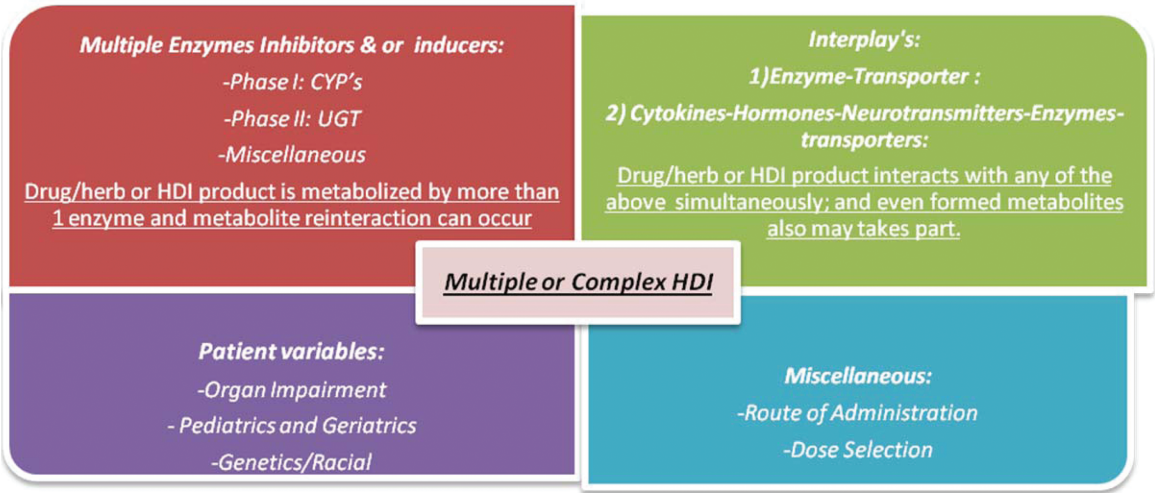

Figure 5. Multiple or complex HDIs: size of the quadrant reflects its probable contribution in it. CYP = cytochrome, HDI = herb-drug interaction, UGT = UDP-glucuronosyltransferase.

and the drugs which interact with apical efflux pump P-gp may enhance CYP3A4 mediated disappearance of substrates during intestinal secretory detoxification.[139,140] As well as P-gp possibly influences first-pass metabolism in a co-operative manner.[141] Thus, the modulation of intestinal and hepatic P-gp and CYP3A4 by herbal medicines represents a potentially important mechanism by which the bioavailability of coadministered drug(s) can be modulated.[142] Time-dependant HDIs mainly depend on the primary metabolite formed, which generally interacts with the same parent metabolizing enzyme and leads to its inhibition or induction which is time dependant and/or concentration dependant and ultimately responsible for complex HDIs (Fig. 4).[34,143] On the contrary, their evidence in support of interplay between CYP3A4 and P-gp mainly comes from limited in vitro and preclinical studies, which generally gets extrapolated for humans.[140] These PK interactions may alter the pharmacodynamic responses. In addition, there could be cases in which, cytokine, hormone, neurotransmitter, enzyme, and transporters all interact and lead to complex interplays, which may result in potential HDIs.

Cytokine–hormone–neurotransmitter–enzyme–transporter interplay(s)

The interplay between endogenous molecules such as cytokines, hormones, neurotransmitter, enzymes, etc is important to maintain the normal homeostasis through feedback loops and healthy condition.[144,145] This interplay indirectly affects the functional ability of the DMEs and transporters too.[146] In diseased state this interplay gets altered and these defects lead to alteration in the entire CHNET interplay and sometimes affecting PK–PD of the administered drugs. (Figs. 6 and 7).[144–157] The CHNET interplay is very difficult to study and use as compared to simply DMEs-transporters interplay (Figs. 6 and 7).

Shapiro LE and Shear NH have reviewed that, apart from posological factors, polypharmacy, and organ dysfunction, pharmacogenetic risk factors and/or individualization also affects HDIs.[158] In the maintenance of normal body physiological condition, the CHNET has central role and in diseased/unhealthy condition these gets altered which changes not only

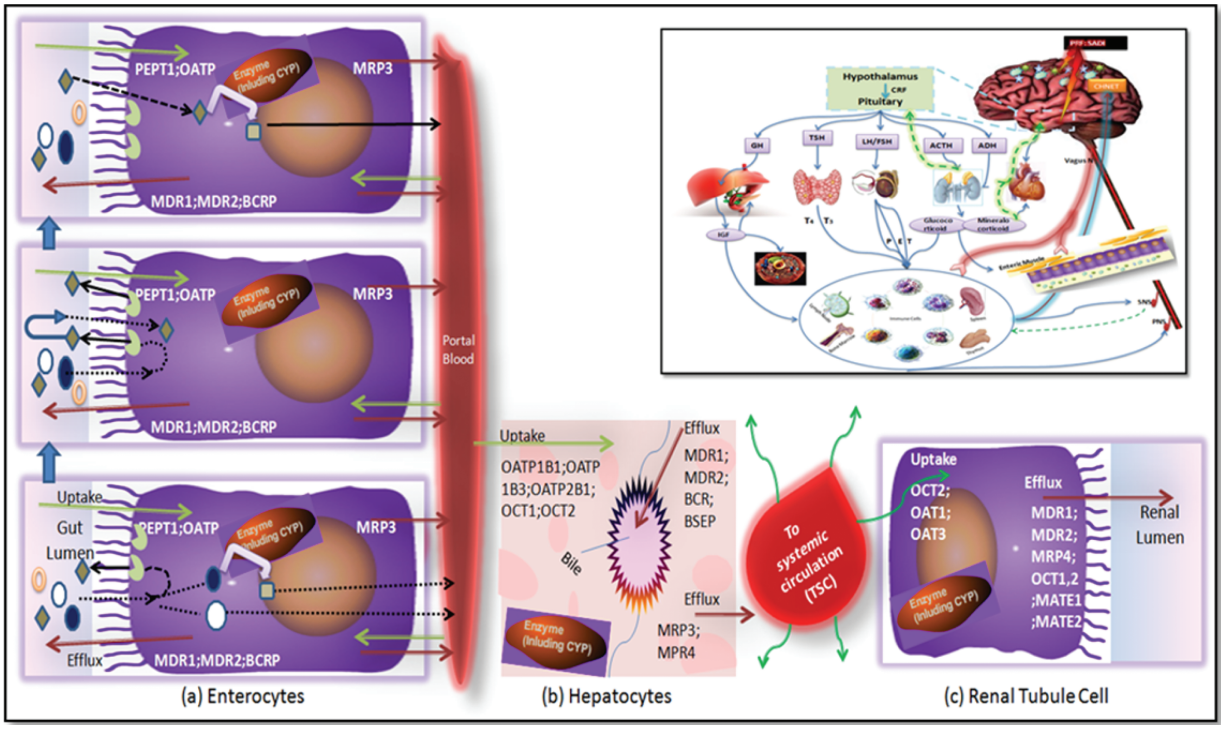

Figure 6. Interplays: (A) CYP3A4 and P-glycoprotein interplay in the enterocytes, (B) hepatocytes, (C) renal tubule cell and the embedded small square contains PRF: SADI (Patient related factors: sex, age, disease/disorder, individualization) which are responsible for alteration in normal physiological balance as a result of imbalanced level of CHNET, which finally responsible for altered pharmacokinetics (PK)-pharmacodynamics (PD) of single drug and even occurrence of Adverse Drug Event/Adverse Drug Reaction (ADE/ADR) and/or suspected unsuspected serious adverse reaction (SUSAR) resulting from DI/herb-drug interaction (HDI). For instance in diabetes the expression of CYP2C11 is decreased, and CYP2E1 increases which might have been triggered or done by altered level of insulin and other hormones as well as altered normal body physiology and hence owing this all the HDI or DI occurs which might be beneficial/harmful/or even fatal. Figure A explains conception of the interaction between CYP3A and P-glycoprotein in the intestine. Three drug molecules are depicted (○ ◆ ●). They are all the same drug and only differentiated by their outcome. Drug is absorbed by passive processes into the enterocytes where it may be metabolized by the enzyme. However, the drug is also subject to active efflux back into the intestine thereby allowing further access to the enzyme upon subsequent passive absorption. The open circle (○) molecule enters the enterocytes, is not metabolized by CYP3A or efflux back into the lumen by P-glycoprotein. It then proceeds in the hepatic portal vein to the liver. The solid circle (●) molecule is absorbed into the enterocytes and is metabolized to the open square product upon its first encounter with the enzyme. The open square (□) metabolite either passes into the hepatic portal blood or back into the gut lumen. However, the shaded diamond molecule is absorbed (◆); it is not metabolized by the enzyme; it is effluxed back into the gut lumen by P-glycoprotein (🔧) and this cycling occurs twice again, where upon the fourth entry into the enterocytes the shaded diamond molecule is metabolized. While the influx transporter helps the drug molecule in absorption by carrier mediated and/or active transporter, and even others like Hsp (⬭) which helps during attachment of drugs/ligand to receptors, for instance Hsp helps during its binding to aromatic hydrocarbon receptor and they has main role in synthesis, transportation, and folding of proteins especially during the stress. This fig explains that the transporter controlling the access of the drug to the enzyme, giving the enzyme multiple opportunities to prevent the intact xenobiotics from entering the bloodstream. Thus, the enzyme and the transporter and other proteineous and nonproteineous molecules are working in a coordinated manner as a protective process to keep foreign substances out of the body.

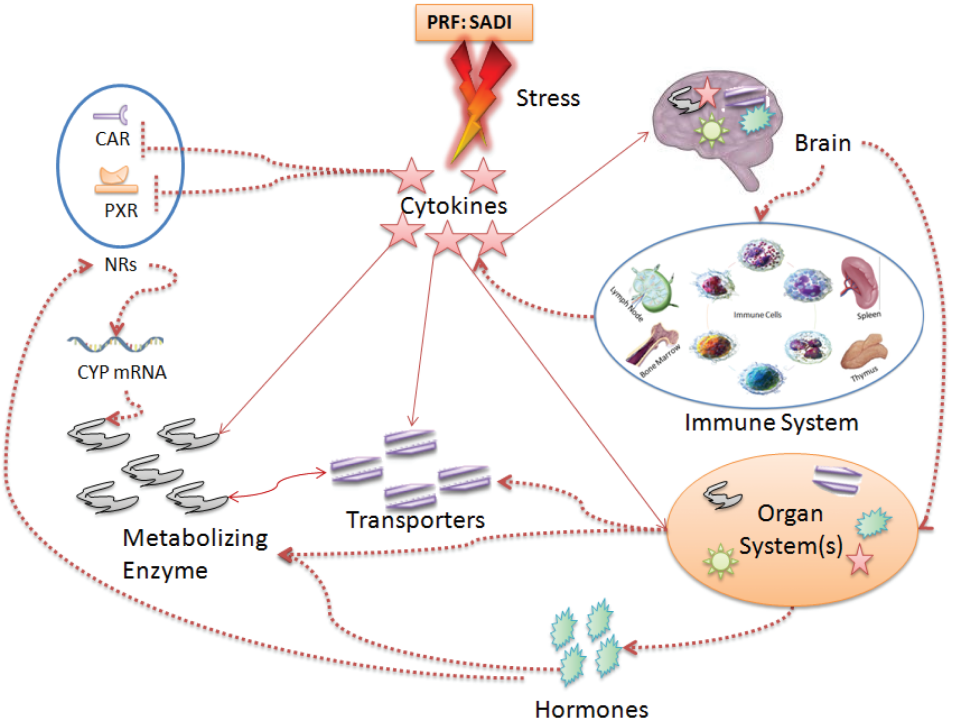

Figure 7. Effect of cytokines–hormones–neurotransmitter–enzymes–transporter (CHNET) interplay(s) on pharmacokinetics: During the disease and/or illness alters the balanced network of CHNET and affects the overall pharmacokinetics (PK)–pharmacodynamics (PD) of the administered drug. The solid lines shows direct impact on functional expression/ability on the corresponding counterpart while dotted lines indirect impact through involvement of other factors such as ROS, NF-kB, gp-130 etc. CAR = constitutive androstane receptor, NF-kB = nuclear factor-kappaB, NRs = other nuclear receptor like: FXR, NR1H4, PRF: SADI = patient-related factors: sex, age, disease, and individualization, PXR = pregnane X receptor, ROS = reactive oxygen species.

psychophysiological[159–161] and social behavior but also changes receptor pharmacology and may induce newer receptor targets[162] in patients. Thus, it can be concluded from the work done by many reviewers and researchers that there can be strong relation between homeostasis and interaction between host–microbiome–virobiota along with external factors which alters normal psychophysiological condition of a patient.[163–166] Finally, because of these all, the level and intensity of CHNET gets altered which ultimately creates individualized CHNET cascade affecting normal PK–PD of the drug along with DI/HDI. These observations call for a fresh look on the topic focusing on drug–disease–drug/herb interactions.

Pharmacodynamic HDIs. Pharmacodynamic interactions occur mainly at receptor level and are classified as direct and indirect HDIs (Fig. 2).[167,168] The direct HDIs are easy to understand and even predict than indirect HDIs.[104,168,169] Medication could be of further risk when used with dietary supplements/herbal medicines that share these pharmacological activities.[170] Few examples of direct interactions are mentioned in Table 1. One of the good examples of indirect pharmacodynamic HDIs is cranberry which potentiates the anticoagulant activity of warfarin.[73] Doubling of the plasma drug concentration may lead to enhanced drug effects and/or adverse effects depending on the therapeutic and safety window.[73,104,168,169] However, less marked changes may still be clinically important for drugs with a steep concentration–response relationship or a narrow therapeutic index.[168] The clinical importance of HDIs depends on factors that are related to co-administered drug/herb (dose, dosing regimen, administration route, pharmacokinetic, and therapeutic range) and PRF:SADI.[104,169,171] In other words the extent of drug interactions with herbs varies markedly among individuals, depending on individualization in drug metabolism and transporters, comedication with other drugs, age, and many of other factors.[104,169]

Methods for herb–drug interaction studies: an overview

There are 3 types of methods to study HDIs, namely in silico, in vitro, and in vivo methods. In silico is a term used for experiments done using a high-performance computer, whereas in vitro and in vivo refers to the experiments done outside of living organism and in living organism, respectively. Each method has pros and cons/limitations (Fig. 8) over the other; hence, sometimes to gain overall picture of HDIs, these methods are used in combination.

In silico methods

There is an increasing use of in silico methods to study the CYPs and their interactions with xenobiotics.[172] In silico approaches have also been used to study the herb–CYP interactions.[173–175] The major in silico methods include simple rule-based modeling, structure–activity relationships, and 3-dimensional quantitative structure–activity relationships.[176] All represent useful tools for understanding the reactions catalyzed by CYPs, predicting possible metabolic HDIs, pharmacokinetic parameters such as clearance, and toxicity.[177] The resulting data based on in silico approaches may be of clinical relevance.[178] A structure–activity relationship analysis was used to investigate the effect of structural modifications of piperine (pentadienyl/piperidine) on the inhibition of the CYP-catalyzed reactions, arylhydrocarbon

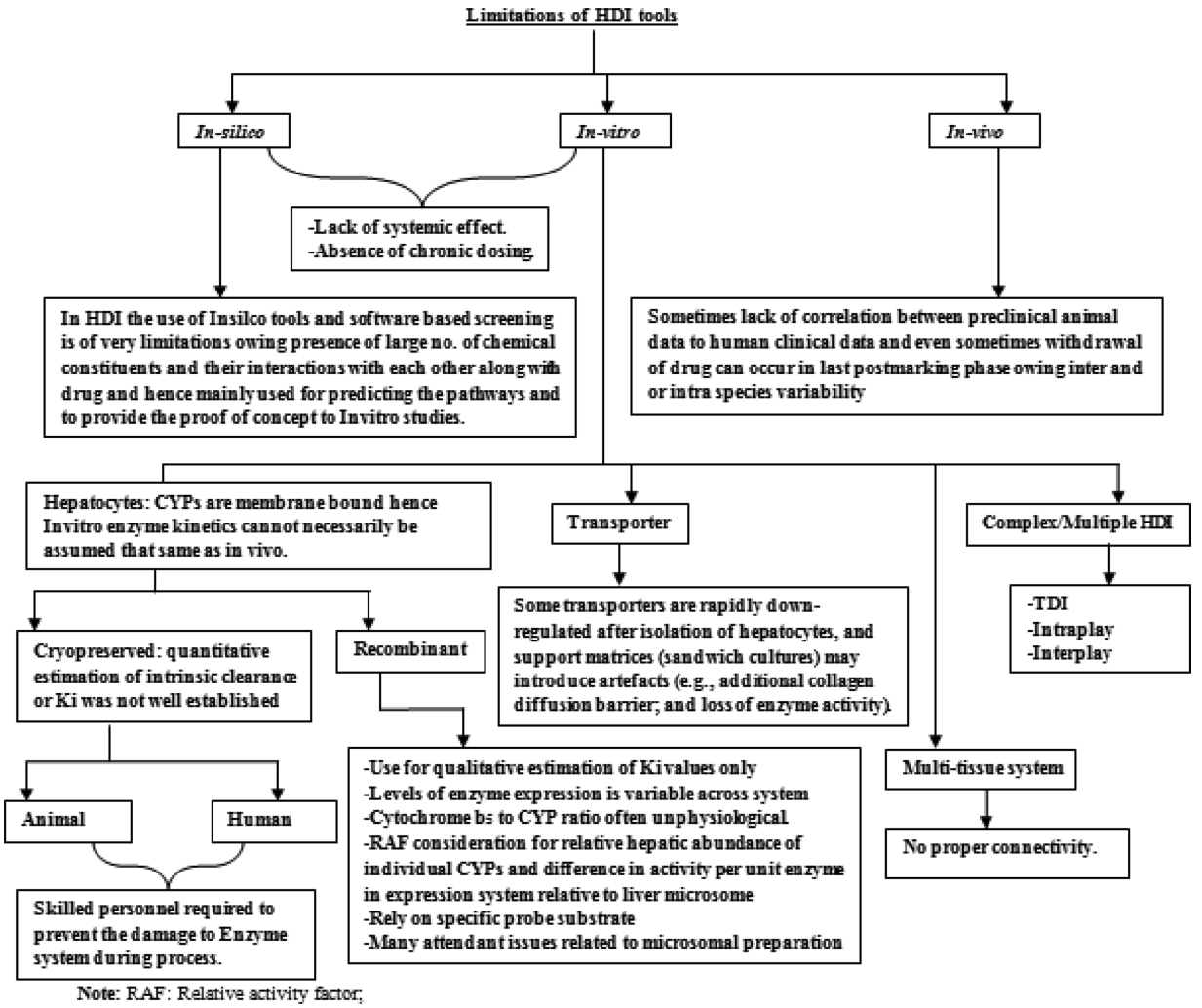

Figure 8. Limitations of HDI tools. HDI = herb–drug interaction.

hydroxylation (CYP1A), and 7-methoxycoumarin-O-demethylation (CYP2) in microsomes prepared from untreated, 3-methylcholanthrene and phenobarbital-treated rat liver.[179] This study has indicated that saturation of the side chain resulted in a marked increase in the inhibition of CYPs, whereas modifications in the phenyl and basic moieties in a few analogs led to maximum selectivity in inhibiting either constitutive or inducible CYP activities.[178,179] Although it is a virtual screening system, in silico studies could provide some early indications of the possible involvement of CYPs in context to HDIs.

In vitro methods

A number of in vitro systems have been established to investigate the drug interactions. For metabolic interactions, the major models include subcellular fractions (ie, liver microsomes, cytosols, and homogenates), B-lymphoblastoid cells, precision-cut liver slices, isolated and cultured hepatocytes or liver cell lines, and cDNA-expressed enzymes.[180] For transporter's studies, Caco-2 and Madin-Darby canine kidney-II cells, oocytes, membrane vesicles, and cDNA-expressed drug transporters are widely used.[181] Each of these systems has advantages cum limitations. However, combination of these methods can provide the most accurate information on how herbal medicines affect CYPs and P-gp. For example, cultured human hepatocytes provide cellular integrity with respect to enzyme architecture and allow the study of phase I and II reactions and transporter.[182,183] There are several CYP screening kits aimed to offer a simple "mix-and-read" fluorescent assay that is designed for high throughput screening in multiwell plates.[184] There are >25 human CYP enzymes having commercial screening kits containing recombinant cDNA-expressed CYP enzymes.[184] cDNA-expressed enzyme systems provide high level of catalytic activity (6-fold higher than an average human liver microsomes sample) and are used for screening of diverse compounds related to metabolism in vitro. However, induction effect of test compounds on CYP enzymes could not be investigated by these systems.[184–186]

Novel approaches such as IdMOC (independent discrete multiple organ co-culture) have been developed to overcome the conventional in vitro systems, in which a critical interaction between organs or cell types gets ignored. Li et al[187] have developed the IdMOC system. The IdMOC allows the coculturing of cells from different organs as physically separated cultures that are interconnected by an overlying medium, akin to the blood circulation connecting the multiple organs in the human

body.[188] This allows, the evaluation of organ-specific effects a drug and its metabolites.[189]

In vivo methods

Although in silico and in vitro models may provide quick screening methods for the herb–CYP interactions, in vivo interaction studies are usually necessary to provide evidence of adjudging their clinical importance. Probe substrates and selective inhibitors can be used to explore the effects of herbs on the activity of specific CYP enzyme in vivo, for example, erythromycin for CYP3A4; USFDA has given a comprehensive list for the same.[190] In clinical trial, there are 2 basic strategies to handle probe drugs, individual administration of a specific probe targeting 1 CYP enzyme and cocktail strategy in which simultaneous administration of multiple probes targeting multiple enzymes at 1 trial session. The cocktail of probe drugs has been used to explore the activities of multiple CYPs[190–192] and could provide information on several metabolism pathways in a single session of clinical trial. This minimizes the complicating influence of intraindividual variability over time.[193] For instance, a cocktail containing tolbutamide (CYP2C9), caffeine (CYP1A2), dextromethorphan (CYP2D6), oral midazolam (intestinal wall and hepatic CYP3A), and intravenous midazolam (hepatic CYP3A) has been used to investigate the effects of St John's wort on the activities of various CYPs in humans.[194] However, the value of the "cocktail approach may be limited due to marked intrasubject variability and the possibility of interaction between the coadministered probes.[195] Zhou et al[196,197] have discussed various factors that determine the degree of change in the steady-state plasma concentration caused by the HDIs in vivo.

Prediction of HDI and softwares for clinical use

The prediction of HDI appears to be more challenging than predicting DDI. However, there has been some success in the prediction of phytoconstituent–drug interaction and/or DDI from in vitro metabolic inhibition data, when the following criteria are met[190,198]:

(1) Drug clearance must be primarily by metabolism.
(2) Drug is not subject to substantial conjugation or other non-CYP metabolism.
(3) The liver is the primary organ of metabolic clearance.
(4) The compound does not possess physicochemical properties that are associated with absorption problems (ie, limited solubility, low gastroenteral permeability).

However, prediction of HDI may be halted by the following factors: (1) Herbal medicines often contain hundreds of constituents with differential quantitative presence of active constituents along with inhibition and/or induction potency for DMEs, transporters, and receptors as a whole formulation; (2) In some cases in which indirect HDI are involved owing to interplays between 1 or more components of CHNET; (3) the inhibition and/or induction of CYPs and P-gp by herbal medicines, which may vary based on related confounding factors; (4) many herbal medicines are used chronically; (5) considerable variability in the active contents of herbal constituents due to quality control problems; (6) presence of extrahepatic metabolism; and active transport in liver; and (7) PRF:SADI. All these factors will contribute to the final outcome of HDIs.

There are several softwares and Web sites available based on traditional Chinese system of medicine and Ayurveda which can help directly and/or indirectly in the development of IM, screening and predicting probable HDIs (Table 3).

Future perspective

Drug–disease–herb interactions

Expression and activity of several important DMEs and transporters gets altered in special population and/or conditions such as pediatric, geriatric, pregnancy, renal, and hepatic failure. Now, it has been well accepted that the alteration in the PK–PD can occur in various pathophysiological conditions as well.[145,146] To understand drug–disease–herb interaction there is a need of tools/techniques, which can focus on pharmacogenetic–drug interaction data from the disease point of view[199]; so that drug–disease–herb interaction can be considered to next level of safety and personalization.[200,201] But, yet no tools/techniques have been developed or used to focus from this aspect. In upcoming time, a comprehensive database (by integrating novel approaches and all the available databases including but not limited to those are mentioned in Table 3) needs to be developed. Such databases will not only be helpful to reduce the time and efforts to understand/predict HDI but also will be helpful to save the resources and minimize/rationalize the preclinical research related to HDIs.

Novel approach to predict HDIs for integrative medicine (whole system strategy)

Scientific fraternity has created well established guidelines for the industry to study drug interaction, drug–drug interactions, but there are no such well established guidelines for the study of HDIs.[202] Hence, there is a need to develop novel approaches, algorithms, databases, and/or integrative tools and techniques to cover all the aspects related to HDIs. The major problem in developing such draft guidance for industry to understand the real clinical scenario of HDIs is that, the presence of n number of phytochemicals in the herb/herbal formulations.

Therefore, the whole herbal formulation needs to be screened for HDI studies. But, for predictive and clinically translational use, one may have to understand and/or develop the connecting link between allopathic and CAM drug(s)/formulation(s). Once that connecting link gets developed using various drug/formulation evaluation criteria's/properties of modern science and CAM system such as Ayurveda, we will be able to study the each other's drug/formulation from each other's point of view.[203–205]

For instance, Ayurveda is one of the most ancient CAM, and Ayurvedic materia medica has been developed based on its basic principles and evaluation criteria to give/predict fate and detailed medicinal properties of the substance/formulation (as a whole) under evaluation.[206,207]For instance, *Rasa* (~taste), *Guna* (~organoleptic and physiochemical properties) used to predict *Vipaka* (~*rasa* after digestion and metabolism) and *Virya* (~Potency), which are useful to understand the probable metabolic path and its pharmacological actions along with possible adverse drug interactions and/or side effects.[206–211] Few attempts have been made in this direction in past by Nanal et al and recently we have coined the new term *Ayurnization* for the same[205] and predicted phytoconstituents from plants which were unstudied/not well studied based on Ayurveda, ethnopharmacology, and reverse pharmacology.[204]

Table 3

Database useful for herb–drug interaction studies[100]

Database	Content	URL
TCM Assistant	TCM herbs, herbal formulas, diseases and patent prescriptions. No structures	http://www.tcmassistant.com
Dictionary of Natural Products (DNP)	Major source of chemical information on natural products, including some biological sources, and pharmacological and toxicological data. Full set of structures	http://dnp.chemnetbase.com
China Natural Products Database (CNPD)	Information on Chinese natural products including >40,000 structures. Full set of structures	http://www.neotrident.com
3D Structure Database of Components from Chinese Herbs	3D structures (>10,000) from Chinese herbs (>2000), with descriptors and data on clinical uses. Full set of structures	
Traditional Chinese Medicines Database (TCMD)	Information and structures for >10,000 compounds from >4,500 species. Full set of structures	http://www.cambridgesoft.com
TCM Knowledge Based Grid	TCM herb database, literature database, traditional Tibetan herb database. No structures	http://www.cintcm.com
Chinese herbal constituents database (CHCD) and Bioactive plant compounds database (BPCD)	Information and structures for >13,000 constituents of _300 commonly used herbs. >2500 compounds active against _80 targets. Full set of structures	
Ethnopharmacological database (GPNDB)	100,000 natural products (3D structures), biological activities, ethnopharmacological data. In-house database of Greenpharma S.A.	http://www.greenpharma.com
Comprehensive Herbal Medicine Information System for Cancer (CHMIS-C)	Integrated information on cancer molecular targets, Chinese herbal recipes and Phytochemical constituents. Some structures	http://sw16.im.med.umich.edu/chmis-c/
TCM Database@Taiwan	Chinese medicine database that contains 3-D structural information of TCM constituents – ready for molecular docking simulation (database currently holds 37,170 (32,364 nonduplicate). TCM compounds from 352 TCM)	http://tcm.cmu.edu.tw/review.php?menuid=3
Metabolism and Transport Drug Interaction Database: Drug Interaction Database Program (DIDB)	Drug–drug (but also herbals, food products) interaction data in humans (includes in vitro and in vivo data); disease–drug interaction data: difference in drug exposure in renally and hepatically impaired subjects versus those with normal renal or hepatic function; pharmacogenetic–drug interaction data: impact of genetic variants of enzymes and transporters on the pharmacokinetic responses to drugs and metabolites	http://www.druginteractioninfo.org
Traditional Knowledge Digital Library (TKDL)	This is a representative database containing 1200 formulations selected from various classical texts of Ayurveda, Unani and Siddha systems of medicine. 500 formulations from Ayurveda, 500 formulations from Unani and 200 Siddha formulations are readily available	http://www.tkdl.res.in/tkdl/langdefault/common/Home.asp?GL=Eng
Ayusoft	AyuSoft is a vision of converting classical Ayurvedic texts into comprehensive, authentic, intelligent and interactive knowledge repositories with complex analytical tools	http://www.ayusoft.cdac.in/
Protein Data Bank	Information of 70,000+ protein structures determined by single crystal x-ray diffraction or high filed 1H-NMR studies	http://www.rcsb.org/pdb
Therapeutic Target Database (TTD)	Information on 1894 targets, 5028 drugs, diseases, and pathways	http://xin.cz3.nus.edu.sg/group/ttd/ttd.asp
Potential Drug Target Database (PDTD)	Information on 830 targets, protein and active site structures, biological functions, diseases, and pathways.	http://www.dddc.ac.cn/pdtd/
Open Proteomics Database (OPD)	Mass spectrometry–based proteomics data	http://bioinformatics.icmb.utexas.edu/OPD
Super*CYP*	This database contain about 1170 drugs, 2785 cytochrome-drug interactions and about 1200 alleles	http://bioinformatics.charite.de/supercyp/
Drug Interactions Checker: (drgs.com)	DI	http://www.drugs.com/drug_interactions.html
Drug Interactions Checker: (Medscape)	DI, HDI,	http://reference.medscape.com/drug-interactionchecker
Drug Interactions Checker: (Medscape)	DI, HDI,	http://www.webmd.com/interaction-checker/
Drug Interactions Checker: (Micromedex: Drug-Relax)	DI	http://www.micromedexsolutions.com/micromedex2/4.14.0/WebHelp/MICROMEDEX_2.htm#Tools/Interactions/Drug_Interactions_iP.htm

(*continued*)

Table 3
(continued).

Database	Content	URL
DRUG-REAX System	Helps identify DI and minimize ADE/ADR, enables clinicians to check for interacting drug ingredients, their effect, clinical significance, and management. Allows the review of up to 128 concurrent clinical conflicts. Presents drug-specific rather than class-specific information to aid accurate interpretation of data. Contains an 8000 unique drug terms dictionary and distinguishes trade names from equivalent generic names	http://www.rubali.com/new/index.php?option=com_content&view=article&id=9:drug-reax-system&catid=8:micromedex&Itemid=125
AltMedDex System	Covers herbals, vitamins, minerals, other dietary supplements, Chinese medicine, acupuncture, and more. Includes data on dosing, pharmacokinetics, and clinical applications. Undergoes extensive review by conventional and alternative medicine professionals to present balanced viewpoints. Answers safety and efficacy issues surrounding CAM options. Provides quarterly updates to ensure the most current research findings are available	http://www.rubali.com/new/index.php?option=com_content&view=article&id=41&Itemid=160
Drug Interaction Facts	More than 1800 detailed monographs covering 20,000 drugs. Detailed significance ratings, onset, severity ratings, documented effects, mechanisms, and management options	http://www.wolterskluwercdi.com/drug-interaction-facts-bound/
Lexi-Interact	Detailed patient management suggestions and monitoring guidelines. Includes more than 1800 generic drugs covering more than 5400 brand names. Data on the most commonly used natural products. Includes integration of extensive cytochrome P450 knowledge	http://webstore.lexi.com/Lexi-Interact
MediQ	Contains approximately 2000 specific substances and approximately 20,000 detailed comments on related interactions, including interactions with about 50 genetic polymorphisms	https://www.mediq.com/
Pharmavista	Screen drug-related problems using clinical decision support database	http://www.pharmavista.ch/content/default.aspx
Epocrates Rx	Adult and pediatric dosing for FDA-approved and off-label indications. Black box warnings, contraindications, adverse reactions, and drug interactions. Safety/monitoring, including pregnancy risk categories, location safety ratings, monitoring parameters, and similar drug names. Pharmacology, including metabolism, excretion, subclass, and mechanism of action. Manufacturer, DEA/FDA status, and approximate retail price	http://www.epocrates.com/products/features
Lexi-Interact	In-depth information on drugs, natural products, interactions, medical calculations. Pharmacogenomics database, IV compatibility data, drug shortage information, patient education	http://www.wolterskluwercdi.com/drug-reference/apps/

CAM = complementary and alternative medicine, HDI = herb–drug interaction.

Hence, in today's perspective, more of such approaches are needed to be developed so that, one may be directly able to correlate, predict, and integrate the available systems of medicine for better result with optimum and rational use of interactions and minimal use of preclinical and clinical studies. Ultimately, that is what the aim of the scientific research is.

Discussion and conclusion

People with chronic disorders want to do everything they can to combat the disease, manage its symptoms, and cope with the side effects of treatment. Because patients of such chronic diseases take the simultaneous treatment by more than one physician and/or system of medicine with or without prior consent of physician, this may lead to the harmful/beneficial/fatal HDIs. Hence, for the safe use of IM there is an ardent need to understand the importance and consequences of HDIs, then only we can reap out the benefits from all the available systems of medicine viz ayurveda, allopathy, naturopathy, traditional Chinese medicines, etc.[16–18] For instance, the importance of HDIs can be highlighted based on in vitro–in vivo studies performed by Patil D et al[20] in which they have shown that the concomitant administration of aqueous stems extract of one of the most widely used Ayurvedic *rasayana* botanical namely *T cordifolia* with cyclophosphamide significantly reverses the mylosuppression without affecting the pharmacokinetics of cyclophosphamide.[18,21,22] They further that such studies could be very helpful to design adjuvant treatment for chronic diseases such as cancer and so on.

Another point worth mentioning here is that there could be differences while studying the effects of crude extract and herbal molecules in context to HDIs and their importance in IM. It has been observed that sometimes, a single component may give

action but may not be as desired as by CAM and may be responsible for unknown side effects and/or SUSARs (suspected unsuspected serious adverse reactions), which are even not expected by the CAM.[18,20–22,212] For instance, Hudson et al[212] have shown that Muscadine grapes skin extracts (MSKEs) contain resveratrol despite of that, when MSKE and resveratrol were separately studied for prostate cancer cell growth inhibition, MSKE and resveratrol targeted distinct pathways to inhibit prostate cancer cell growth. Therefore, one cannot surely predict the effect or pharmacological response of whole extract based on their major phytoconstituents only. The effects of inhibition and/or induction of DMEs and/or transporters on in vivo pharmacokinetics are highly variable and depend on several factors associated with the drug, herbal medicine, and individualization. Therefore, the strategies such as "Whole system strategy" are needed to be developed to focus on real-time clinical scenario. In upcoming time, development of a comprehensive database (by integrating novel approaches and all the available databases including but not limited to those are mentioned in Table 3) for predicting and understanding HDIs will not only be helpful to reduce the time and efforts to understand/predict HDI but also will be helpful to save the resources and minimize/rationalize the preclinical research related to HDI. Apart from this, the pharmacovigilance program also needs to be reenergized. Indeed, in this perspective, WHO has also widen their pharmacovigilance program to include herbals, traditional and complementary medicines, blood products, biological, medical devices, and vaccines.[213,214]In conclusion, we believe that to extract maximum benefits from IM the apt understanding of the potential threats/benefits and/or consequences of HDIs could go long way in alleviating most of the human sufferings.

Acknowledgments

None.

Conflicts of interest

Authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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