

REVIEW

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Current perspectives in herbal and conventional drug interactions based on clinical manifestations

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Abstract

Background: Herbs are an important source of pharmaceuticals. Herbs are traditionally used by millions of peoples for medicine, food and drink in developed and developing nations considering that they are safe. But, interaction of herbs with other medicines may cause serious adverse effects or reduces their efficacy. The demand for “alternative” medicines has been increased significantly, which include medicine derived from plant or herbal origin. The objective of this review article mainly focuses on drug interactions of commonly used herbs along with possible mechanisms. The method adopted for this review is searching of herb-drug interactions in online database.

Main text: Herb-drug interaction leads to pharmacological modification. The drug use along with herbs may show pharmacodynamic and pharmacokinetic interactions. Pharmacokinetic interaction causes alteration in absorption, distribution, metabolism and elimination. Similarly, pharmacodynamic interaction causes additive or synergistic or antagonist effect on the drugs or vice versa. Researchers had demonstrated that herbs show the toxicities and drug interactions like other pharmacologically active compounds. There is lack of knowledge amongst physician, pharmacist and consumers related to pharmacological action and mechanism of herb-drug interaction. This review article focuses on the herb-drug interaction of danshen (*Salvia miltiorrhiza*), Echinacea (*Echinacea purpurea*), garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), goldenseal (*Hydrastis canadensis*), green tea (*Camellia sinensis*), kava (*Piper methysticum*), liquorice (*Glycyrrhiza glabra*), milk thistle (*Silybum marianum*) and St. John's wort (*Hypericum perforatum*) along with probable mechanisms and clinical manifestation based on case studies reported in literature.

Conclusion: Herb-drug interactions may lead to serious side effects. Physician, pharmacist and patients must be more cautious while prescribing and or consuming these herbs.

Keywords: Herb-drug interactions, Danshen, Echinacea, Garlic, Ginkgo, Green tea

Background

Interaction is referred to as when the effect of one drug is changed due to the presence of another compound (food, herbal or drug) [1]. The demand for “alternative” medicines has been raised significantly, which include medicine derived from plant, animal and mineral source, i.e. herbal origin [2]. Herbal medications comprise of many phytochemicals, thus, may increase the chances of herb-drug interactions (HDIs) [3]. The global dietary

supplement market size in 2019 was expected to reach about USD 123.28 billion. The same was projected to increase at a CAGR of 8.2% during the span of 2020–2027 [4]. Fifty-two million Americans (40% adults) accounted for use of complementary and alternative medicines reported in the survey of Centers for Disease Control and Prevention USA [5]. A 2011 survey by the Harvard Opinion Research Program revealed that most Americans regularly consume dietary supplements for boosting the immune system [6]. Herbals are considered to be the best option as alternative medicine all around the world due to less cost, easy availability and less side effects as compared

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to synthetic medicines. People should be sure of herbal drugs, owing synthetic drug has adverse effects not only in developed nations but also in developing nations. The consumption of herbal products and food supplements is not reported by people to their physicians or pharmacist. Almost all herbal products are easily available (OTC) in the market. The herbs contain various pharmacological properties due to the presence of multiple chemical constituents. Many times, the label of herbal products contain half-truth or misleading information. Given above are the major factors for HDIs, thereby increasing the likelihood of the HDIs not being identified and resolved in time. Furthermore, clinical trials addressing the safety and risk of coadministered drugs with certain herbal products showed that the outcomes are greatly affected by pharmacogenetics and/or individual.

There is lack of information about use of herbals by patients to physician and pharmacist. Many physicians are unaware about of the possible risks of HDIs. There appears to be dearth of knowledge amongst physician, pharmacist and consumers related to pharmacological action and mechanism of HDIs [7]. As HDIs occur between conventional drugs and herbal products, identification and awareness of exact HDIs become necessary. This review article focuses on the HDIs along with probable mechanisms and clinical manifestation based on case studies reported in the literature.

Method

To collect all cases of HDIs and adverse effects, a selective literature search using publicly available electronic databases (especially the PubMed database, Scopus, and Korean databases) was performed. We used the search items including “Herbal Drug Interactions”, “drug safety pharmacology”, “Danshen Interaction”, “Echinacea Interactions”, “Garlic Interactions”, “*Ginkgo Biloba* Interactions”, “Goldenseal Interactions”, “Green Tea Interactions”, “Kava Interactions”, “Licorice Interactions”, “Milk Thistle Interactions”, “St. John’s Wort Interactions” alone and combined with the terms “herbal hepatotoxicity”, or “herb induced liver injury”. The search was primarily focused on English-language case reports, case series and clinical reviews, published till Nov. 2020. The literature with language other than English was used by converting them into English.

Mechanism involved in herb-drug interactions

Mechanism of HDIs is often clinically significant since it influences both the time course and methods of circumventing the interaction. Different mechanisms of HDIs were reported. It mainly includes the change in the gastrointestinal functions which leads to overall changes in transportation of the drug in the body. The HDI mechanism is broadly classified into pharmacokinetic and pharmacodynamic interactions.

Pharmacokinetic interactions

Inhibition and induction of transport and efflux proteins The absorption, distribution and elimination of drugs is widely affected by the ATP-binding cassette family which are required for drug transportation.

I. P-Glycoprotein (P-gp)

The absorption, distribution and elimination/reabsorption of many clinically important therapeutic substances are regulated by P-gp family proteins. Direct interaction with binding sites on the P-gp molecule takes place through competitive or non-competitive inhibition or induction of the efflux of drugs, due to modulation of P-gp by herbal constituents. The pharmacokinetic interaction based on P-gp occurs mainly by depletion of energy required for driving the translocation of P-gp-bound drug substrate, which takes place due to inhibition of ATP binding, hydrolysis or coupling of ATP-hydrolysed molecules by the phytochemicals present in herbs [8].

II. Multidrug resistance-associated protein-2 (MRP2)

MRP2 family is ATP-dependent, which is responsible for the transport of hydrophobic anionic conjugates and extrudes hydrophobic neutral molecules. MRP2 from liver cells exports bulky hydrophilic compounds like glutathione, glucuronide, sulfate conjugates, camptothecin and paracetamol into the bile [9].

Alteration of gastrointestinal functions Alteration of absorption of concomitantly administered medicines along with herbal medicines takes place through several mechanisms: alteration in gastric pH, formation of insoluble complexes due to complexation and chelation, alteration in gastrointestinal motility and alteration in gastrointestinal transit time [10].

Herb-drug interactions at metabolism level The enzymes responsible for the metabolism of synthetic drugs or their transporters are either inhibited or induced by herbal products, which cause HDIs. The enzyme degrades, deactivates or conjugates to drugs before excretion. The inhibition or induction of this enzyme by herbs causes HDIs.

I.Enzyme inhibition The half-lives of drugs can be prolonged by inhibition of drug-metabolizing enzymes. Due to increase in half-lives of drug, plasma concentration of drug may hike unexpectedly after more doses which results into prolonged action or toxicity. Efficacy of drug may be lowered by inhibiting drug transporters, which decreases absorption of therapeutic agents. Inhibition can be of two types, viz. reversible inhibition and irreversible

inhibition. The systemic exposure of the victim drug due to a decrease in metabolic clearance and/or increase in bioavailability is manifested by reversible inhibition. Competitive inhibition occurs when herb binds to the active sites of the enzyme and prevents the binding of synthetic drug and enzyme [8, 11]. Irreversible inhibition or quasi-irreversible inhibition is characterised by time-dependent inhibition or mechanism-based inhibition. Irreversible noncovalent binding of an herb to the enzyme takes place in irreversible inhibition. Unlike reversible inhibition, the interaction can continue after removal of the perpetrator since recovery of enzyme activity depends on de novo protein synthesis [12].

II. Enzyme induction Due to enzyme induction, plasma concentration of drug reaches subtherapeutic levels. Toxicity may be due to enhanced blood levels caused by induction of drug transporter. The enzyme induction by herbs may result in a reduction of serum drug concentrations. If metabolite is active, it may result in toxicity [13].

Metabolism occurs in two phases. Phase I reactions involve conversion to a newly formed derivative or cleavage of original drug via oxidation, reduction and hydrolysis reactions. In phase I, P450 enzymes and their subfamilies CYP1A, CYP1B, CYP2C, CYP2D, CYP2E and CYP3A play an important role. These enzymes naturally are present in the liver endoplasmic reticulum and also in the intestine [14]. Phase II reactions involve conjugation with an endogenous substance like glucuronic acid and sulfate. UDP-glucuronosyltransferase and sulfotransferase enzymes catalyse phase II conjugation reaction. Donation of a cofactor through a reaction which is catalysed by transferase causes conjugation of a substrate with a nucleophilic group (amino, hydroxyl, thiol, etc.) [15].

Alteration in renal elimination Herbal products interact with renal functioning, leading to alteration in elimination of drug via inhibition of tubular secretion, tubular reabsorption or interference with glomerular filtration [16]. Certain herbal diuretics increase the glomerular filtration rate, and few act as direct tubular irritants [17].

Pharmacodynamic interactions

Pharmacodynamic interactions are either additive (or synergistic) or antagonistic. Additive or synergistic interaction potentiates the action of synthetic drug. Antagonistic interaction reduces the efficacy of synthetic drugs [18].

Herbal-drug interactions

The herbs which were frequently used by physicians and also as home remedies for various ailments in alternative system of medicines are selected for this review.

Danshen (*Salvia miltiorrhiza*)

Danshen is used as an antibacterial, antioxidative, antineoplastic, anticoagulation and anti-inflammatory. Danshen contains diterpenoids (tanshinones and royleanones) and phenolic acids including danshensu, caffeic acid, protocatechuic aldehyde, protocatechuic acid, salvianolic acid A-E, lithospermic acid and rosmarinic acid. Danshen also contains essential oils, triterpenoids, flavone, amino acids, metallic elements and many others [19].

Danshen shows haemostasis effects like platelet aggregation inhibition, interference with the extrinsic blood coagulation, antithrombin III-like activity and promotion of fibrinolytic activity. Danshen has reported to increase area under the plasma drug concentration-time curve (AUC), elimination half-lives ($t_{1/2}$) and maximum plasma concentrations (C_{max}) and decrease total body clearance (CL) and apparent volume of distribution (V_d) of R- and S- isoform of warfarin in rats. In humans, there was increase in international normalized ratio (INR) after taking danshen and warfarin together [20]. Case report reported interaction between warfarin and danshen, leading to increase in INR, which potentiated anticoagulant effect of warfarin and increased risk of bleeding [21]. Another case was reported which lead to abnormalities of clotting in patient having rheumatic heart disease, caused by danshen and warfarin concomitant use [22].

A sequential pharmacokinetic interaction study reported induction of CYP3A4 enzyme in the gut by danshen. The confidence intervals of C_{max} , $t_{1/2}$, oral clearance (CL/F) and AUC zero to infinity (AUC_{∞}) of midazolam before and after oral administration of danshen tablets were (0.559, 0.849), (0.908, 1.142), (1.086, 1.688) and (0.592, 0.921), respectively, was to be 90%. There was a decline in bioavailability of midazolam due to danshen use [23].

Echinacea (*Echinacea purpurea*)

Echinacea contains alkaloids, caffeic acid derivative, cichoric acid, flavonoids and phenolic acids. *Echinacea* is worldwide used for its immunomodulatory and anti-inflammatory properties. The plant is also reported to show larvicidal activity and antibacterial and antiviral activities, especially against influenza viruses [24].

In in vivo clinical studies, 12 healthy subjects were dosed 1600 mg/day with *E. purpurea* extracts (for 8 days) along with caffeine, tolbutamide and midazolam to evaluate CYP1A2, CYP2C9 and CYP3A enzyme activities, respectively. The results obtained showed *Echinacea* extract inhibited hepatic CYP1A2 and CYP2C9, and induced CYP3A4 enzyme activity, which lead to 27% decrease in caffeine CL/F, 12% decrease in tolbutamide CL/F and 42% increase in the systematic clearance and reduced AUC by 23% of midazolam respectively [25]. Similarly, another in vivo assessment showed that *E. purpurea* extract inhibited CYP1A2 and induced CYP3A4 [26]. Thus, it is recommended not to use

drugs that are substrate of *CYP1A2*, *CYP2C9* and *CYP3A4* enzyme along with concomitant use of *Echinacea* extract.

Garlic (*Allium sativum*)

Garlic mainly contains organosulfur compounds such as allicin, diallyl disulfide, diallyl trisulfide and S-allyl cysteine. Garlic is used as antihyperlipidemic, antimicrobial, anti-inflammatory, antiprotozoal, anticancer and immunomodulatory activity. Garlic has been reported to show toxicity at higher doses. In contrast, some studies also showed intoxication after consumption of garlic [27].

The two in vivo pharmacokinetic trials were conducted to study the effect of garlic on the antiviral drug saquinavir. The study found that ingestion of garlic increased expression of duodenal P-gp to 131% in subjects. The average AUC and C_{max} of saquinavir was decreased by garlic up to 51% and 54% respectively, in subjects with concomitant use along with garlic. The AUC values and C_{max} values returned up to 60–70% of their values after the 10-day washout period. Saquinavir is metabolised by the enzyme cytochrome P450 (*CYP3A4*) and is also a substrate of P-gp. Thus, increased clearance and decreased bioavailability of saquinavir are possible due to induction of P-gp along with concomitant use of garlic [28, 29].

Clinical study shows that the intake of S-allyl cysteine (active constituent of garlic) inhibits platelet aggregation [30]. A human survey found that a significant number of patients who used herbs in conjunction with warfarin had higher INR levels, indicating that this combination had potential or additive effects. Thus, inhibition of platelet aggregation shows an additive anticoagulant effect, which is a possible mechanism for warfarin and garlic interaction, which ultimately increases the anticoagulant effect. Increased anticoagulant may increase the risk of bleeding [31].

The randomized clinical trial of garlic-chlorzoxazone cocktails was given for 28 days on healthy subjects. The pre-supplementation and post-supplementation effect of garlic on *CYP2E1* enzyme was evaluated by measuring 6-hydroxychlorzoxazone/chlorzoxazone serum ratio. A controlled trial showed a decrease in 6-hydroxychlorzoxazone/chlorzoxazone serum ratio by about 22%, which suggests inhibition of *CYP2E1* activity by garlic [32]. Similarly, another study showed a 40% decrease in 6-hydroxychlorzoxazone/chlorzoxazone serum ratio [33].

A case report showed abnormal INR level in patients using a cocktail of fluindione-garlic. Garlic has been previously reported to inhibit some cytochrome P450 isoforms. Thus, garlic can putatively increase fluindione metabolism, thereby garlic acting as an enzymatic inducer. INR level decreased from 2.4 to 1.8 (post-supplementation of garlic for 12 days), and INR level increased to 2.8 (7 days after stopping garlic). A low INR level reduces the anticoagulant effect, increasing the risk of blood clotting (the cause of stroke). Another mechanism could be inhibition of

fluindione binding to plasma proteins, but no such studies have been reported [34]. It is thus suggested that concomitant use of saquinavir, warfarin, chlorzoxazone and fluindione with garlic should be prevented.

Ginkgo (*Ginkgo biloba*)

Ginkgo biloba leaf contains flavonol glycosides (kaempferol, quercetin, myricetin, apigenin, isorhamnetin, luteolin and tamarixetin) and terpene trilactones (ginkgolide A, B, C, J, K, L, M, P, and Q and bilobalide), proanthocyanidins and organic acids. *G. biloba* leaf extract is used in the treatment of Alzheimer's disease, neurodegenerative disease, cerebral insufficiency, neurosensory problems, eye ailments, vascular insufficiencies, age-related memory deficit and oxidative stress. In addition, *G. biloba* is leaf used as anti-angiogenesis, anti-inflammatory, and anti-asthmatic [35].

In *in vivo* clinical trials, 10 healthy volunteers were given *G. biloba* extract (GBE) to test its effect on *CYP2C9* using tolbutamide as a probe. The AUC for tolbutamide after taking GBE was reduced by 16% as compared to AUC before use of garlic along with tolbutamide. Although the interaction is considered minor, caution must be taken during concomitant use [36].

An open-label study in healthy volunteers showed a decrease in the AUC and C_{max} of midazolam by 34% and 31% respectively when used along with GBE. This research found that GBE induces *CYP3A* metabolism, which leads to a decrease in midazolam concentrations [37].

In a comparative clinical study, the C_{max} of nifedipine was nearly doubled in two subjects when GBE was taken at the same time. The probable mechanism of action is inhibition of *CYP3A* by GBE. Increased nifedipine causes severe and longer-lasting headaches, with dizziness or hot flushes [38].

The human trial reported significantly reduced C_{max} of omeprazole (from 0.69 ± 0.27 to 0.48 ± 0.27 mg/ml) and omeprazole sulfone (from 0.20 ± 0.07 to 0.13 ± 0.06 mg/ml) and an increase in C_{max} of 5-hydroxyomeprazole (from 0.28 ± 0.14 to 0.45 ± 0.21 mg/ml) post-administration of *G. biloba* with omeprazole. Omeprazole is metabolized to 5-hydroxyomeprazole in the body. Also, after post-administration of *G. biloba*, renal clearance of 5-hydroxyomeprazole was significantly decreased (from 2.70 ± 1.17 to 1.53 ± 0.79 mL/min/kg). The mechanism for this interaction is increased hydroxylation of omeprazole by induction of *CYP2C19* [39].

A single oral dose of GBE did not show any change in the pharmacokinetics of talinolol in 10 healthy, non-smoking male volunteers. C_{max} of talinolol was raised by 36%, AUC (0–24) by 26% and AUC_{∞} by 22% respectively. A study suggests that long-term use of GBE prejudiced talinolol disposition in humans, by affecting the activity of drug transporters like P-gp [40].

Randomized controlled trials showed elevation in AUC and C_{max} of fexofenadine by 55% and 68% respectively.

Probable mechanism for this is inhibition of P-gp-mediated efflux in humans by GBE. The AUC and C_{max} of fexofenadine were expressively increased after coadministration quercetin (constituent of ginkgo) as compared to that of the placebo treatment.

A case report suggested that fatal cerebral haemorrhage was associated with concomitant use of *G. biloba* and ibuprofen intake in healthy men. Potential inhibition of platelet-activating factor takes place due to ginkgolide B that is a component of *G. biloba*. *G. biloba* has been reported with bleeding complications. The interaction takes place possibly due to the additive effect of GBE on ibuprofen by the inhibition of the TXA₂-dependent platelet aggregation [41].

A case study showed that there was an increase in BP in a man, with coadministration of thiazide diuretics and GBE. The blood pressure increased further for a few weeks. BP returned to normal level when both diuretics and GBE were stopped. Due to the severity of complication of the interaction, the responses were not rechallenged. Diuretics are known to lower the BP, but use of GBE leads to the opposite pharmacodynamic effect (increased blood pressure). The possible mechanism for this interaction could be agonism. There are no clinical trials recorded for increase in blood pressure by GBE, but the combination should be prevented [42].

In a case study, fatal seizures were reported with anti-convulsant medications like valproic acid. GBE has been reported to induce CYP2C19 enzyme activity. The CYP450 enzyme is reported to metabolise valproate, chiefly by CYP2C9 and CYP2C19. Thus, this coadministration of valproic acid and *Ginkgo biloba* extract should be prevented [43].

A case study reported that a man with a persistent and painful erection of the penis that had lasted for 4 h was admitted to a hospital. Metabolism of risperidone by CYP2D6 and CYP3A4 has been recorded in literature. Both the enzymes CYP2D6 and CYP3A4 are inhibited by GBE, which is a mechanism or interaction between risperidone and GBE. Simultaneous use of GBE and risperidone increases the serum concentration of risperidone and increases the hazard of adverse effects, such as priapism [44].

Negative pharmacokinetic interaction of efavirenz was reported, in a case study (47-year-old HIV infected patient), with terpenoids (component of *G. biloba*). The probable mechanism of interaction was either by induction of CYP3A4 and P-gp. Induction of CYP3A4 and P-gp by terpenoids lowers the efavirenz plasma level in patients (from 1.26 to 0.48 mg/l). The lowering of human plasma efavirenz level results in virological failure. So, it is recommended that the combination should be avoided [45].

Flavonoids are a component of *G. biloba* bound to benzodiazepine binding site, which possess GABAergic activity. Trazadone is used to treat behavioural disturbances

as it possesses hypnotic and sedative activity. The CYP3A4 enzyme is responsible for metabolism of trazadone into active compound 1-(m-chlorophenyl) piperazine (mCPP). Flavonoids increase the activity of CYP3A4 in humans. A case study reported that flavonoids act on benzodiazepine receptors and increase the GABAergic activity by increasing mCPP production (mCPP enhances the release of GABA), which leads to increased GABAergic activity and leads to coma in patients [46].

Goldenseal (*Hydrastis canadensis*)

Goldenseal mainly contains berberine, 3,4-dimethoxy-2-(methoxycarbonyl) benzoic acid, 3,5,30-trihydroxy-7,40-dimethoxy-6,8-C-dimethyl-flavone, chilenine, (2R)-5,40-dihydroxy-6-C-methyl-7-methoxy-flavanone, 5,40-dihydroxy-6,8-di-C-methyl-7-methoxy-flavanone, noroxyhydrastinine, oxyhydrastinine and 40,50-dimethoxy-4-methyl-30-oxo-(1,2,5,6-tetrahydro-4H-1,3-dioxolo-[4,5]-benzo [1,2-e]-1,2-oxazocin)-2-spiro-10-phtalan [47]. Goldenseal is reported in folk medicine for the treatment of urinary disorders, gastrointestinal disturbances and skin ailments [48].

In *in vivo* clinical study was performed for the action of goldenseal on CYP isoform enzyme, which reported inhibition of CYP2D6 and CYP3A4/5 by 40% [49].

A study on humans was performed to determine CYP2D6 activity using debrisoquine. By evaluating debrisoquine urinary recovery ratios, 50% inhibition of CYP2D6 activity was observed by post-supplementation of goldenseal along with debrisoquine, which lead to a decrease in debrisoquine urinary recovery ratios [50].

Randomized clinical trials in healthy humans showed that AUC_{∞} and C_{max} increased from 107.9 ± 43.3 to 175.3 ± 74.8 ng.h/ml and from 50.6 ± 26.9 to 71.2 ± 50.5 ng/ml respectively for midazolam, with concomitant use of goldenseal. AUC and C_{max} of midazolam were increased by inhibition of CYP3A4/5 [51].

Berberine is a chemical found in goldenseal extract. A clinical trial was performed on humans to check the effect of berberine on pharmacokinetics of cyclosporin A. The results obtained from this trial showed an increase in AUC of cyclosporin A from 104 to 123 mg/l. This study proves berberine mediated increase in cyclosporin A bioavailability by inhibition of CYP3A4 [52].

Green tea (*Camellia sinensis*)

Green tea mainly contains catechins, polyphenols and epigallocatechin-3-gallate. Green tea possesses antioxidant, antimutagenic, antidiabetic, anti-inflammatory, antibacterial and antiviral properties. Green tea is used for weight loss and preventing ageing and prostate and other cancers [53].

An *in vivo* study reported that catechins (present in green tea extract) inhibit folic acid uptake. Catechins are competitive inhibitors of DHFR, which adversely affect folate uptake. DHFR is responsible for folate intestinal

absorption. Folate is reduced to tetrahydrofolate and methylated to 5-methyltetrahydrofolate during intestinal absorption of folate before it is absorbed in the blood [54]. *In vivo* studies in humans reported reduction in C_{max} and AUC of folic acid by 58.4% and 43.9%, during concomitant use of folic acid and green tea, leading to a decrease in bioavailability of folic acid. The probable mechanism of interaction is inhibition of carrier-mediated absorption of folates [55].

A clinical trial in humans reported that green tea weakly inhibits CYP450 3A4, which is the main metabolizing enzyme of simvastatin [56]. A study showed that consumption of green tea with simvastatin leads to increase in C_{max} of simvastatin lactone (metabolite of simvastatin lactone prodrug) from 3.70 to 7.21 ng/mL, before and after supplementation of green tea. Similarly, the AUC of simvastatin lactone increased from 6.3 to 12.5 ng.h/mL. The subject improved tolerance to simvastatin after the patient stopped drinking green tea and simvastatin [57].

Green tea is a source of vitamin K [58]. Green tea products accentuate the anticoagulant effect of warfarin, leading to bleeding complications. Exogenous intake of vitamin K antagonises the effect of warfarin. A study on humans showed a decrease in INR level from 3.79 to 1.14 (after 1 month) on concomitant consumption of green tea and warfarin. The INR level increased to 2.55 on the discontinuation of green tea [59].

Kava (*Piper methysticum*)

Kava contains kavain, dihydrokavain, methysticin, dihydromethysticin, demethoxyyangonin, and yangonin. Kava has a beneficial effect in euphoria, analgesia, neuroprotection, and anticonvulsant properties. Kava is also used in the treatment of anxiety [60].

The active components of kava (pyrones) are reported to have neuropharmacologic interactions with the central nervous system receptors. Kava also has weak effects on GABA or benzodiazepine receptors [61]. A study showed additive pharmacodynamic effects between α -pyrones and other GABA-active sedatives [62]. A case study showed a lethargic and disoriented state in patients during concomitant use of kava and alprazolam (benzodiazepine) [63]. Previous studies showed that this interaction is possible due to the additive effect of kava on benzodiazepine receptors, leading to life-threatening conditions.

Kava inhibits CYP2E1, and chlorzoxazone is a CYP2E1 probe. Clinical trials reported that kava showed a significant reduction in 6-hydroxychlorzoxazone/chlorzoxazone serum ratios by 40%. It is, thus, suggested that kava should not be taken simultaneously with chlorzoxazone [49].

Kava is reported to have dopamine antagonism property. A case report in a 76-year-old Parkinson's disease patient showed reduced activity of levodopa (a precursor of dopamine). On further investigation, it was reported that the

patient simultaneously consumed kava and dopamine, which lead to decrease in dopamine efficacy (decreased dopamine level) due to an antagonising property of kava [64].

Liquorice (*Glycyrrhiza glabra*)

Biologically active compounds present in liquorice are glycosides (glycyrrhizic acid), flavonoids (chalcones, liquiritin, isoliquiritin, liquiritin apioside and isoprenoid-substituted flavonoids), chromenes (coumarins and dihydrostilbenes) and saponins (triterpenoid saponins). Liquorice is reported for wide-ranging biological activities like antiviral, antimicrobial, antioxidant, antiallergic, hepatoprotective, neuroprotective, anti-inflammatory and dermatological activities [65].

Glycyrrhizin is a potent inducer of the CYP3A4-metabolizing enzyme. CYP3A4 catalyses sulfoxidation of omeprazole. A study reported that glycyrrhizin induces CYP3A4-catalysed sulfoxidation of omeprazole leading to a decrease in C_{max} of omeprazole, during simultaneous use of liquorice and omeprazole [66].

Glycyrrhizin induces CYP3A4 enzyme (which catalyses midazolam 11-hydroxylation), leading to a reduction in plasma concentrations of midazolam. This inhibition was confirmed by an *in vivo* study, where mRNA expression of CYP3A4 and other CYP450 family members in mice was decreased significantly by liquorice. Human study confirmed an interaction between midazolam and liquorice [67].

Milk thistle (*Silybum marianum*)

Silybin A and B, isosilybin A and B, silychristin A, silyhermin, neosilyhermine A, neosilyhermine B, mariamides A and B, quercetin, morin, chlorogenic acid and caffeic acid are some of the major chemical constituents present in milk thistle. Milk thistle is widely used in jaundice and calculi of the liver and gallbladder and is useful in controlling haemorrhages [68].

Metronidazole is a substrate of CYP3A4-metabolizing enzyme. A clinical trial on 12 human subjects confirmed increased CL of metronidazole (by 29.51%) with concomitant use of milk thistle. It also decreased $t_{1/2}$, C_{max} and AUC, as a cause of induction of both intestinal P-gp and CYP3A4 [69].

Milk thistle decreased the AUC of E-3174 (active metabolite of losartan) and increased the AUC of losartan, reported in a clinical trial on 12 healthy men. The study reported that the decrease in losartan AUC is dependent on inhibition of CYP2C9 [70].

Talinolol C_{max} increased potentially from 172.68 ± 61.53 to 219.20 ± 52.77 ng/ml (after 14 days) after simultaneous administration of milk thistle as compared to placebo treatment, in human studies. AUC of talinolol increased by 36.2%, and oral clearance of talinolol decreased by 23.1% during milk thistle-talinolol coadministration, by inhibition of P-gp [71].

St. John's wort (*Hypericum perforatum*)

The major active constituents present in St. John's wort are hyperforin and hypericin (pseudohypericin, isohypericin, protohypericin, protopseudohypericin, Cyclopseudohypericin) and also flavonoids (kaempferol, quercetin, luteolin, biapigenin), tannins and volatile oils. St. John's wort is used as an antidepressant, antiviral and antibacterial. It also shows sedative and astringent properties. It is used traditionally for the treatment of excitability, neuralgia, sciatica, fibrositis, anxiety, menopausal neurosis and depression and as a nerve tonic and topical application for wound treatment [72].

The study confirmed that long-term use of SJW may cause reduced clinical effectiveness of CYP3A4 substrate drugs by CYP3A4 induction, which may lead to an increase in dosage of the drug [73]. The study showed direct induction of intestinal P-gp/MDR1 by SJW in humans [74].

CYP2C19 carries out demethylation of amitriptyline to nortriptyline, at low amitriptyline concentration. When the concentration of amitriptyline is higher, the CYP3A4 enzyme carries out its demethylation [75, 76]. P-gp is a drug transporter which is responsible for efflux of amitriptyline from gut epithelial cells to the gut lumen, which causes co-regulation of systemic availability. Increase activity of P-gp causes reduced systemic availability [77]. A clinical trial showed that concomitant use of amitriptyline and SJW extract LI160 decreases the AUC of amitriptyline (by 22%) and nortriptyline (by 41%), which is a metabolite of amitriptyline in humans. The pharmacokinetics of St. John's wort is affected by induction of CYP3A4 and/or induction of P-gp [78].

Atorvastatin is a substrate of CYP3A4 and P-gp; thus, its use with SJW should be prevented. In a human trial, concomitant treatment with a SJW product reduced the efficacy and effect of atorvastatin, resulting in an increase in LDL cholesterol levels of 0.32 mmol/l, or about 30% of the expected treatment. The possible mechanism of action is increased in CYP3A4 and P-gp activity [79].

Cyclosporine is widely used to prevent rejection of organs after organ transplantation. Various case reports have reported of serious organ rejection after transplantation due to simultaneous use of cyclosporine with SJW [80–83]. The efficacy of cyclosporine is decreased, which causes rejection of organs [73, 74]. Thus, serious and potentially fatal interactions between cyclosporine and SJW are likely to occur via induction of CYP3A4 and/or P-gp by St. John's wort.

MDR1/P-gp mediates the intestinal absorption and distribution and renal excretion of digoxin. SJW is reported to induce P-gp drug transporter. Clinical trials showed that concomitant use of SJW and digoxin lead to an increase in efflux function of P-gp into the intestinal lumen, which lead to a decrease of digoxin AUC by 25% [84, 85].

A case report on four patients showed a median decrease of 47% of the original methadone concentration, during concomitant use of methadone and SJW [86].

A study on humans showed a two-fold increase in CL of alprazolam after administration of alprazolam with SJW for 14 days. The increase in CL of alprazolam was observed due to CYP3A4 enzyme induction. The increased CL leads to a decrease in alprazolam blood concentration [73].

Imatinib is predominantly metabolized by cytochrome CYP3A4. Concomitant use of SJW and imatinib lead to increased imatinib CL by 43% (12.5 to 17.9 l/h), imatinib AUC was decreased by 30% (from 34.5 to 24.2 mg. h/ml) and C_{max} was also significantly decreased [87, 88].

HIV-1 protease inhibitors are substrates of the CYP3A4 enzyme. A clinical trial was performed to evaluate the effect of SJW on plasma concentrations of the HIV-1 protease inhibitor (indinavir), which was found to decrease plasma levels of indinavir in 8 volunteers by an average of 57% [89].

A trial performed in 5 cancer patients showed decreased plasma levels of SN-38 (active metabolite of irinotecan) by 42% on post-supplementation of SJW and irinotecan as compared to the placebo treatment [90].

NNRTI and nevirapine are substrates of multidrug transporter P-gp and are extensively metabolized via the cytochrome CYP3A4 enzyme system. A human study showed a decrease in blood concentration of nevirapine by increasing its oral clearance by 35%, due to induction of CYP3A4 enzyme [91].

In a human subject, it was found that SJW significantly induced the activity of CYP2E1 (approximately 140%) on comparing pre-supplementation and post-supplementation ratios. The two clinical trials found that SJW extract lead to increase in the hydroxychlorzoxazone/chlorzoxazone serum ratios. This increase in ratio is due to induction of CYP2E1 enzyme [32, 33].

Serotonin reuptake in the central nervous system is inhibited by bupropion [92]. Serotonin reuptake is weakly inhibited by SJW. Various reports of SJW interacting with SSRIs have been reported, leading to various side effects, including serotonin syndrome. The side effect is due to an additive effect of two similarly acting drugs [93]. Dystonia is a syndrome which causes sustained muscle contractions, producing twisting and repetitive movements and postures. Dystonia syndrome is a very well-recognised side-effect of many medicines (antipsychotics and serotonin reuptake inhibitor drugs) affecting dopamine concentrations. A 58-year-old female reported prolonged orofacial dystonia. On evaluation, it was found that the woman was consuming bupropion and St. John's wort together. Both bupropion and St. John's wort are reported to inhibit the reuptake of dopamine, potentially resulting in additive effects on dopaminergic transmission and hence causing dopaminergic side effects such as dystonia [94].

Table 1 Herb-drug interactions (HDIs) of some herbs with possible mechanism, outcome and level of HDIs

Herb	Drug	Possible mechanism	HDI outcome	Level of HDIS	References	
Danshen	Warfarin	Additive effect	Potentiated anticoagulant effect	+++	[19–21]	
	Midazolam	CYP3A4 induction	Decreased F of midazolam	++	[22]	
Echinacea	Caffeine	CYP1A2 inhibition	Decreased CL/F of caffeine	++	[24, 25]	
	Midazolam	CYP3A4 induction	Increased CL and decreased F of midazolam	+	[24, 25]	
	Tolbutamide	CYP2C9 inhibition (weakly)	Reduces CL/F of tolbutamide	+	[24, 25]	
Garlic	Saquinavir	P-gp induction	Increased CL and decreased F of saquinavir	+++	[27, 28]	
	Warfarin	Additive effect	Increased anticoagulant effect	++	[29, 30]	
	Chlorzoxazone	CYP2E1 inhibition	Decreased serum 6-hydroxychlorzoxazone/chlorzoxazone ratio	++	[31, 32]	
Ginkgo biloba	Fluindione	P450 inhibition	Decreased INR level	++	[33]	
	Tolbutamide	CYP2C9 inhibition	Decreased AUC of tolbutamide	+	[35]	
	Midazolam	CYP3A inhibition	Decreased AUC and C_{max} of midazolam	++	[36]	
	Nifedipine	CYP3A inhibition	C_{max} of nifedipine was doubled	+++	[37]	
	Omeprazole	CYP2C19 induction	Decreased C_{max} of omeprazole and increased C_{max} of 5-hydroxyomeprazole	+	[38]	
	Talinolol	P-glycoprotein inhibition	Increased C_{max} and AUC of talinolol	++	[39]	
	Fexofenadine	P-gp-mediated efflux inhibition	Increased AUC and C_{max} of fexofenadine	+++	[40]	
	Ibuprofen	Additive effects	Increase anticoagulant effect	+++	[96]	
	Diuretic (thiazide)	Agonism	Increased blood pressure	+++	[41]	
	Valproic acid	CYP2C19 induction	Fatal seizure	++	[42]	
Green tea	Antipsychotic drug (risperidone)	CYP2D6 and CYP3A4 inhibition	Increased C_{max} of risperidone and causes priapism	++	[43]	
	Efavirenz	CYP3A4 and P-gp induction	Virologic failure associated with decreased efavirenz blood concentration	++	[44]	
	Trazodone	CYP3A4 induction	Enhancement of GABAergic activity leading to coma	++	[45]	
	Goldenseal	Debrisoquine	CYP2D6 inhibition	Decreased debrisoquine urinary recovery ratios (DURR)	+++	[48, 49]
		Midazolam	CYP3A4/5 inhibition	Increased AUC and C_{max} of midazolam	+++	[48, 50]
	Cyclosporin A	CYP3A4 inhibition	Increased blood concentration of cyclosporin A	++	[48, 51]	
Green tea	Folic acid	Carrier-mediated absorption inhibition	Decreased F of folic acid	+++	[53, 54]	
	Simvastatin	CYP3A4 inhibition	Increased AUC and C_{max} of simvastatin	+++	[55, 56]	
	Warfarin	Antagonism effect	Decreased anticoagulant effect	++	[57, 58]	
Kava	Benzodiazepine (Alprazolam)	Additive effect on GABA receptors	Increased benzodiazepine effect	+++	[60–62]	
	Chlorzoxazone	CYP2E1 inhibition	Decreased 6-hydroxychlorzoxazone/chlorzoxazone serum ratios	+++	[48]	
Liquorice	Dopamine	Dopamine antagonism	Reduced dopamine efficacy	++	[63]	
	Omeprazole	CYP3A4 induction	Decreased plasma concentrations of omeprazole	++	[65]	
	Midazolam (benzodiazepines)	CYP3A4 induction	Decreased plasma concentrations of midazolam	++	[66]	
Milk thistle	Metronidazole	P-gp & CYP3A4 induction	Decreased blood concentration of metronidazole	++	[68]	
	Losartan	CYP2C9 inhibition	Increased AUC of losartan.	++	[69]	
	Talinolol	P-gp inhibition	Increased AUC and C_{max} and decreased CL/F of talinolol	++	[70]	

Table 1 Herb-drug interactions (HDIs) of some herbs with possible mechanism, outcome and level of HDIs (Continued)

Herb	Drug	Possible mechanism	HDI outcome	Level of HDIS	References
St. John's wort	Amitriptyline	CYP3A4 and P-gp induction	Decreased blood concentration of amitriptyline	++	[72–77]
	Atorvastatin	CYP3A4 and P-gp induction	Reduced efficacy of atorvastatin	+	[72, 73, 78]
	Cyclosporine	CYP3A4 and P-gp induction	Cyclosporine exhibits a relatively small therapeutic window	++	[72, 73, 79–82]
	Digoxin	CYP3A4 and P-gp induction	Decreased blood concentration of digoxin	++	[72, 73, 83, 84]
	Methadone	CYP3A4 and P-gp induction	Decreased blood concentration of methadone	+++	[72, 73, 85]
	Alprazolam	CYP3A4 induction	Decreased blood concentration of alprazolam	+++	[72]
	Imatinib	CYP3A4 induction	Decreased blood concentration of imatinib	+++	[72, 86, 87]
	Indinavir	CYP3A4 induction	Decreased blood concentration of indinavir	+++	[72, 88]
	Irinotecan	CYP3A4 induction	Decreased blood levels of SN-38	+++	[72, 89]
	Nevirapine	CYP3A4 induction	Decreased blood concentration of nevirapine	++	[72, 90]
	Chlorzoxazone	CYP2E1 induction	Increase in hydroxylchlorzoxazone/chlorzoxazone serum ratio	++	[31, 32]
	Bupropion	Additive effects	Orofacial dystonia	+++	[91–94]
	Buspiron	Additive effect on 5-HT reuptake	Hypomaniac episode, serotonin syndrome	+++	[94]

P-gp P-glycoprotein, F Bioavailability, AUC area under the plasma drug concentration-time curve, C_{max} maximum plasma concentrations, CL total renal clearance, CL/F oral clearance

+Mild HDI

++Moderate HDI

+++Major HDI

Buspiron is a partial agonist at 5-HT_{1A} receptors. St. John's wort is testified to be a non-selective 5-HT reuptake inhibitor, which upregulated the postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors. A case study reported that the concomitant administration of buspiron and St. John's wort medications leads to overstimulation of the 5-HT_{1A} receptors, therefore leading to the development of serotonin syndrome and hypomaniac episode [95].

A systematic representation of herb-drug interactions of herbs with possible mechanism, outcome and level of HDIs is given in Table 1.

Conclusion

Herb-drug interactions may lead to serious side effects. The reviewed studies clearly indicate that herbal medicines can interact with allopathic or modern medicines and show unwanted effects. Most of the interaction may have negligible clinical significance, but some may lead to life-threatening effect on public health. Our review suggests to physician, pharmacist and common people to avoid such combination in practice. Patients should be aware of the herb-drug interactions for their safety. In this review, we have discussed in details herb-drug interaction of most commonly used herbs in a regular practice by physicians all over the world. It is, therefore, important that health care professionals should take into

account of herb-drug interactions when prescribing drugs to patients.

Abbreviations

5-HT: 5-hydroxy tryptamine; ATP: Adenosine triphosphate; AUC: Area under plasma drug concentration-time curve; AUC_∞: AUC zero to infinity; CAGR: Compound annual growth rate; CL/F: Oral clearance; CL: Body clearance; C_{max}: Maximum plasma concentrations; CYP: Cytochrome-P; DHFR: Dihydrofolate reductase; GABA: Gamma-aminobutyric acid; GBE: *G. biloba* extract; HDIs: Herb-drug interactions; INR: International normalized ratio; mCPP: 1-(m-chlorophenyl) piperazine; MDR: Multidrug resistance; MRP2: Multidrug resistance-associated protein-2; NNRTI: Non-nucleoside reverse transcriptase inhibitors; OTC: Over the counter; P-gp: P-Glycoprotein; SJW: St. John's wort; t_{1/2}: Elimination half-lives; TXA₂: Thromboxane A₂; UDP: Uridine diphosphate; USD: United States dollar; V_d: Apparent volume of distribution

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