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REVIEW

Herb–drug interaction studies of herbs used in treatment of cardiovascular disorders—A narrative review of preclinical and clinical studies

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About 70% of the world population is currently using medicinal herbs as complementary or alternative medicine, which is increasing at a tremendous pace in both developed and developing countries in the last two decades (World Health Organization Medicines Strategy 2002–2005). This increase in consumer demand of medicinal herbs continues despite the rarity of scientific data to establish their safety and efficacy profile. Its popularity is also attributed to several factors, including easy availability, cost effectiveness leading to better purchasing power and general perception that they are safe. Herbs are often administered concomitantly with therapeutic drugs for the treatment of major ailments, raising the potential for herb–drug interactions (HDIs). The major pathways postulated for HDIs involves the cytochrome P450 (CYP450)-mediated inhibition or induction and transport and efflux proteins. In our review, we highlight frequently used herbal medicines for the treatment of cardiovascular disorders (CVD), their established HDIs studied using in vitro tools and in vivo pharmacokinetic and pharmacodynamic assays and case reports. Herbs have been divided into different sections on the basis of availability of HDI data in relevance to cardiovascular drugs: herbs reported to interact with cardiac drugs, herbs yet to be reported for interaction with drugs of any class and herbs reported to interact with drugs of other therapeutic category but not with cardiac drugs. The amount of active phytoconstituents present in the selected herbs and their extent of bioavailability are also mentioned. This review can serve as a quick reference database for physicians and health care professionals involved in CVD treatment, aimed at maximizing clinical outcomes with reduction in adverse and toxic effects.

KEYWORDS

cardiovascular diseases, cardiovascular drugs, cardiovascular herbs, CYP inhibition, herb–drug interaction, herbs

1 | INTRODUCTION

Herbal remedies are considered to be the best choice as complementary medicine in the western countries, especially in the United States and Europe. In 2014, it was reported that the annual sales of dietary herbal supplements increased by 6.8% in the United States, with an estimated total reaching more than $6.4 billion (Smith et al., 2015), with China and India being the top exporting countries, and Hong Kong, Japan, the United States and Germany being the leading importers. A study by the Confederation of Indian Industry (CII) states that the Ayurvedic sector in the country will achieve a gross market size of $4.4 billion, or roughly ₹30,000 crore by the end of 2018 with

the overall market size of the Indian wellness industry, which is put at $11.8 billion (Confederation of Indian Industry, 2018). There has been a surge in the demand of "alternative" medicine, including those derived from plant or herbal origin. There is also a substantial increase in self-administration of herbal medicines among the general public (Ekor, 2014). In the context of increasing demand and use of herbal remedies by the patients and general public and subsequent interest of the regulatory authorities, it is necessary to encourage extensive research regarding the safety and efficacy of herbal products including the possibility of interactions when there is concurrent administration of herbal medicines with modern drugs (Zhang, Onakpoya, Posadzki, & Eddouks, 2015). This is because all herbal medicines and dietary supplements are complex mixture of more than one active phytoconstituent, which increases the possibility of herb–drug interactions (HDIs) (Izzo, Borrelli, & Capasso, 2002). Most of the people who consume herbal products and supplements do not reveal about this to their pharmacist or physician, thereby increasing the likelihood of the HDIs not being identified and resolved in time. Nevertheless, data from recent studies suggest that a serious potential for interactions exist between some commonly administered herbal remedies and widely used standard pharmaceuticals, including those used in the treatment of cardiovascular diseases (Izzo, Hoon-Kim, Radhakrishnan, & Williamson, 2016).

In 2015, there was an estimated 422.7 million cases of cardiovascular diseases (CVD) and 17.92 million CVD deaths reported across the globe. The estimated age-standardized prevalence of CVD in India in 2016 was 5,681 per 100,000 (Roth et al., 2017). The absolute estimated prevalence of CVD in India (54.6 million) is >60%, larger than in the United States (33.6 million). Between 1990 and 2016, deaths due to CVD in India rose by around 34% from 155.7 to 209.1 deaths per lakh (Prabhakaran, Jeemon, et al., 2018). It is estimated that the leading cause of mortality in India is CVD, which accounts for 28·1% of all deaths (Prabhakaran, Singh, et al., 2018). About 65.7% of people above 60 years of age in India still prefer complementary and alternative medicine (CAM) as the initial choice of therapy (Sharma, Dubey, Malhotra, Manocha, & Handu, 2017). Consumption of nonprescribed CAM in unmonitored fashion compromises the effective medical management of CVD, as it increases the risk of HDI (Grant, Bin, Kiat, & Chang, 2012). In cardiac therapy, the narrow therapeutic window of drugs and the wide range of cardiac medications available for treatment are also the reasons of major concern for HDI. People with chronic diseases frequently use CAM therapies in an unsuitable manner to manage their condition, and thus increase the potential or possibility of occurrence of HDI (AARP and National Center for Complementary and Alternative Medicine, 2011). The major focus of the present review is to provide an overview on the safety and efficacy of some of the commonly used herbal medicines in treatment of CVD, including their possible HDIs. The review is prepared based on careful examination of pre-existing systematic reviews and research articles published in reputed databases and searched up to 2018 in their entirety. Also HDI reported on the basis of clinical case studies are also presented.

2 | ROLE AND ABUNDANCE OF CYTOCHROME P450 (CYP) ENZYMES IN HUMANS

The literature suggests that the CYP enzymes are predominantly responsible for HDI. CYP enzymes are conventionally divided into various families and subfamilies (Rosenkranz et al., 2012). The various families of CYP possess a high degree of substrate specificity. CYP families 1, 2 and 3 are primarily involved in the metabolism of xenobiotics, thus playing a principal role in the production and excretion of endogenous compounds such as bile acids, hormones and fatty acids (Amacher, 2010; Norlin & Wikvall, 2007). The most significant CYP subfamilies in humans responsible for drug metabolism are 1A2, 2A6, 3A4, 3A5, 2C9, 2C19, 2D6 and 2E1 (Satoh et al., 2009; Wang & Chou, 2010).

CYP1A1 and 1A2 are the two vital members of the CYP1A subfamily in humans. CYP1A1 is mainly present in the extra-hepatic tissues of kidneys, intestines and lungs, while CYP1A2 makes up for about 15% of total hepatic CYP content (Martignoni, Groothuis, & de Kanter, 2006). Most of the members of the CYP2B subfamily play a less significant role in metabolism, except CYP2B6 (Pavek & Dvorak, 2008). The second most abundant subfamily is CYP2C, constituting over 20% of the total human CYP hepatic enzymes, with CYP 2C8, 2C9 and 2C19 being the three most active members, all of which are responsible for the metabolism of most endogenous and xenobiotic compounds (Lewis, 2004). CYP2E1 is the most active member of the 2E subfamily which constitutes less than 2% of total CYP content (Leclercq et al., 2000).

CYP3A is the most prominent and abundant subfamily, which constitutes over 40% of the total CYP isoforms in humans. (Levels may vary 40-fold among individuals depending upon genetic makeup.) It is highly expressed in the liver and intestines and is responsible for the metabolism of more than half of the drugs in use today (Ferguson & Tyndale, 2011; Singh, Kashyap, Pandey, & Saini, 2011). The enzyme specific substrates and inhibitors are particularly useful in pharmacokinetic and toxicological studies such as enzyme inhibition and induction as well as HDI studies.

3 | MECHANISM OF HDI

3.1 | Induction and inhibition of metabolic enzymes (enzyme-mediated HDIs)

The CYP super family of enzymes is responsible for oxidative, per oxidative and reductive biotransformation of xenobiotics (foreign chemical substances) and endogenous compounds (Hiratsuka, 2011; Nebert & Russell, 2002). Induction is described as the increase in the activity of intestinal and hepatic enzymes because of the increased mRNA transcription, leading to higher protein levels than normal. As a result, there is an increase in the rate of drug metabolism, which affects the oral bioavailability as well as the systemic disposition of drugs. During preformulation development of an oral dosage form,

pre-systemic metabolism of drug is taken into consideration in order to decide the effective dose required to achieve therapeutic systemic bioavailability. An interruption of pre-systemic metabolism by co-administration of an herbal product can cause significant changes in plasma concentration of the given drug. Certain herbal products have been reported to be capable of inducing CYP enzymes. Administration of prescription drugs and enzyme-inducing herbal products simultaneously can therefore bring about sub-therapeutic plasma levels of the former with therapeutic failure as a possible clinical effect (Rosenkranz et al., 2012).

Apart from enzyme induction, herbal products are also capable of inhibiting enzyme activities. The inhibition of CYP and other metabolic enzymes usually has a competitive nature with its effects being instantaneous and inhibitor concentration dependent (Zhang & Wong, 2005). Most inhibitors are the substrates of the respective CYP enzymes (Zhou, 2008). This results in significant alteration of pharmacokinetic profiles of xenobiotics. A decrease in the pre-systemic intestinal metabolism (as predicted during preformualtion studies) and hepatic metabolism of the drug by co-administered herbal formulation results in an increase in the bioavailability of drug due to increased absorption and distribution, this increase in the plasma concentration of drug beyond therapeutic level as well as its ultimately accumulation results in manifestation of toxic side effects of drug. At the same time, induction of pre-systemic and hepatic metabolism of drug due to interaction of co-administered herb with intestinal or hepatic CYP enzymes might result in sub-therapeutic levels of drug leading to decreased bioavailability. Drug accumulation is another equally, clinically significant effect of enzyme inhibition that is caused due to subdued hepatic clearance. In the case of drugs with narrow therapeutic window or steep dose–response profiles, these effects are of particular concern.

3.2 | Inhibition and induction of transport and efflux proteins (transporter-mediated HDIs)

The ATP-binding cassette (ABC) family of drug transporters plays an important role in the absorption, distribution and excretion of various medications. P-gp, a 170-kDa plasma glycoprotein encoded by the human MDRI gene, is the most studied member of this family. It is essentially present in a number of body tissues with the apical epithelial surfaces of the bile canaliculi of liver, the pancreatic ductal cells, the proximal tubules of kidneys, the columnar mucosal cells of the small intestine, colon and the adrenal glands being the sites with most abundant concentrations (DeGorter, Xia, Yang, & Kim, 2011; Marzolini, Paus, & Buclin, 2004). It is principally involved in the absorption and elimination of drugs from the intestine, liver, brain and kidneys. These proteins specifically take part in the process of direct intestinal, hepatobiliary and urinary excretion of drugs and their respective metabolites (Szakács, Váradi, Özvegy-Laczka, & Sarkadi, 2008). Thus, co-administration of herbs can result in modulation of P-gp, or its competitive affinity for its binding sites can potentially result in an alteration of the pharmacokinetic profile of drugs.

3.3 | Dual enzyme- and transporter-mediated HDIs

Both transporter and CYP functions are known to be affected by some herbal products. Both P-gp and CYP3A4 constitute an efficient barrier for most of the orally absorbable drugs with an extensive overlapping in their substrate molecules (Christians, Schmitz, & Haschke, 2005). When conventional drugs and herbal products are co-administrered, modifications in the normal activity of P-gp efflux and CYP are observed, which in turn has an influence on the pharmacokinetic disposition of CYP3A and P-gp substrate drugs, leading to lowered efficacy and/or occurrence of toxicity (Markowitz et al., 2003).

3.4 | Alteration of gastrointestinal functions

Herbal medicines are also capable of altering the absorption and disposition of concomitantly administered conventional medicines by alteration of the pH of gastrointestinal tract and other biochemical factors that affect the dissolution properties as well as the absorption of pH-dependent drugs. In addition, phenomena like complexation and chelation can lead to the formation of complexes that are insoluble in nature and their competition with site-specific substrates at the sites of absorption greatly affects the rate of absorption of medicines. Plants containing anthranoids such as Cassia (*Cassia senna*), Rhubarb (*Rheum officinale*), Cascara (*Rhamnus purshiana*) and soluble fibres like Guar gum and Psyllium are reported to decrease GI transit time, thereby decreasing the drug absorption. These plants are known to increase GIT motility. On concomitant administration with prescribed drugs, significant changes in the absorption of drugs has been reported as a result of decreased GI transit time (Fugh-Berman, 2000). In a study carried out on *Polygonum paleaceum*, a Chinese herbal plant, a potential to decrease the motility of GIT, thereby delaying gastric emptying and inhibition of defecation reflex were reported in mice (Zhang & Wong, 2005).

3.5 | Alteration in renal elimination

Some herbal products are capable of interfering with renal functions, leading to alteration in the renal elimination of drugs. The inhibition of tubular secretion and/or reabsorption, or interference with glomerular filtration are responsible for such type of interaction (Bagnis, Deray, Baumelou, Le Quintrec, & Vanherweghem, 2004). In addition, there are certain herbal products consumed as diuretics. The mechanism of diuresis by these herbal products is complex and non-uniform. Certain herbal products do not affect electrolyte secretion but induce the glomerular filtration rate (GFR), while some others act as direct inducers of both tubular secretionas well as GFR (Al-Ali, Wahbi, Twaij, & Al-Badr, 2003; Crosby et al., 2004).

3.6 | Search strategy and data sources used

A systematic literature search was performed using several electronic literature databases such as PubMed, Medline database and the

National Center for Complementary and Integrative Health website. All databases were searched up to 2018 in their entirety. The search terms included the following: herb–drug interactions, cardiovascular herbs, CVD, CYP inhibition and induction and cardiovascular drugs. We searched for data on products of herbal origin used in the treatment of CVD using suitable key words, and each of the individual herbs is discussed in this review.

3.7 | Selection criteria

Articles selected for review met the following inclusion criteria: articles on herbs used in the treatment of CVD, articles on CYP induction/inhibition by herbal drugs, articles and case reports with preclinical and clinical studies involving cardiovascular herbs written with an emphasis on the possibility of HDIs.

4 | HERBS ADMINISTERED IN CVD AND THEIR REPORTED HDI WITH CARDIOVASCULAR DRUGS

This part of our review focuses on the herbs for which HDI with cardiovascular drugs are reported in the literature, performed either through preclinical or clinical studies (rats or humans) or suitable case reports. These herbs are reported to affect the pharmacokinetics of certain cardiovascular drugs through various mechanism of HDI as discussed earlier. The reported HDI studies of some commonly used herbs for the treatment of CVDs are summarized in Table 1.

4.1 | *Piper longum*

Piper longum L. (Piperaceae), also known as "long pepper" is widely distributed throughout the Indian subcontinent. Piperine is the major active and most abundant phytoconstituent of *Piper longum*. The piperine content in *Piper longum* on dry weight basis is 3–5%. It also consists of a large number of other alkaloids and related compounds, such as methyl piperine, iperonaline, piperettine, asarinine, pellitorine. An amide dehydropipernonaline isolated from the *Piper longum* fruit is reported to possess coronary vasorelaxant activity (Shoji et al., 1986). As per Iwashita and associates, various extracts of *Piper longum* consist of constituents that non-competitively subdue platelet aggregation activity as a result of thromboxane A2 receptor antagonism (Iwashita et al., 2007). Piperine, as a beta-adrenergic receptor blocker antagonist is reported to exhibit negative inotropic and negative chronotropic activity. Piperlonguminine (PL), a major alkaloid from fruits, shows anti-hyperlipidemic and anti-inflammatory activity. As per the study performed by Bhardwaj and co-workers, piperine inhibited CYP3A4 mediated metabolism of verapamil with an IC_{50} 36 ± 8 μM and P-gp mediated efflux of digoxin and cyclosporine with IC_{50} values of 15.5 and 74.1 μM respectively, in human Caco-2 cells lines (Bhardwaj, 2003).

Piper longum, in human liver microsomes potently inhibited CYP1A2 mediated phenacetin O-deethylation metabolism with IC_{50} value of 8.8 μM, inhibition was NADPH-independent, while other CYPs were not significantly inhibited (Song et al., 2014). Piperine (35 mg/kg p.o.) is reported to alter the pharmacokinetics of docetaxel (7 mg/kg i.v.) in rats, resulting in an increase in the C_{max} (from 1,625.52 ± 355.53 to 6,603.58 ± 1889.89 ng/ml) and AUC (from 48,091.93 ± 5,392.78 to 77,780.29 ± 11,963.62 min ng/ml) ($p < .001$) (Li et al., 2016). In a crossover study performed by Bano et al., six healthy human volunteers were treated with piperine (20 mg) daily for 7 days followed by a single dose of propranolol (40 mg) and theophylline (150 mg) on two different occasions. Results demonstrated a reduction in T_{max} with increased C_{max} and AUC for propranolol. A higher C_{max}, longer elimination half-life and higher AUC was observed for theophylline (Bano et al., 1991). These studies help to establish evidence of bioavailability enhancement of drugs that act as substrates of CYP3A4, CYP2D6 and CYP1A2 enzymes (verapamil, propranolol and theophylline, respectively) with concomitant administration of piperine. Also interaction with digoxin and cyclosporine were studied that were mediated through P-gp inhibition. Hence, patients suffering from cardiovascular complications should practice care during simultaneous administration of herbal products such as *Piper longum* containing piperine and piperlongumine with the drugs mentioned above.

4.2 | *Curcuma longa*

Curcuma longa L, or turmeric belonging to the Zingiberaceae (ginger) family, is a perennial herb cultivated extensively in India and China. The primary active constituent of *Curcuma longa* are curcuminoids, a group of flavonoids consisting of curcumin (90%), mono-dexmethoxy curcumin and bis-desmethoxy curcumin. Curcuma consists of an average of 1.56% of curcumin on a dry weight basis (Tayyem, Heath, Al-Delaimy, & Rock, 2006). The cardioprotective properties of turmeric include lowering of cholesterol and triglycerides, reduced tendency of low density lipoprotein (LDL) to undergo lipid peroxidation and inhibition of platelet aggregation (Ramírez-Tortosa et al., 1999). Curcumin, despite its limited oral bioavailability of 60–66% (Ravindranath & Chandrasekhara, 1981) was identified as an inhibitor of p300-HAT, a well-known cardiac hypertrophy inducer in a culture of cardiomyocytes thus preventing heart failure in heart failure models of two different types: in vivo hypertensive salt sensitive Dahl rats and in a surgically induced rat model of myocardial infarction (Morimoto et al., 2008). Curcuminoids are known to affect CYP1A2 (constitutes about 13% of the total human liver CYP enzymes) and is responsible for the metabolism of arylamines like theophylline (Liu, Sridhar, & Foroozesh, 2013). Curcumin is reported to competitively inhibit CYP1A2 with IC_{50} value of 40.0 μM, using in vitro CYP enzymes expressed using cell membrane of *E. coli*. Curcumin, with an IC_{50} of 24.5 μM, acts as a competitive inhibitor of the CYP2B6 enzyme (Appiah-Opong, Commandeur, van Vugt-Lussenburg, & Vermeulen, 2007). In another research, curcumin was reported to inhibit CYP3A4 (IC_{50}11.93 ± 3.49 μM) and CYP2C9

TABLE 1 Reported HDI study of some commonly used herbs for the treatment of CVDs

Herbs	Active phytoconstituents	Reported pharmacological activities	CYP, P-gp induction/inhibition	Interacting drugs
Piper longum	Piperine, methyl Piperine, Dehydropipernonaline, Iperonaline, Piperettine, Asarinine, Pellitorine	Coronary vasorelaxant, negative inotropic & negative chronotropic effect, anti-hyperlipidemic & anti-inflammatory effects. (Bhardwaj, 2003; Iwashita, Saito, Yamaguchi, Takagaki, & Nakahata, 2007; Shoji et al., 1986)	CYP3A4, CYP2D6 and CYP1A2 (inhibition)	Verapamil, Digoxin *(P-gp inhibition)* (Bhardwaj, 2003) Propranolol, (Bano et al., 1991)
Curcuma longa	Curcuminoids	Anti-hyperlipidemic & anti-platelet effect (Morimoto et al., 2008; Ramírez-Tortosa et al., 1999)	CYP3A4, CYP1A2, CYP2B6, CYP2C19, CYP2C9 (inhibition) P-gp inhibition	Losartan, rosuvastatin (OAT, P transporter inhibition), warfarin, Clopidogrel (P-gp inhibition). Pharmacokinetic interactions (Zhou et al., 2017)
Fucus vesiculous (seaweed)	Carbohydrates, proteins, lipids	Hypocholesterolem-ic, antioxidant, anti-hypertensive. (Ardiansyah et al., 2006; Jiménez-Escrig & Cambrodón, 1999; Jiménez-Escrig & Sánchez-Muniz, 2000)	CYP1A (induction), CYP2C9 (inhibition)	Amiodarone (Rodrigues, Alves, Abrantes, & Falcão, 2013), Valsartan (Nakashima et al., 2005; Vitalone et al., 2011)
Zingiber officinale (rhizome)	Gingerols, shogaols, volatile oil, monoterpenoids and sesquiterpenoids, including camphene, borneol, zingiberene, sesquiphellandrene, and bisabolene.	Anti-platelet and anti-hypertensive activity (Ghayur & Gilani, 2005)	CYP2C9 (potent inhibition) CYP2C19, CYP3A4 (moderate inhibition)	Nifedipine (Young et al., 2006) Phenprocoumon (Krüth, Brosi, Fux, Mörike, & Gleiter, 2004) (PD-based study)
Terminalia belerica	Glucoside, tannins, Gallic acid, ethyl Gallate, Chebulinic acid	Anti-hypertensive, antioxidant activity (Khan & Gilanii, 2008)	CYP3A4 CYP2D6	Diltiazem (Athukuri & Neerati, 2017)
Salvia miltiorrhiza (Danshen)	Diterpene compounds and phenolic acids, Tanshinone I, tanshinone IIA, cryptotanshinone, dihydrotanshinone, baicalin, β-sitosterol, ursolic acid and daucosterol	Anti-hyperlipidemic, anti-hypertensive activity, treatment of coronary artery disease. (Cheng, 1987; Zhou, Shao, & Duan, 1999)	CYP3A4 (induction) CYP1A2, CYP2C9, CYP1E1, CYP2C6, CYP2C11 (inhibition)	Warfarin (Qiu et al., 2010; Wu & Yeung, 2010)
Allium sativum (garlic)	Allicin, Diallyl disulfide, Alliin, Ajoene & arginine	Vasorelaxant, anti-thrombotic, antiatherosclerotic, anti-hyperlipidemic, (Koscielny et al., 1999; Orekhov & Grünwald, 1997; Suetsuna, 1998)	CYP2C9, CYP3A4 & CYP2D6 (inhibition) P-gp induction	Atorvastatin (Reddy et al., 2012), Cilostazol (Mateen, Rani, Naidu, & Chandrashekar, 2011) (PD-based study)
Ginkgo biloba	Terpenoids and flavonoids as ginkgolide-A and-B, bilobalide, quercetin, kaempferol, rutin and quercitin	Antioxidant, antiatherosclerotic, cardioprotective, vasorelaxant (Kim et al., 1998; Mansour, Bahgat, El-Khatib, & Khayyal, 2011; Rodríguez et al., 2007)	CYP1A2, CYP3A, and CYP2C9 (inhibition) CYP2C19 (induction)	Diltiazem (Ohnishi et al., 2003), Cilostazol (Aruna & Naidu, 2007).
Glycyrrhiza glabra	Triterpene, saponins, glycyrrhizin and glycyrrhetic acid.	Antioxidant, anti-platelet, vasorelaxant (Ross, 2001) (Yu et al., 2005; Yu & Kuo, 1995)	CYP2B6, CYP2C9, CYP2C19 (inhibition) CYP3A4 (induction)	Atorvastatin, simvastatin, and lovastatin (P-gp inhibition). (Dayyih, Mallah, Al-Ani, & Arafat, 2016)
Panax ginseng	Ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids	Protection against myocardial and cerebral ischaemia, antioxidant and anti-free radical effects (Chen, 1996)	CYP3A4 (induction), CYP2C11 (inhibition)	Warafrin (PD-based study) (Lee, Ahn, Ahn, Doo, & Lee, 2008).
Radix puerariae Lobatae (Gegen)	Puerarin, coumarins, puerarols, triterpenes, and triterpenoid glycosides	Cardioprotective, anti-hypertensive effects. (Shibata, Murakami, Nishikawa, & Harada, 2011)	CYP 1A2 (induction) CYP2D6, CYP3A4, and OATs (inhibition)	Warfarin (Ge, Zhang, & Zuo, 2016).

(IC_{50} 14.58 ± 4.57 μM) (Shamsi et al., 2017). Curcuminoid extract is also reported to inhibit CYP2C19 with a IC_{50} value of 7.4 ± 1.2 μM, (Volak, Ghirmai, & Cashman, 2008), which is responsible for the metabolism and conversion of clopidogrel (as a pro-drug) into its active metabolite (Holmes, Perel, Shah, Hingorani, & Casas, 2011; Liu et al., 2012). Curcumin pre-treatment (100 mg/kg, for 7 days) in rats is reported to enhance plasma concentrations of losartan (10 mg/kg) and its metabolite EXP3174 (Liu et al., 2012). Curcumin is reported to alter the pharmacokinetics of a number of cardiovascular drugs such as rosuvastatin by inhibition of OATP transporters; warfarin and clopidogrel by inhibition of P-gp in rats and dog plasma (Zhou et al., 2017), thereby affecting their cholesterol lowering and anti-coagulant action respectively (Bahramsoltani, Rahimi, & Farzaei, 2017). Subsequently as per a case report, curcuma was reported to result in clinical interaction with clopidogrel leading to GIT bleeding, which was manifested due to CYP3A4 inhibition (Levy, Attias, Ben-Arye, Goldstein, & Schiff, 2017).

4.3 | *Fucus vesiculosus* (seaweed)

Most algae consumed as human food are benthic macroalgae belonging to phyla Rodophyta, Clorophyta and Phaeophyta family. Red seaweeds of the genus *Porphyra*, green seaweeds of the genus *Ulva* and brown seaweeds of the genus *Laminaria* are the most common edible algae (McHugh, 1991). Air-dried seaweeds consist of carbohydrate 3–47%, protein 33–75% and lipid 1.5–4%, with the ash content of 0–35% (Indergaard, 1991; Mabeau & Fleurence, 1993). The moisture content of fresh seaweeds varies from 80 to 90%, while in the air-dried algae it is 10–20% (Holland, Unwin, & Buss, 1991; Nisizawa, Noda, Kikuchi, & Watanabe, 2004). Hypocholesterolemic and anti-hypertensive effects of seaweeds in experimental animals is attributed to the water-soluble fractions of seaweeds or isolated algal polysaccharide (Ardiansyah et al., 2006; Jiménez-Escrig & Sánchez-Muniz, 2000). Seaweeds are also reported to possess antioxidant properties, and thus provide cardioprotective action. It is known to decrease LDL concentration and increase HDL concentration (Antonio Jiménez-Escrig & Cambrodón, 1999). In an in vitro CYP inhibition study, algal phenols from seaweeds have been reported to inhibit CYP1A enzyme (IC_{50}: 17.9–33 μg/ml) (Parys et al., 2010). In a 14-day HDI study in rats, the bioavailability of amiodarone (50 mg/kg, p.o.) was found to decrease by 55.4% in the presence of *Fucus vesiculosus* seaweed extract (575 mg/kg, p.o.), thereby establishing in vivo CYP1A induction potential (Rodrigues et al., 2013). In addition, a case report of a 50-year-old female patient indicated adverse reaction involving co-administration of *Fucus vesiculosus* supplement with valsartan (metabolized by CYP2C9) leading to hypertransaminasemia. This study further supports its interaction potential with cardiovascular drugs (Nakashima et al., 2005; Vitalone et al., 2011). Thus, it can be advised that botanicals and nutraceuticals obtained from or containing *F. vesiculosus* should be administered with care, especially when being concomitantly administered with conventional cardiovascular drugs acting as substrates of CYP1A and CYP2C9 enzymes.

4.4 | *Zingiber officinale* (rhizome)

Zingiber officinale or ginger (family Zingiberaceae) is a plant rhizome native to Asia. It is reported to consist of carbohydrates, fats, protein, fibres and volatile oil. Gingerols, a group of phenols is responsible for the pungency of fresh ginger. Fresh ginger consists of a 5-deoxy derivative of gingerol called paradol. Dehydrated forms of gingerols, that is, shogaols, are responsible for the pungency exhibited by dry ginger. The volatile oil content (1–3%) in ginger is responsible for its distinctive odour, and is mainly composed of monoterpenoids and sesquiterpenoids, including camphene, borneol, zingiberene, sesquiphellandrene, and bisabolene (Chrubasik, Pittler, & Roufogalis, 2005; Langner, Greifenberg, & Gruenwald, 1998). A number of studies conducted in animals propose that ginger may show blood pressure lowering effect by the inhibition of voltage-dependent calcium channels as well as by the stimulation of muscarinic receptors (Ghayur & Gilani, 2005). All three gingerols, 6-, 8-, and 10-gingerol are documented to effectively inhibit CYP2C9 activity, showing moderate inhibition of CYP2C19 and CYP3A4, and weak inhibition of CYP2D6. 8-gingerol exhibited potent inhibition of P450 enzymes with IC_{50} values of 6.8, 12.5, 8.7 and 42.7 μmol/L for CYP2C9, CYP2C19, CYP3A4, and CYP2D6, respectively (Li et al., 2013). Ginger has been widely documented for its anti-hypertensive and anti-platelet activity. Ginger has been reported to result in some pharmacodynamic based HDI. It has been studied for its capacity to alter blood clotting. One study conducted in humans proposed that the intake of 1 g of ginger powder may produce a synergistic effect on inhibition of platelet aggregation in patients suffering from hypertension when administered in combination with nifedipine (Young et al., 2006). In another study, a dose of 10 g of ginger powder brought about a significant reduction of ADP- and epinephrine-induced platelet aggregation in patients suffering with coronary artery disease (Bordia, Verma, & Srivastava, 1997). A case report of a 76-year-old white European woman on long-term phenprocoumon therapy, experienced over anticoagulation which was reported to occur due to concomitant consumption of ginger leading to prolongation of partial thromboplastin time (Krüth et al., 2004).

In view of the above-mentioned reports, it can be proposed that concomitant administration of ginger with anticoagulants and anti-hyperlipidemics may result in potential PD-based HDIs.

4.5 | *Terminalia bellerica*

Terminalia bellerica Roxb (family: Combretaceae) is found extensively throughout the Indian subcontinent. It is reported to consist of gallic acid, chebulinic acid, glucosides and tannins. The amount of gallic acid reported to be present in *Terminalia bellerica* extract is about 4.16% w/w, with oral bioavailability of 42% in rats (Konishi, Hitomi, & Yoshioka, 2004; Meena et al., 2018). *Terminalia bellerica* is known to act as an antioxidant, anti-hypertensive, hepatoprotective and antipyretic agent. It has been evaluated for its anti-hypertensive effect in hypertension models: in rats under anaesthesia, in isolated guinea-pig

atria model and in thoracic aorta of rabbit (Khan & Gilanii, 2008; Dwivedi, et al., 1988). "Triphala" a well-known Ayurvedic polyherbal formulations is the mixture of three (tri) fruits (phala) consisting of *Emblica officinalis*, *Terminalia bellirica* and *Terminalia chebula*. *Terminalia bellerica* Linn is reported to contain gallic acid (4.30 ± 2.09 mg/g). The formulation through CYP450–CO complex assay exhibited 23% inhibition of the rat liver microsomes. Further, the ethanolic solution of standardized formulation demonstrated inhibitory activity on CYP3A4 (IC_{50}:119.65 ± 1.91 μg/ml) and CYP2D6 (IC_{50}:105.03 ± 0.98 μg/ml). Gallic acid is also reported to inhibit both the enzymes at IC_{50} values of 87.24 ± 1.11 μg/ml and 92.03 ± 0.38 μg/ml, respectively (Ponnusankar, Pandit, Babu, Bandyopadhyay, & Mukherjee, 2011). Gallic acid (50 mg/kg) and ellagic acid (50 mg/kg) are reported to enhance oral bioavailability of Diltiazem (15 mg/kg) in male Wistar rats by increasing the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ and decreasing CL by almost two fold each ($p < .05$) (Athukuri & Neerati, 2017). Therefore, we propose that further in vivo studies involving humans or animals to evaluate the effect of concomitant administration of *Terminalia bellerica* with conventional cardiovascular drugs metabolized by CYP3A4 and CYP2D6 needs to be carried out to identify potential HDI.

4.6 | *Salvia miltiorrhiza* (Danshen)

Salvia miltiorrhiza (family: Labiatae) also known as "Danshen" or "Red Sage" consist of more than 30 diterpene compounds as the chief lipophilic phytoconstituents. The major diterpene phytoconstituents of *Salvia miltiorrhiza* are dihydrotanshinone I: 0.086 to 0.86 mg/g; cryptotanshinone: 0.24 to 1.8 mg/g; tanshinone I: 0.064 to 1.4 mg/g; tanshinone IIA: 0.64 to 2.4 mg/g. However, oral bioavailability is low owing to poor water solubility and low dissolution rate (Cai et al., 2016; Hu, Luo, Zhao, & Jiang, 2005). The herb is also reported to consist of about 15 different phenolic acids, which are the chief hydrophilic components of danshen. In addition to diterpenes and phenolic acids, danshen also consist of β-sitosterol, ursolic acid and daucosterol obtained from its alcoholic extract. Danshen is referred to be significantly effective in activating blood circulation, dispersing of clots and prevent blood sludging (Cheng, 1987; Zhou et al., 1999). The most vital and recurrent clinical use of danshen includes treatment of angina pectoris, coronary artery spasm, myocardial infarction, hyperlipidaemia and hypertension. In comparison to the hydrophilic constituents present in the extracts, lipophilic constituents such as tanshinones possess more potent inhibitory effects on CYP enzyme activities. Tanshinone I, tanshinone IIA, cryptotanshinone and dihydrotanshinone I are reported to inhibit CYP1A2 with IC_{50} values ranging from 0.02 to 3.0 μM using both HLMs and recombinant CYP1A2 enzyme assay (Wang, Cheung, Lee, Or, & Yeung, 2010; Zhou, Chan, & Yeung, 2012). Likewise, tanshinone I, dihydrotanshinone I and cryptotanshinone inhibited CYP2E1 with IC_{50} values in the range of 0.7 to 10 μM. Cryptotanshinone and dihydrotanshinone I also inhibited CYP2C9 with IC_{50} values ranging from 7.5 to 33 μM. Tanshinone I, tanshinone IIA, and cryptotanshinone exihibited weak inhibitory action (IC_{50} > 75μM) against CYP2D6 and CYP3A4 (Zhou et al., 2012). Nevertheless, dihydrotanshinone I is documented to exert a potent inhibitory action towards CYP3A4 with IC_{50} value at 1.2–3.2 μM (Qiu et al., 2013; Wang et al., 2010). Qiu and co-workers reported that administration of single dose of the extract (1 g) caused the mean C_{max} of midazolam to increase by 87% compared to that of control. After 10 days of administration of danshen extract (1 g, 3 times a day) in 12 healthy male human volunteers, a decrease in C_{max}, $AUC_{0-\infty}$ and $T_{1/2}$ of midazolam was observed by 79.9, 66.6, and 43.8%, respectively. The in vitro study demonstrated that inhibition of CYP3A could be due to dihydrotanshinone I present in the extract, while tanshinone IIA and cryptotanshinone could induce CYP3A. The study indicated that single-dose administration of danshen extract resulted in inhibition of intestinal CYP3A, but multidose administration can cause induction of intestinal and hepatic CYP3A (Qiu et al., 2013). A 3-day treatment of *Salvia miltiorrhiza* (200 mg/ kg/day) in rats resulted in inhibition of warfarin (2 mg/kg) hydroxylation. The steady-state plasma concentration of warfarin increased by 23% on co-administration of danshen. The results suggested that CYP1A1, CYP2C6 and CYP2C11-mediated warfarin metabolism was inhibited by tanshinones (Wu & Yeung, 2010). This indicates potential HDI between warfarin and *Salvia miltiorrhiza*. Another pharmacokinetic study in healthy human volunteers, on multiple dose administration of danshen tablets (1 g for 14 days), resulted in induction of CYP3A4 in the gut (Qiu et al., 2010).

Therefore, owing its potential CYP inhibition and induction potential coupled with in vitro and in vivo drug interaction potential; co-administration of *Salvia miltiorrhiza* with aforementioned drugs should be avoided.

4.7 | *Allium sativum* (garlic)

Allium sativum or Garlic (family: Amaryllidaceae) is a rhizome known for its anti-thrombotic and anti-atherosclerotic cardioprotective properties (Koscielny et al., 1999; Orekhov & Grünwald, 1997). Seven dipeptides present in garlic extracts are responsible for its anti-hypertensive property (Suetsuna, 1998). Allicin present in garlic is known to attenuate dexamethasone induced hypertension in rats, thus imparting anti-hypertensive property. The phytoconstituents of *Allium sativum* which are responsible for its pharmacological actions are allicin, alliin, ajoene, diallyl disulfide and arginine. The amount of allicin reported to be present is 332 ± 5 μg/g with around 95% of absorption after oral intake in humans (Farías-Campomanes, Horita, Pollonio, & Meireles, 2014; Lawson & Wang, 2005). As per the study by Beatrice and co-workers in human Fa2N-4 hepatocytes, garlic is reported to affect the metabolism of drugs such as warfarin mediated by CYP2C9, 2D6 and 3A4. Reduction of greater than 90% activity of CYP2C9 enzyme was observed following administration of 50 μg/ml of garlic extract for 4 days (Ho et al., 2010). Garlic (1% w/w) has been documented to pharmacokinetically interact with atorvastatin (10 mg/kg) in rats which resulted in an increase in C_{max}, AUC and MRT of atorvastatin ($p < .05$) (Reddy et al., 2012). Garlic is also reported to modify the pharmacodynamics of cilostazol in a study

carried out in 14 patients with type II diabetes mellitus. After administration of 600 mg of aged garlic extract, inhibition of platelet aggregation with cilostazol at all time points was tested, with maximum inhibition shown at 4 hours (Mateen et al., 2011). In another study performed in healthy human volunteers, after administration of garlic extract (GarliPure®, 600 mg caplet) for 4 days, induction of P-glycoprotein activity was observed with no effect on CYP3A4, in the human intestine and liver using saquinavir as a substrate (Hajda et al., 2010). Thus, owing to its potential to inhibit CYP2C9 enzyme activity in vitro and induce P-gp activity in vivo, along with its pharmacodynamic interaction with cilostazol, we propose that the concomitant administration of garlic supplements along with conventional drugs of antiplatelets or hypercholesteraemic class should be monitored vigilantly.

4.8 | *Ginkgo biloba*

Ginkgo biloba or Maidenhair (family: Ginkgoaceae), the leaves of which are reported to contain terpenoids and flavonoids such as ginkgolide-A and ginkgolide-B, bilobalide, quercetin, kaempferol, rutin and quercetin (Trumbeckaite et al., 2007). The total flavonoid content in *Ginkgo biloba* extract is 22–27% (Yang, Li, Wu, & Liu, 2014). These phytoconstituents are responsible for its antioxidant and antiatherosclerotic property (Rodríguez et al., 2007). It is also reported to possess cardioprotective and vasorelaxant effect (Mansour et al., 2011). By acting as a platelet activating factor antagonist, it produces anti-platelet adhesive and anti-thrombotic effect (Kim et al., 1998). *Ginkgo biloba* has been investigated in human liver microsomes for their in vitro potential to interact with the major human CYP P450 isozymes. For terpene trilactones such as ginkgolides (A, B, C and J), bilobalide and flavanol glycosides; weak or negligible inhibitory activity was reported. For the flavanol aglycones kaempferol, quercetin, apigenin, myricetin, tamarixetin; IC_{50} values were reported against CYP1A2, CYP3A and CYP2C9 at concentrations less than 10 μg/ml (von Moltke et al., 2004). The extract of *Ginkgo biloba* was found to significantly inhibit CYP2C9 (IC_{50}:14 ± 4 μg/ml), and CYP1A2 (IC_{50}:106 ± 24 μg/ml), CYP2E1 (IC_{50}:127 ± 42 μg/ml), and CYP3A4 (IC_{50}:155 ± 43 μg/ml) to a lesser extent (Gaudineau, Beckerman, Welbourn, & Auclair, 2004). A noteworthy inductive effect on CYP2C19 activity was exerted by *Ginkgo biloba*. Leaf extract of *Ginkgo biloba* (20 mg/kg) is reported to alter the pharmacokinetics of diltiazem (30 mg/kg) after oral administration in rats. The results of the study indicated that the concomitant use of *Ginkgo biloba* leaf extract increased the bioavailability of diltiazem by inhibition of both intestinal and hepatic metabolism, at least partially, via a mechanism-based inhibition of CYP3A (Ohnishi et al., 2003). An HDI study performed in 18 healthy volunteers to investigate the interaction potential of *Ginkgo biloba* with omeprazole (CYP2C19 substrate) revealed that *Ginkgo biloba* (140 mg, bid for 12 days) causes induction of both omeprazole (40 mg) hydroxylation as well as renal clearance of its metabolite 5-hydroxyomeprazole (Yin, Tomlinson, Waye, Chow, & Chow, 2004). In a pharmacodynamic interaction study in 10 healthy male volunteers, *Ginkgo biloba* (120 mg) in combination with cilostazol (100 mg) (CYP3A4 and CYP2C9 substrate) was found to interact significantly ($p < .05$) to potentiate prolongation of bleeding time in comparison to that of the individual doses (Aruna & Naidu, 2007).

Thus, concomitant administration of *Ginkgo biloba* with cardiovascular drugs (substrates of CYP3A4 and CYP2C19) with narrow therapeutic range may affect their pharmacokinetic profile up to a significant extent resulting in HDI.

4.9 | *Glycyrrhiza glabra*

Glycyrrhiza glabra L or liquorice root (family: Fabaceae) has been used as a folk medicine since old ages in Europe as well as in many eastern countries. The principal active phytoconstituents of *Glycyrrhiza glabra* L are the triterpene saponins, glycyrrhizin and glycyrrhetic acid, which are supposed to be partially accountable for its anti-inflammatory, anti-diuretic, anti-epileptic, anti-allergic, antioxidant activity and potential to act in hypotension (Ross, 2001). Liquorice is also documented to inhibit platelet aggregation and exert a vasorelaxant effect (Yu et al., 2005; Yu & Kuo, 1995). *Glycyrrhiza glabra* L root is reported to contain about 5–24% w/w of glycyrrhizin with poor oral bioavailability. Glycyrrhetic acid, the major metabolite of glycyrrhizin shows better absorption (43–77%) and bioavailability than glycyrrhizin (8–9%) (Fenwick, Lutomski, & Nieman, 1990; Wang, Kurosaki, Nakayama, & Kimura, 1994). The extract and glycyrrhizin are reported to exhibit greater interaction potential with CYP2D6 in comparison to that of CYP3A4, with crude extract showing a comparably greater inhibition potential (IC_{50}:125.16–132.49 μg/ml) with both the CYP enzymes than glycyrrhizin (IC_{50}: 153.8–156.25 μg/ml) for CYP2D6 using fluorometric assay (Pandit, Mukherjee, Ponnusankar, Venkatesh, & Srikanth, 2011). Both the *Glycyrrhiza glabra* extract and glycyrrhizin are reported to affect the bioavailability of cyclosporin in rats with notable decrease in the C_{max} and AUC of cyclosporin by activation of P-glycoprotein and CYP3A4 enzyme functions (Hou, Lin, & Chao, 2012). In another 14 day study, glycyrrhizin (150 mg) was reported to substantially decrease C_{max} and $AUC_{0\text{-}t}$ of midazolam (7.5 mg/kg) by 20% in sixteen human volunteers. This effect was observed as a result of induction of CYP3A4 activity by glycyrrhizin. Thus, co-administration of drug substrates of CYP3A having narrow therapeutic range with liquorice might result in sub-therapeutic levels of drugs (Tu et al., 2010). In another study, the effect of liquorice beverage (4 ml/kg) on the pharmacokinetics of atorvastatin, simvastatin, and lovastatin (80 mg/kg each) was studied in Sprague–Dawley rats. Liquorice demonstrated effect on the PK parameters of statins by significantly increasing C_{max} and AUC of the three statins ($p < .05$), thereby suggesting an increase in their bioavailability. This could be due to the inhibitory effect of liquorice on the efflux mechanism in GIT and the inhibitory effect or saturation of P-gp transporters on the biliary wall, resulting in more absorption of the drug via the portal vein and escape of more drugs from the liver into the systemic circulation respectively (Dayyih et al., 2016). Thus, owing to the in vivo inhibitory action of *Glycyrrhiza glabra* against CYP2D6 enzyme as well as the

GIT efflux and P-gp function and induction of CYP3A4, it has the potential to interact with a number of cardiovascular drugs, including statins.

4.10 | *Panax ginseng*

Panax ginseng (family: Araliaceae) is a medicinal plant in traditional Chinese medicine consisting of ginsenosides, polysaccharides, peptides, alcohols and fatty acids as bioactive phytoconstituents (Lee, 1992). More than 20 ginsenosides have been obtained from different species of ginseng in varying amounts (2–20%) with bioavailability of around 85% (Chang Huang et al., 2010; Gillis, 1997; Kim et al., 2014). Ginseng is reported to provide protection against myocardial as well as cerebral ischaemia and possess antioxidant and anti-free radical activity (Chen, 1996). Ginsenosides have been reported to inhibit CYP3A4 activity (IC_{50}:10 μM) (Etheridge, Black, Patel, So, & Mathews, 2007). Herbal supplement of *Panax ginseng* (2 g/kg), after 3 days of oral administration in rats is reported to more potently inhibit CYP2C11 activity in comparison to standard inhibitor quinidine (80 mg/kg) administered for same period of time (Jang, Park, & Chung, 2004). In another study, healthy human volunteers were administered single oral dose of midazolam (8 mg) as probe substrate, before and after 28 days of administration of *Panax ginseng* (500 mg dose) twice a day. The pharmacokinetics of midazolam was altered after administration of *Panax ginseng* with a major drop in the C_{max} and AUC value. The results suggested induction of CYP3A enzyme activity in the liver as well as in the gastrointestinal tract. Patients consuming this herb concomitantly with drugs which act as CYP3A substrates having narrow therapeutic ranges should be examined meticulously for acceptable therapeutic response (Malati et al., 2012). *Panax ginseng* has been documented to interact with warfarin (2 mg) in 25 patients with ischaemic stroke (Lee et al., 2008). *Panax ginseng*, on two occasions have been reported to clinically interact with phenelzine, first in a 64 year old woman showing symptoms of headache and tremulousness after ingestion of ginseng capsules and second in a 43 year old woman under therapy for depression who showed maniac like symptoms on co-administration of ginseng preparation (Shader & Greenblatt, 1985, 1988). *Panax ginseng* is reported to induce CYP3A4 and inhibit CYP2C11 activity and pharmacodynamically interact with warfarin and the clinical reports suggest its interaction with phenelzine thus establishing its HDI potential.

4.11 | Radix Puerariae lobatae (Gegen)

The dried root of *Pueraria lobata* (Wild) is known as *Radix puerariae lobatae* or Yege, (family: Fabaceae or Leguminosae). It is a twining perennial herb native to South East Asian regions of China, Korea and Japan. More than 70 phytoconstituents have been identified from *Radix puerariae* such as isoflavones, isoflavone glycosides, triterpenes and triterpenoid glycosides and to a minor extent, coumarins and puerarols. Therapeutic actions of the herb for the treatment of CVD are attributed to isoflavones and isoflavone glycosides. Puerarin is the most abundant isoflavone compound obtained from the roots and responsible for cardioprotective and anti-hypertensive action (Shibata et al., 2011). The amount of puerarin present in *Radix puerariae* is about 0.3570 ± 0.0016 mg/g with reported oral bioavailability of 7% (Anukunwithaya et al., 2018; Yu, Yan, Zhen, & Rao, 2002). Different in vitro and in vivo experiments along with clinical investigations showed the *Radix puerariae* herbal extract or its total flavones products could increase micro-circulation, improve blood flow, and prevent coronary artery diseases, as well as lower hypertension. In an in vitro study, puerarin is reported to inhibit activity of CYP2C19 by 37.9% and CYP2D6 by 27.6% with IC_{50} values of 400 μg/ml and 100 μg/ml, respectively (Kim, Kim, Jung, Chun, & Rhew, 2014). Further, an in vivo study reported that *Radix puerariae* herbal extract and puerarin in Wistar rats could induce the activity of CYP1A1/2, CYP2A1 and CYP2C11, and inhibit the activity of CYP2B1, CYP2E1 and CYP3A (Guerra et al., 2002). In addition, a clinical study conducted showed that puerarin induces CYP1A2 expression and inhibits CYP2D6 activity. These results indicated HDI potential of *Radix puerariae* or its products, including puerarin, extract or total flavones present in the herb (Zheng et al., 2010). In an in vivo pharmacokinetic study carried out in rats, the decoction of the herb on co-administration with methotrexate considerably increased methotrexate levels. The authors proposed that the mechanism of these interactions might be of competitive type occurring between components of *Radix puerariae* or their metabolites with methotrexate for the organic anion transporters (OATs) (Chiang et al., 2005). In one of the more recent PK-PD-based study in rats, Gegen (240 and 480 mg/kg) was found to accelerate Phase I metabolism of warfarin (0.2 mg/kg) by the induction CYP enzyme activity as well as increased the activity of mRNA and protein expression of vitamin K epoxide reductase by 30% (p = .02), thereby supressing the anticoagulation effect of warfarin (Ge et al., 2016). Thus, owing to the CYP induction and inhibitory effect of Gegen and its active constituent peurarin and also its in vivo interaction with warfarin, it can be advised to vigilantly monitor the concomitant administration of Gegen containing herbal medications in cardiac disease patients.

5 | HERBS POSTULATED TO INDUCE HDI WITH CARDIOVASCULAR DRUGS

A large number of herbs used in treatment of CVD are studied for their CYP interaction potential (inhibition or induction) but have not yet been studied for their potential to affect the pharmacokinetics or pharmacodynamics of cardiovascular drugs and drugs of other classes. Thus, based on the documented reports available in literature on CYP interaction potential, an attempt has been made to postulate their HDI potential. These herbs and their hypothesized drug interactions are listed in Table 2.

TABLE 2 Herbs yet to be reported for herb–drug interaction with cardiovascular drugs (Postulated HDI)

Herbs	Active phytoconstituents	Reported pharmacological activities	CYP, P-gp induction/ inhibition	Postulated HDI
Terminalia chebula (Myrobalan)	Gallic acid, ellagic acid, chebulic acid, chebulinic acid, punicalagin & tannic acid	Treating palpitations and tachycardia (Jokar, Masoomi, Sadeghpour, Nassiri-Toosi, & Hamedi, 2016)	CYP3A4, CYP2D6, and CYP2B6 (induction)	Cardiovascular drugs metabolized by CYP3A4, CYP2D6, and CYP2B6 eg: Clopidogrel, Metoprolol, Timolol etc.
Acorus calamus	Sesquiterpenes, α and β-asarones (safrole), calamendiol and isocalamendiol, tannins.	Anti-stress (Patel, Vaghasiya, Thakor, & Jariwala, 2012; Shah & Gilani, 2009)	CYP3A4 and CYP2D6 (inhibition)	Cardiovascular drugs metabolized by CYP3A4, CYP2D6 eg: Enalapril, amlodipine, captopril etc.
Curcuma zedoaria	Sesquiterpenoids, monoterpenoids, epicurzerene, curzerene, curdione, curzerenone, curcumenene, 1, 8-cineole.	Hypotensive, antioxidant (Dosoky, Setzer, Dosoky, & Setzer, 2018)	CYP3A4 (inhibition)	Cardiovascular drugs metabolized by CYP3A4.
Inula racemosa (Pushkarmool)	Alantolactone, isoalantolactone, dihydroalantolactone, dihydroisoalantolactone, β -sitosterol	Hypotensive, delays cardiac ischaemia and ventricular arrhythmia	CYP3A4 (inhibition)	Cardiovascular drugs metabolized by CYP3A4.
Terminalia arjuna	Arjunic acid, arjunetin, arjungenin	Anti-hyperlipidemic, diuretic, antioxidant (Chabukswaret al., 2010; Ojha, Nandave, Kumari, & Arya, 2010; Lokhande, Dhaware, Jagdale, Chabukswar, & Mulkalwar, 2007)	CYP3A4, CYP2D6, CYP2C9, and CYP1A (inhibition)	Cardiovascular drugs metabolized by CYP3A4, CYP2D6, CYP2C9, and CYP1A eg: Clopidogrel, Rosuvastatin, Fluvastatin etc.

5.1 | *Terminalia chebula* (Myrobalan)

Terminalia chebula (family: Combretaceae) is one of the widely used herb in India for the treatment of diseases such as dementia, diabetes and cardiovascular related complications. Fruits of myrobalan is reported to contain steroidal sapogenins, saponins, anthraquinone derivatives, flavonoids, and tannins; with tannins being the most prominent phytoconstituent. The tannin content of *Terminalia chebula* is between 32%–45%, which includes gallic acid, ellagic acid, chebulinic acid, chebulic acid, punicalagin, and tannic acid. *Terminalia chebula* has a stimulating effect on the heart and is useful in the management of tachycardia and palpitations. It is known to increase the force of contraction as well as the cardiac output without having any effect on the heart rate (Jokar et al., 2016). The standardized myrobalan formulation known as Triphala churna, when dissolved in ethanol showed significant potential to inhibit CYP3A4 and CYP2D6 enzyme activity with IC_{50} values of 119.65 ± 1.91 μg/ml and 105.03 ± 0.98 μg/ml respectively (Ponnusankar et al., 2011). In a study conducted by Celik et al., ellagic acid which is one of the important constituent of *Terminalia chebula* demonstrated the potential to significantly inhibit CYP2B and CYP2E enzyme activities when administered at a dose of 10 mg/kg/day for 14 consecutive days in rats (Celik et al., 2013).

On the basis of aforementioned documented evidences, we propose that patient suffering from CVD are advised to either avoid or exercise care while co-administering herbal products containing *Terminalia chebula* with cardiovascular drugs which are the substrate of CYP3A4, CYP2D6 and CYP2B enzymes.

5.2 | *Acorus calamus*

Acorus calamus L. or *Calamus* (family: Acoraceae) is a semiaquatic plant with grass-like monocot. *Acorus calamus* is reported to contain sesquiterpenes such as calamendiol, calamenone and isocalamendiol, phenylpropanes, cis-isoasarone such as β-asarone (safrole), eugenol methyl ether (80%), bitter substances such as the sesquiterpene diketone known as acorone, ketones (shyobunones), tannins and so on (Mazza, 2002; Wu et al., 2017). *Acorus* species contains α and β-asarones as the principal active constituents in extracts from different parts of the plant (Björnstad, Helander, Hultén, & Beck, 2009). The amount of α and β-asarones reported to be present in 2 g of *Acorus calamus* powder using UPLC analysis was in the concentration range of 0.014–0.031% and 0.152–0.558% and have low bioavailability due to high lipophilicity (Lu et al., 2014; Wu & Fang, 2004; Ying et al., 2014). *Acorus calamus* L has been documented to possess antihypertensive, hypolipidemic and cardiac stimulant activity (Patel et al., 2012; Shah & Gilani, 2009). *Acorus calamus* extract was analysed for in vitro CYP interaction potential using CYP450-carbon monoxide complex (CYP450-CO) assay. Extract exhibited higher inhibition potential against CYP3A4 (IC_{50}:46.84 ± 1.83 μg/ml to 32.99 ± 2.21 μg/ml) in comparison to that of the standard inhibitors and lower IC_{50} value than that of phytoconstituent α-asarone against

CYP3A4 and CYP2D6 with IC_{50} values of 65.16 ± 2.37 to 42.15 ± 2.45 μg/ml respectively. Lower IC_{50} values for the extract depicts that there might be certain other active phytoconstituents in extract which in combination are responsible for the inhibition of the CYP enzymes in addition to that of α-asarone (Pandit, Ponnusankar, Bandyopadhyay, Ota, & Mukherjee, 2011).

5.3 | *Curcuma zedoaria*

Curcuma zedoaria (family: Zingiberaceae) is commonly known as "white turmeric" or "zedoary," its rhizomes are similar to that of ginger from the outside (ash grey-coloured) and like turmeric from within (brownish red). Various parts of *Curcuma zedoaria* have been utilized for the treatment of haematologic and circulation abnormalities (Lobo, Prabhu, Shirwaikar, & Shirwaikar, 2009). Rhizome oil of *C. zedoaria* is principally composed of sesquiterpenoids (80–85%) and monoterpenoids (15–20%). The reported major components include epicurzerene (19.0–46.6%), curzerene (10.4%), curdione (7.0–19.6%), curzerenone (22.3–31.6%), debromo filiforminol (31.5%), 1, 8-cineole (18.5–40.8%), sesquiphellandrene (21.5%), p-cymene (18.4%), curcumenene (18.7%) and α-phellandrene (14.9%). On the basis of phytochemical studies on *Curcuma* oils, sesquiterpenoids, and monoterpenoids have been identified as the major active constituents. The essential oil of *Curcuma* species is reported to possess a wide range of pharmacological activities such as anti-inflammatory, antiproliferative, hypocholesterolaemic, antidiabetic, diuretic, antirheumatic, hypotensive, antioxidant and cyclooxygenase-1 (COX-1) inhibitory activities (Dosoky et al., 2018). *Curcuma zedoaria* has been investigated for its effect on CYP3A4 enzymes in a Caco-2 cell model treated with methanolic extract of rhizome for a period of 72 h. The extract considerably decreased the activity of CYP3A4 by 85–98% (IC_{50}: 0.014 mg/ml) (Hou et al., 2007). It still requires studies in animals to establish its pharmacokinetic and pharmacodynamic HDI potential. Therefore, we propose that owing to the CYP3A4 inhibition potential of *Curcuma zedoaria*, further in vivo studies are warranted to identify the effects of concomitant administration of *Curcuma zedoaria* on conventional cardiovascular drugs.

5.4 | *Inula racemosa* (Pushkarmool)

Inula racemosa (family: Compositae) has been extensively utilized as an indigenous medicine, expectorant and in veterinary medicine in India, China and Europe (Seca, Grigore, Pinto, & Silva, 2014). It consists of alantolactone, isoalantolactone, dihydroalantolactone, dihydroisoalantolactone, beta-sitosterol, daucosterol and isoinunal, with alantolactone and isoalantolactone being principal active phytoconstituents (Tan, Tang, Hu, & Shuai, 1998). Roots of *Inula racemosa* have been demonstrated to possess cardioprotective properties (Chabukswar, Kuchekar, Jagdale, Lokhande, & Raut, 2010). Ojha and co-workers demonstrated the cardio protective potential of *Inula racemosa* extract (100 mg/kg) in myocardial ischaemic-reperfusion injury in rats. The study showed that there was improved antioxidant status, haemodynamic and left ventricular contractile function following inhibition of oxidative stress (Ojha et al., 2010). In a study conducted by Lokhande et al., using an isolated frog heart, the constituents of *Inula racemosa* were found to inhibit the action of adrenaline and might also act on the beta-receptor (Lokhande et al., 2007). Primary active phytoconstituent alantolactone was evaluated to determine its inhibitory effect on CYP activity in human liver microsomes (HLMs) and recombinant cDNA-expressed enzymes using LC–MS/MS. Alantolactone exhibited potential to inhibit CYP3A4 activity with IC_{50} values of 3.599 and 3.90 μM, respectively. Alantolactone strongly in a dose-dependent manner non-competitively inhibited CYP3A4 activity in HLMs. The inhibition was also validated by in vivo study in mice by oral treatment of alantolactone (25, 50, 100 mg/kg) for 15 days (Qin et al., 2015). Further PK-PD-based in vivo studies with conventional medicines are needed to establish the HDI potential for *Inula racemosa*. In HLMs, CYP3A4 is the most significant drug metabolizing enzyme, which takes part in the metabolism of over 50% of all marketed drug formulations. Thus, owing to its CYP3A4 inhibition potential, in vivo studies in higher animals are warranted to determine its HDI potential.

5.5 | *Terminalia arjuna*

Terminalia arjuna (Roxb.) Wight and Arn (family:Combretaceae) is a well-studied cardioprotective herb. It is reported to consist of triterpenoids such as arjunin, arjunic acid, arjungenin, arjunolic acid and glycosides such as arjunetin, arjunoside I, arjunoside II as well as flavonoids and β-sitosterol (Dwivedi & Chopra, 2014). Triterpenoids of Arjuna are principally responsible for cardiovascular activity. Stem bark of Arjuna possesses inotropic, chronotropic and diuretic properties (Dwivedi, 2007). Methanolic extract of *Arjuna* was reported to contain high content of phenolics and flavonoids with significant antioxidant capacity (Mohammad, Sadika, Mohammad, Mohammad, & Mohiuddin, 2016). Bark powder/extract of Arjuna is capable of reducing the total cholesterol and triglyceride (TG) levels (Gupta, Singhal, Goyle, & Sharma, 2001). Alcoholic and aqueous bark extracts of *Terminalia arjuna* and its various phytoconstituents such as arjunic acid, arjunetin and arjungenin were assessed for their inhibitory potential against CYP3A4, CYP2D6 and CYP2C9 enzymes. Alcoholic and aqueous bark extract of *Terminalia arjuna* showed strong inhibition of all three enzymes in HLM with IC_{50} values less than 35 μg/ml compared to that of standard phytoconstituents. in vitro studies suggest that *Terminalia arjuna* extracts consist of constituents that possess significant inhibitory activity against CYP1A at IC_{50} values of >50 μM and potently inhibits CYP3A4, CYP2D6 and CYP2C9 enzyme activity, which is likely to result in clinically important HDIs facilitated via change in plasma concentration of conventional drugs due to major CYP isozymes inhibition (Varghese, Savai, Pandita, & Gaud, 2015). However, the in vivo CYP interaction/HDI potential of *Terminalia arjuna* and its active phytoconstituents is yet to be established. Therefore, its interaction with cardiovascular drugs in higher animals cannot be predicted and demands further studies.

TABLE 3 Herbs with established HDI potential with other therapeutic agents

Herbs	Active phytoconstituents	Reported pharmacological activities	CYP, P-gp induction/ inhibition	Interacting drugs
Tinospora cordifolia	Berberine, palmatine, tinosporone, tinocordifolioside	Chemopreventive, hypolipidemic, cardiotonic, anti-inflammatory (Kumar & Nagar, 2014; Sharma et al., 2011)	CYP3A4, CYP2D6, CYP2C9, CYP1A2 (inhibition)	Glibenclamide, losartan (Guo, Chen, Tan, Klaassen, & Zhou, 2012; Sahu, Ahmed, Sangana, Punde, & Subudhi, 2018)
Withania somnifera	Withanolides, withaferins, isopellertierine, anferine	Diuretic, hypoglycaemic, hypocholesterolemic effects, cardiotonic (Andallu, 2012; Kaileh et al., 2007; Singh, Sharma, Dudhe, & Singh, 2010; Visavadiya & Narasimhacharya, 2007).	CYP1A (inhibition)	Phenacetin (Savai, Pandita, & Chintamaneni, 2015)
Moringa oleifera	Quercetin, kaempferol, benzyl glucosinolate, β-sitosterol	Hypocholesterolemic, anti-hypertensive. (Anwar, Latif, Ashraf, & Gilani, 2007; Ghasi, Nwobodo, & Ofili, 2000)	CYP1A2, CYP3A4, CYP2D6 (inhibition)	Metformin (Idakwoji *et al*., 2015) Pioglitazone (Umathe, Dixit, Bansod, & Wanjari, 2008)

6 | HERBS WITH AN ESTABLISHED POTENTIAL FOR HDI WITH DRUGS OF OTHER THERAPEUTIC CLASSES

This section of review comprises of those cardiovascular herbs for which CYP interaction/HDI potential is established either through in vitro or in vivo studies (humans or rats) and case reports with drugs belonging to other therapeutic categories. These herbs are yet to be studied for HDI with cardiovascular drugs. The list of herbs in this section has been summarized in Table 3.

6.1 | *Tinospora cordifolia*

Tinospora cordifolia (Wild) Miers (family: Menispermaceae) also known as Guduchi or Gudmar is found in the tropical regions of Asia, Africa and Australia and utilized in Indian Ayurvedic system as a tonic, vitalizer, and for treatment of metabolic diseases (Sharma, Velu, Indrani, & Singh, 2013). The chief phytoconstituents of *Tinospora cordifolia* include berberine, tembetarine, palmatine, magnoflorine, tinosporone, tinosporaside, tinocordifolioside, tinosporic acid, cordifolisides A to E, syringen, β and ∂-sitosterol. It has been reported to show varied pharmacological actions such as anti-ischaemic, hypolipidemic, blood purifier, cardiotonic, diuretic, anti-inflammatory, antispasmodic (Kumar & Nagar, 2014). The reported amount of berberine present in *Tinospora cordifolia* is about 0.319% w/w on dry weight basis (Srinivasan, Unnikrishnan, Shree, & Balachandran, 2008). In a dose-dependent manner, it is found to lower the levels of calcium and sodium and upsurge the levels of potassium in Wistar rats. Hence, it can be administered as an anti-arrhythmic and may be beneficial for the treatment of atrial as well as ventricular fibrillation (Sharma et al., 2011). A study performed by Bahadur et al., aimed at determining the interaction potential of *Tinospora cordifolia* with CYP microsomes with the help of specific high throughput screening assays. *Tinospora cordifolia* inhibited CYP3A4, CYP2D9, CYP29 and CYP1A2 with IC_{50} values of 136.45, 144.37, 127.55, and 141.82 μg/ml, respectively (Bahadur et al., 2016). The study conducted by Sahu et al documented the drug interaction potential of *Tinospora cordifolia* (100 and 400 mg/Kg) with glibenclamide (1 mg/kg) in rats. Significant effects were detected in terms of increase in C_{max}, AUC and T_{max} and decrease in the clearance (Cl) of drug. Increase in C_{max} and AUC suggested higher plasma concentration which may be due to increased absorption and decreased metabolism of Glibenclamide in presence of *Tinospora cordifolia* extract. This pharmacokinetic study results are also backed by the CYP inhibition and metabolism study where the extract has been reported to inhibit CYP2C9 activity (IC_{50} < 0.1 mg/ml), however the extract also inhibited CYP2C19, 2D6 and 1A2 enzymes (IC_{50} < 1 mg/ml). The study proposed that the bioavailability of glibenclamide, being a CYP2C9 substrate could be high in clinical conditions when concomitantly administered with *Tinospora cordifolia* extract for an extended period (Sahu et al., 2018). A two-phase randomized crossover clinical study in healthy male subjects was performed to deteremine CYP inhibition potential of berberine in humans. After administration of berberine (300 mg, t.i.d., p.o.) for 2 weeks; midazolam, omeprazole, dextromethorphan, losartan and caffeine were administered to assess enzyme activities of CYP3A4, 2C19, 2D6, 2C9 and CYP1A2, respectively. Repeated administration of berberine resulted in decrease in CYP2D6, 2C9 and 3A4 activities. This study suggested that berberine mediated HDI needs to be considered when berberine is administered along with drugs acting as substrates of CYP2D6, 2C9 and 3A4 enzymes (Guo et al., 2012).

6.2 | *Withania somnifera*

Withania somnifera (L.) Dunal (family: Solanaceae) also known as Ashwagandha or winter cherry has been utilized in Ayurveda as a *rasayana* (rejuvenation) and accredited to improve longevity and vitality since ancient times (Mishra, Singh, & Dagenais, 2000). The pharmacologically active phytoconstituents are isopellertierine, anferine

(alkaloids), withanolides, withaferins (steroidal lactones), sitoindoside VII and VIII (saponins), and sitoindoside XI and X (withanoloides). *Withania somnifera* is also reported to be rich in iron (Singh et al., 2010). Amount of withanolides in extracts of different species of withania varies between 1.2 to 2.4% w/w on a dry weight basis (Chauhan, Joshi, Jain, & Jain, 2019). Ashwagandha has been analysed in clinical studies with human subjects for its diuretic, hypoglycaemic, and hypocholesterolemic effects (Andallu, 2012). It is reported to act as a promising agent in the management of inflammatory mechanism of CVD and possess cardiotonic as well as hypolipidemic activity (Hemalatha, Wahi, Singh, & Chansouria, 2006; Kaileh et al., 2007; Singh et al., 2010; Visavadiya & Narasimhacharya, 2007). A study performed by Jay Savai et al., suggested that the methanolic extract of *Withania somnifera* (500 mg/kg) on in vivo administration in rats considerably induced CYP1A enzyme activity with EC_{50} value of >640 μg/ml and consequently altered phenacetin pharmacokinetic profile ($p < .05$), signifying a potential for HDI (Savai et al., 2015).

6.3 | *Moringa oleifera*

Moringa oleifera Lam. (family: Moringaceae) or drumstick plant, is native to the Indian subcontinent, various parts of which have been used since old days as food as well as medicine (Mbikay, 2012). Seeds, roots and leaves of *Moringa oleifera* are reported to contain 4-(R-L-rhamnopyranosyloxy)-benzyl glucosinolate and benzyl glucosinolate. *Moringa oleifera* leaves contain quercetin-3-O-glucoside and lower amounts of kaempferol-3-O-glucoside, 3-caffeoylquinic acid and 5-caffeoylquinic acid as active phyotconstituents with quercetin being the most prominent phytoconstituent (Bennett et al., 2003). Quercetin is found in dried leaves, at concentrations of 100 mg/100 g, as quercetin-3-*O*-β-d-glucoside (Atawodi et al., 2010). The concentrations of saponins in freeze-dried leaves range between 64 and 81 g/kg of dry weight (Makkar & Becker, 1996). *Moringa* leaves consist of various biologically active constituents consisting of nitrile, thiocarbamate and glycosides, which are responsible for lowering of blood pressure, and thereby can be utilized for the purpose of stabilizing the blood pressure (Anwar et al., 2007). Furthermore, *Moringa* leaves also contain β-sitosterol, which has cholesterol lowering effect (Ghasi et al., 2000). In a fluorescence study, *Moringa* exhibited inhibition potential against CYP3A4 (IC_{50}:127.36 ± 2.98 μg/ml) and CYP2D6 (IC_{50}:146.50 ± 3.46 μg/ml) (Ahmmed et al., 2015). Furthermore ethanolic extract of *Moringa oleifera* demonstrated selective inhibition of CYP1A2 (IC_{50}:13.8 ± 9.8 μg/ml) (Taesotikul, Navinpipatana, & Tassaneeyakul, 2010). Concomitant administration of ethanolic extract of *Moringa oleifera* leaves (375, 750 and 1,500 mg/kg) with metformin (150 mg/kg) is reported to produce pharmacodynamic HDI resulting in greater anti-hyperglycaemic activity than either of them alone in alloxan induced diabetic rats (Idakwoji et al., 2015). Quercetin (2, 10 and 20 mg/kg), the active phytoconstituent of *Moringa* is reported to alter the pharmacokinetics of pioglitazone (10 mg/kg) in rats resulting in an increase in its bioavailability owing to CYP3A inhibition by quercetin (IC_{50}:1 μm) (Umathe et al., 2008). Further in vivo studies involving cardiovascular drugs are still required to establish its HDI potential. The results of the studies reviewed propose the possibility of occurrence of potential HDI of *Moringa oleifera* extract with drugs acting as a substrate of CYP1A2, CYP3A4 enzymes.

TABLE 4 Evidence pertaining to HDI potential of Herbs and their active phytoconstituents

Herb	In vitro studies	In vivo studies: Animal	In vivo studies: Human	Clinical case reports
Piper longum	*	*	*	_
Curcuma longa	*	*	_	*
Seaweed *(Fucus vesiculosu)*	*	*	_	*
Terminalia chebula (Myrobalan)	*	*	_	*
Acorus calamus	*	_	_	_
Zingiber officinale (rhizome)	*	_	*	*
Curcuma zedoaria	*	_	_	_
Pushkarmool *(Inula racemosa)*	*	_	_	_
Terminalia belerica	*	*	_	_
Terminalia arjuna	*	_	_	_
Salvia miltiorrhiza (Danshen)	*	*	*	_
Garlic *(Allium sativum)*	*	*	*	_
Ginkgo biloba	*	*	*	_
Glycyrrhiza glabra	*	*	*	_
Panax ginseng	*	*	*	*
Radix puerariae lobatae (Gegen)	*	*	_	_
Tinospora cordifolia	*	*	*	_
Withania somnifera	*	_	_	_
Moringa oleifera	*	*	_	_

7 | DISCUSSION

Herbal remedies follow modern pharmacological principles that are similar for conventional drugs, except for the fact that the herbs are composed of numerous active phytoconstituents that are responsible for the pharmacological action and contribute to the overall activity of the herb. These phytoconstituents also undergo metabolism and are excreted through similar pathways as that of the conventional drugs. Therefore, HDIs are manifested through the same pharmacokinetic and pharmacodynamic mechanisms as that for drug–drug interactions (Izzo, Di Carlo, Borrelli, & Ernst, 2005). For long, as per USFDA guidelines in the R&D development stage, conventional drugs are extensively evaluated for CYP potential using suitable in vitro and in vivo tools to predict the possibility of potential drug- drug interactions. However today herbal medicines are being widely prescribed and consumed for the treatment of various disorders. As a result the possibility of herb–drug interaction cannot be neglected and needs to be addressed. Till date, however there are no defined guidelines for the evaluation of HDIs. The present review highlights the exhaustive list of herbs, which are used in the treatment of CVD and which are either reported to cause HDI or postulated to induce HDI. Also the herbs which are yet to be reported for HDI with cardiovascular drugs are also discussed. The summary of the literature evidences pertaining to CYP interaction/ HDI potential of herbs and their active phytoconstituents are reported in Table 4.

7.1 | Herbs reported to cause HDI

Piper longum, *Curcuma longa*, Seaweed *(Fucus vesiculosus)*, *Zingiber officinale (Rhizome)*, *Terminalia belerica*, Danshen, *Allium sativum* (Garlic), *Ginkgo biloba*, *Glycyrrhiza glabra*, *Panax ginseng*, *Radix puerariae lobatae* (Gegen).

7.2 | Herbs postulated to cause HDI

Terminalia chebula (myrobalan), *Acorus calamus*, *Curcuma zedoaria*, *Inula racemosa* (Pushkarmool), *Terminalia arjuna*.

7.3 | Herbs with established HDI potential but yet to be reported for HDI with cardiovascular drugs

Tinospora cordifolia, *Withania somnifera and Moringa oleifera*.

8 | CONCLUSION

The present review focuses on the comprehensive list of herbal medicines that are commonly consumed for the treatment of CVD. The review also highlights the important studies carried out to evaluate their efficacy and establish their safety profile. With the extensive research being carried out to study the phytoconstituents present in these herbs, it has been possible to establish correlation between efficacy of herbs and its respective active phytoconstituents as these phytoconstituents are responsible for the activity of the herb as well as act as contributing factor for the various mechanisms involved in HDI as discussed earlier. Also the review focuses on all studies undertaken for evaluation of CYP potential, as this helps to understand whether these herbs, or their phytoconstituents are capable of inhibiting or inducing these metabolizing enzymes that play a major role in the disposition of many drugs. Further, the documented HDI study in the class of cardiovascular drugs is also elaborated. This review also attempts to analyse herbs that may cause significant HDI based on reported CYP studies. This article can further be utilized as a suitable database for physicians and health care professionals while treating patients with CVD, thereby aiming at improving clinical outcomes and preventing adverse effects.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

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