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Common phyto-remedies used against cardiovascular diseases and their potential to induce adverse events in cardiovascular patients

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Abstract

Cardiovascular diseases (CVDs) remain the leading cause of death globally. In addition to conventional medications, a plethora of herbal products continue to offer therapeutic alternatives to patients to assuage suffering. Nonetheless, concomitant administration of herbs and conventional medicine are not always safe which could mimic, oppose or magnify the effect of the latter leading to serious herb-drug interactions, most of which escape pharmacovigilance. The paucity of relevant information to clinicians in relation to herb-drug interactions, the inadequacy of evidence-based knowledge coupled with the lack of mechanistic facts poses a momentous threat to meet desired therapeutic outcomes in CVD patients. In this endeavor, key scientific databases have been explored to review common herbal products that might interfere clinically with conventional drugs used for CVDs and related complications. Ten common medicinal plants have been included and representative case reports whereby herbal products are thought to be inducers of adverse events are also discussed. It is anticipated that the present review will be a pinnacle of evidence and hence serve as an up-to-date fundamental repertoire of recent scientific findings to promote better understanding of adverse herb-drug events amongst clinicians and enhance rapport between clinicians and patients for subsequent counseling. Indeed, acknowledging the risks attributed to herb-drug interactions is fundamental in the management of CVDs and related implications which should not be underestimated or considered as trivial by both health-care professionals and herbal consumers.

Keywords: Medicinal plants; Cardiovascular diseases; Herb-drug interactions; Pharmacovigilance; Drugs

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally [93]. A recent bulletin from the World Health Organization (WHO) in 2013 estimated that 17.3 million people died from CVDs and it is forecasted that by 2030 mortality figures will reach 23.3 million [83]. The underlying pathology of CVD is atheromatous vascular disease, resulting in a plethora of other disorders such as coronary artery disease (CAD), cerebrovascular disease, peripheral vascular disease, and the subsequent development of heart failure and cardiac arrhythmias [80]. Obviously, the most opted treatment for CVDs remains conventional drug therapies for example diuretics, vasodilators, anticoagulants, antiplatelet agents and β-blockers [93].

A plethora of herbal products are employed routinely by patients to manage and/or treat chronic cardiovascular conditions and related complications [12]. There is no denying to the blatant fact that the use of herbal products for prophylactic and curative purposes is thriving worldwide with the strong perception that natural products are safe and with minimal side effects. Indeed, a recent report from the WHO showed that 80 % of the emerging world's population still relies on natural products from traditional medicine for healing [83]. Interestingly, more than 2000 plants have been documented to be used in traditional systems of medicine and some of these are providing comprehensive relief to the people suffering from CVDs and related complications, specially hyperlipidemia and ischemic heart disease amongst others [4, 12].

A multiplicity of plant based extracts are currently approved for use in a number of developed countries.

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Instances of such legitimate practices include the use of; ginseng root and St John's wort in Germany, and *Matricaria chamomilla*, *Hypericum perforatum* and *Plantago major* in France [3]. Nonetheless, in developing countries there is a dearth of policies that regulate the sale of herbals. Furthermore many herbal extracts are sold as dietary supplements in many countries bypassing policies in place for their regulation [6].

Additionally, a wealth of literature has emerged that tend to suggest that the concomitant use of herbal products and conventional medicines gives rise to serious herb-drug interactions. Indeed, it is hypothesized that the likelihood of such interactions is increased in patients employing drugs with a narrow therapeutic index for example; warfarin, cyclosporin and digoxin. The majority of cases reported have been initiated by the alteration of drug metabolism carried by the Cytochrome P450 enzyme system triggered by another co-administered drug, food or natural product [16, 31]. Interestingly, herb-drug interactions have been postulated to raise or lower the pharmacological or toxicological effects of any of the components inducing the interaction [60].

Moreover, panoply of factors complicate the use of herbal medicines and have been identified as; lack of scientific evidence of safety and efficacy, regulatory oversight, quality control and knowledge regarding herb-drug interactions amongst users and health-care providers. In addition, under-reporting of adverse events leads to an underestimation of adverse effects and subsequently the failure for many countries to adopt a reliable pharmacovigilance system [65]. Likewise, studies from Nigeria, Kuwait, United Arab Emirates, Oman and Australia have shown that health care professionals, in particular pharmacist's knowledge was poor when it came to evaluate the side effects and interaction profiles of the herbal products they supplied. Additionally there is a dearth in mechanistic knowledge that governs alteration in metabolism of a drug by another one, in particular herbal products and few systematic reviews have been generated to help clinicians in devising better counseling strategies [37, 38, 65, 75, 81].

To this effect, the present review endeavors to overview up-to-date information on common herbs used for CVD and emphasize on potential drug-herb interactions in CVD patients. It is anticipated that the present compilation will contribute towards raising awareness among health care professionals as well as herbal-products consumers on various herbs that may induce unexpected side effects and/or result in severe drug-herb interactions in CVD patients. In this endeavor, major scientific databases such as EBSCOhost, PubMed Central, Science direct and Emerald amongst others have been probed with key terms "cardiovascular drugs," "herbal products for CVD", "complementary therapies," "herb-drug interaction," and "cardiovascular disease interactions" to identify citations, abstracts, medicinal case reports and articles on herbal products and CVDs and related complications. Abstracts and titles were evaluated for relevance. Case reports, case series, validated mechanisms, interaction effects, and basic science research were included. Publications not relevant to the discussion of herbal products for CVDs were excluded. Ten medicinal plants (*Aconitum spp., Allium sativum, Citrus paradisi, Cratageus spp., Ephedra sinica, Ginkgo biloba, Ginseng, Hypericum perforatum, Leonurus cardiaca*, and *Stephania tetrandra*) were included in the present review together with a number of case reports.

Herbal medicines and CVDs

Herbal medicine, also known as phyto-remedies has always been involved in assuaging human suffering since time immemorial and its use is still burgeoning worldwide. This surge in interest relates to the inability of modern medicine to successfully address the chronicity of many modern illnesses. Indeed, the scientific community can no longer ignore the worldwide exponential surge in public enthusiasm for disease management through the use of herbal products as more than half of FDA-approved drugs are natural products or derivatives. Panoply of reports have established the fact that patients with chronic diseases such as insomnia, chronic fatigue and CVD tend to use herbal therapies to manage their ailments [81].

Herbal medicine contain a multiplicity of biologically active natural products from which various drug leads that have/are being derived for the development of commercial drug preparations. For example, ephedrine from *Ephedra sinica* (ma-huang), digitoxin from *Digitalis purpurea* (foxglove), salicin (the source of aspirin) from *Salix alba* (willow bark), and reserpine from *Rauwolfia serpentina* (snakeroot) amongst others. Likewise, a number of herbal products have been employed worldwide for the management of CVD and this culture has been passed on to the modern generation [37].

However, it is estimated that 70 % of individuals who use herbal medications do not report such practice to their prescribers and pharmacists. For instance, whenever cases of side effects have been reported, allergic reactions and toxic-effects of the concomitant intake of herbal products with drugs have been observed. Additionally, it was found that the acquaintance of health professionals to such events was poor. The lacuna of such knowledge exposes a large percentage of individuals to the possible adverse effects from herb-drug interactions and other potential side effects [81].

Unless practitioners and health authorities develop appropriate approach including pharmacovigilance tools to

obtain the complete medication history, including the concomitant use of herbs; monitoring and recognizing drug-herb interactions will still remain a major barrier in patient's care [41]. Physicians-patients communication should be enhanced and the former must be ready to investigate about patient's use of herbs in a non-judgmental approach, which otherwise will only prompt patients hide valuable information. Indeed, patients should be treated as a partner and the use of herbs must not be made unconventional [12].

The nature of herb-drug interactions

In general any orally administered drug has to pass through the protective line of cytochrome P450 enzymes (CYP450) and transport proteins before making its way to the bloodstream; this constitutes the first-pass effect. The diversity of cytochrome isoenzymes is vast and hence depicted by a specific nomenclature bearing Arabic numerals. Among the isoenzymes 3 families (CYP1, 2 and 3) have been identified to exert a pivotal role in drug metabolism and are concentrated in the liver and the intestine. Moreover, drug metabolism is a never ending process whereby every second drug is metabolized by isoenzyme Cytochrome P3A4 (CYP3A4). Additionally, there is mounting evidence that alteration of the 170 kDa phosphorylated glycoprotein; p-glycoprotein (p-gp) - a major transmembranous efflux transporter of the intestinal mucosa plays a crucial role in herb-drug interactions. Nonetheless, secondary metabolites found in plants have the potential to alter the first-pass effect since some of them can mimic substrates for enzymes and transport proteins. The result of these effects gives rise to herb-drug interactions [51]. Two types of interactions exist:

1. Pharmacokinetic herb-drug interactions (PKHDI) arise whenever the absorption, distribution, metabolism or elimination of one drug is modified by another one. In this case the hepatic metabolism of drugs is altered due to actuation or suppression of primarily the CYP3A4 isoenzyme of the CYP450 family. The effects of these changes have the potential to induce important clinical consequences [5].
2. Pharmacodynamic herb-drug interactions (PDHDI) are the result of the change in effect of a drug by another one. A wide diversity of clinically relevant pharmacokinetic interactions are due to modifications of CYP450 system; transmembrane pump, hepatic or renal insufficiency, as well as mechanisms still being elucidated. PDHDI may be:
   (a) Additive or synergistic: the administration of more than one drug having the same pharmacological effects together augments their desired as well as side effects. For example, when methotrexate and sulfonamides are used concomitantly there is a high risk that this combination precipitates megaloblastic anaemia due to the antifolate effect of both agents.
   (b) Antagonistic: the concomitant use of two pharmacological agents decreases the effect of one or both agents. This can be epitomized by a loss of glycemic control in diabetic patients whenever systemic corticosteroids and oral hypoglycaemic agents are administered in combination [74].

Aconitum spp. (Ranunculaceae)-Monkshood root

The use of the *Aconitum* species, such as *A. kusnezoffii* and *A. carmichaeli* is commonly advocated by traditional Chinese Medicines (TCM) practitioners for the management of pain caused by trigeminal and intercostal neuralgia, rheumatism, arthritis, bruises, and fractures. The major metabolites isolated form the plant up to date include diterpenoid ester alkaloids, including aconitine. Interestingly, it is hypothesized that these constituents are responsible for a major number of deaths from cardiovascular collapse and ventricular tachyarrythmias in Hong Kong and Australia. It has been established that the alkaloids activate sodium channels and excite cardiac, neural and muscular tissues above normal levels. Furthermore, they have the potential to induce mild diaphoresis and can slow pulse rate due to its effect on brainstem centers and direct effects of aconite on the myocardium may result into ventricular fibrillation. Additionally, a number of side effects including bradycardia, hypotension to fatal ventricular arrythmia can arise due to contact with leaves or sap from *Aconitum* plants [28].

Allium sativum (L.) (Alliaceae)-Garlic

Allium sativum is probably one of the earliest known medicinal plant exploited as a versatile medicinal plant employed for the prophylaxis, management and treatment of many disease conditions in man. Its basic properties make it a valuable plant for the prevention of hypercholesterolaemia, hypertension, artherosclerosis as well as cancer. Garlic is also known to be an antimicrobial and it is exploited by a number of communities around the world as an immune booster. Amongst the plethora of metabolites that the garlic plant synthesizes up to date only a few have been shown to exhibit therapeutic properties and have been identified as organosulfur compounds and named as allicin, alliin and ajoene [17].

The interaction of *A. sativum* supplements with antihypertensive, anticoagulant, antiplatelet and antilipidemic drugs is well documented. It is hypothesised that *A. sativum* metabolites bear configuration that can exert agonist and inhibitory effects similar to these drugs on

drug targets hence undeniably altering their therapeutic and toxic potential [12]. During a randomized trial where subjects were administered three preparations of *A. sativum* versus placebo it was observed that *A. sativum* did not significantly alter LDL-cholesterol, HDL-cholesterol, triglycerides, or total cholesterol-HDL ratio [53]. Moreover, studies in rats have demonstrated that *A. sativum* can interact pharmacodynamically with antihyperlipidaemia and antihypertensive medicines, such as atorvastatin, propranolol, hydrochlorothiazide or captopril. Moreover, a high dose of oral atorvastatin (l0 mg/kg) has been shown to induce kidney damage if used either alone or in combination with high concentrations of *A. sativum* (1 % in the food), while low doses of atorvastatin (2.5 mg/kg) in combination with high concentrations of *A. sativum* (0.75 % in the food) has low nephrotoxic potential [65]. Additionally, available data from previous studies have depicted that bleeding from garlic occurs in individuals ingesting large doses of garlic which is an average consumption of four cloves daily. Interestingly studies tend to show that ajoene is the metabolite that inhibits platelet aggregation and raises by many folds the risk of hemorrhaging in patients under anticoagulant or antiplatelet agents. In line with this, it is recommended that the intake of garlic supplements should be halted for about 10 days in patients about to undergo surgery, and this practice is of paramount importance in patients under anticoagulant and antiplatelet drug therapy [73].

Citrus paradisi Macfad. (Rutaceae) - Grapefruit

Citrus paradisi is a food plant high in pectins and lycopene hence used as a dietary intervention to lose weight and improve cardiovascular health. Its bioactive constituents, namely naringenin and bergamottin have been reported to inhibit the CYP3A4 enzyme in small-intestine enterocytes [1]. This results in an increase in the area under the curve (AUC) in blood of CYP3A4 substrate drugs. A plethora of conventional drugs are metabolized by the CYP3A4 system and include mainly calcium channel blockers, cyclosporine, statins, midazolam, estrogen, and terazosin. Additionally, the bioavailability of these medications is increased and their effect is potentiated which results into dangerous hypotension, myopathy, or liver toxicity. A study carried out on postmenopausal women taking estrogen has shown that grapefruit juice may increase the risk of breast cancer by inhibiting estrogen metabolism by CYP3A4 [5]. A number of drugs have been found to interact with grapefruit juice and it has been established that it is an average daily consumption of 227 g of grapefruit juice that will suppress the activity of cytochrome enzymes and that the concomitant use with cardiovascular drugs such as antiarrhythmic drugs will result into cardiotoxicity, bradycardia and liver injury. When taken with calcium channel blockers it can cause tachycardia as well as peripheral edema. It is recommended that patients under cardiovascular drug treatment should not consume grapefruit for about 24 to 72 h prior to drug use [54]. A number of reports tend to show that many antilipidemic agents mostly artorvastatin, lovastatin and simvastatin interact with the herb. Additionally it has been established that a considerable number of drugs employed in the management of cardiovascular disease such as carvedilol, felodipine, nifedipine, nisoldipine, nicardipine, nitrendipine, nimodipine and verapamil also interact with grapefruit juice [41, 61, 66] are summarized in Table 1 [24]. Interestingly, it has been shown that the herb can also interfere with the absorption of several drugs and results in a reduced plasma concentration of fexofenadine and the beta-blockers celiprolol and talinolol has been found in patients [54].

Cratageus spp. (Rosacea) - Hawthorn

Hawthorn extract has a long standing traditional use in treating panoply of disorders including anxiety, asthma, hypertension, dyslipidemia, hypotension, angina, arrhythmias, heart failure, and indigestion. Interestingly, the most revealing data from the plant advocates positive benefits in chronic congestive heart failure patients (CHF) [9].

Based on existing studies carried on rats fed on a hyerlipidemic diet, *Crataegus* extract has been found to inhibit the scale up of cholesterol, triglycerides, and phospholipids in LDL and very low-density lipoprotein ultimately preventing the manifestation of atherosclerosis. In addition, extracts of *Cratageus* spp. can induce positive inotropic and exert vasodilatory effects increasing myocardial perfusion and reducing afterload. Interestingly, when used as a complementary therapy for CHF, the plant has been effective in relieving the patient's symptom as well as improving physiologic outcomes [49]. *Cratageus* can potentiate the activity of digitalis hence, its concomitant use with the drug has to be monitored carefully. Given the hypothesis that *Crataegus* spp. can enhance the activity of digitalis, the single

Table 1 The effect of grapefruit on the AUC of drugs employed in cardiology

Drug	Approximate increase in AUC
Artovastatin	150
Felodipine	225
Lovastatin	1200
Nifedipine	100
Nisoldipine	300
Nitrendipine	130
Simvastatin	1500
Verapamil	40

study involving both agents in humans found out that the pharmacokinetic profile of digoxin does not differ with or without concomitant hawthorn use. Furthermore, these findings can be corroborated with the results from a systematic review carried on 5,577 patients reporting that adverse events due to hawthorn were not significant in nature and no drug interaction reports or deaths were reported [5].

According to another study, employing high doses of *Crataegus* extract induces a cardioprotective effect on ischemic-reperfused heart while not interferring with the coronary blood flow. Conversely, other studies carried out in cats and dogs administered oral and parenteral oligomeric procyanins of *Crataegus* showed an increase in coronary blood flow. Furthermore, double-blind clinical trials have demonstrated simultaneous cardiotropic and vasodilatory actions of *Crataegus* as well as its potential to lower blood pressure as part of its action in lowering peripheral vascular resistance [63, 78]. Given this insufficiency of data on the reported safety and efficacy of the plant health care professionals are strongly discouraged to promote use of the plant's extract in patients prescribed with heart failure medications [7, 57].

Ephedra sinica Stapf. (Ephedraceae)- Chinese ephedra or Ma huang

Ephedra sinica has a long standing use in TCM to treat respiratory symptoms and febrile illness. This plant has been in extensive use in TCM as an anti-asthmatic and decongestant for 5000 years [11]. In addition, *E. sinica*, also referred to as Chinese ephedra or Ma Huang, was in common use as a performance enhancer, fat burner, and to manage weight before its prohibition from the United States in April 2004 due to serious adverse effects such as lethal arrhythmias, stroke, vasoconstriction, and myocardial infarction [11]. A multiplicity of dietary supplements containing *E. sinica* are still in popular use in many western countries despite their prohibition by the Food and Drug Administration in America [11].

The alkaloids of the plant are the main active ingredient of *E. sinica.* These alkaloids show both direct agonism at the adrenergic receptors as well as indirect agonism by stimulating the release of norepinephrine from presynaptic neurons [11]. Clinical results involve tachycardia, hypertension, diaphoresis, bronchodilation, agitation, and mydriasis with a retained light reflex. These sympathomimetic effects have been suggested to be responsible for the reported adverse events in human and mortality in animal studies [11].

During the past decade, the FDA has identified more than 100 ephedra containing products that have been postulated to be the cause of more than 800 reports of adverse reactions. A plethora of adverse reactions reported included insomnia, nervousness, tremor, headaches, hypertension, seizures, arrhythmias, heart attack, and stroke as well as lethality [11]. Moreover a case report of myocardial infarction in a 29-year-old patient following ephedrine use exemplifies the long-term danger of such products and is the first report of coronary artery aneurysm associated with its use [14]. Due to deleterious effects on the cardiovascular system, the FDA proposes a maximum daily dose of 24 mg with equal intake every 6 h. This rule also specifies that labels should be attached ephedrine-containing products specifying its use for no more than 7 days and warning consumers that exaggerated intake of the product may result in heart attack, stroke, seizure or death [11].

Ginkgo biloba L. (Ginkgoaceae) - Ginkgo

Ginkgo biloba commonly called the maidenhair tree is one of the oldest living fossil on the planet dating well over 200 million years. *G. biloba* forms part of one of the most popular herbs used worldwide and is advocated mainly for cerebral insufficiency, memory loss, Alzheimer's disease, peripheral vascular disease and circulatory disorders [28]. The use of the root and kernels of *G. biloba* is widely documented in TCM.

A number of scientific reports tend to support the fact that *G. biloba* extract is primarily employed against cerebral insufficiency and exerts secondary effects on vertigo, tinnitus, memory, and mood. Similarly, an investigation on 327 demented patients showed that 120 mg of *G. biloba* extract produced improvements in dementia [69]. Despite the fact that Ginkgo is now an accepted drug in Europe, it is still considered as a dietary supplement in the United States available in 40-mg tablets of extract. In Europe, the recommended maximal daily dose of the plant's extract is 120 -mg where a 40-mg tablet is taken three times with meals. Multiple adverts effects from *G. biloba* extract have been reported and include gastrointestinal disturbances, headache, and skin rash. Several case reports of bleeding, including subarachnoid hemorrhage, intracranial hemorrhage, and subdural hematoma, have been associated with *G. biloba* [30, 40, 67, 77].

A concentrated extract of *G. biloba* leaves was developed in the West in the 1960s. Many of its secondary metabolites have been identified and named for e.g. quercetin, kaempferol, isorhamnetin and terpene trilactones. Interestingly, other metabolites from the plant such as ginkgolides and bilobalides have been found to have antiplatelet activity and hence its concomitant use with anticoagulant agents such as warfarin and heparin as well as analgesic agents such as aspirin, triclopidine and clopidogrel is not recommended. Additionally, a combination of ginkgo with antiplatelet agents, anticoagulants or antithrombotics results in hyphema, subphrenic hematoma as well as intracranial hemorrhage [43, 45]. Interestingly, it has been found in clinical trials that the

herb can induce the CYP450 system and in doing so depletes the levels and lowers the effectiveness of drugs metabolised by this enzyme such as like nicardipine [73].

Panax quinquefolius (L.) and *Panax ginseng* C.A.Mey. (Araliaceae) - American ginseng and Asian ginseng

The use of Ginseng as an herbal medicine dates now more than 2000 years in China, Korea and Japan, and it is only in the last twenty years or so that it has gained popularity in the United States, Canada and Europe. Ginseng varieties have been garnering increasing interest recently for their effects on the cardiovascular system. Its major active components are ginsenosides and up to date the structure of about 40 distinct ginsenosides has been elucidated. Indeed, ginseng possesses diverse pharmacological effects including immune modulation, anti-diabetic and anti-cancer effects. Interestingly, in the cardiovascular system, ginseng has been found to trigger nitric oxide release, vasorelaxation, improve lipid profiles, and has been used as a treatment for hypertension and heart failure [20, 33, 40, 71, 90, 94].

Two species namely *Panax quinquefolius* and *Panax ginseng* are considered to harbor significant therapeutic outcomes. Chemically, more than one factor differentiates *P. quinquefolius* and *P. ginseng*. One important parameter that differentiated the two is the presence of ginsenoside Rf in *P. ginseng* versus the presence of pseudoginsenoside F ll in *P. quinquefolius* [59]. Compared with the long standing use and the widespread research on *P. ginseng,* data on *P. quinquefolius* is relatively limited. Ginseng abuse syndrome includes hypertension, behavioral changes, and diarrhea. Ginseng can mimic estrogen effects since its active component ginsenosides shares a similarity with the chemical structure of testosterone, estrogen, and glucocorticoids. This points to the fact that Ginseng should therefore not be employed by pregnant women and or receiving hormone replacement therapy. Furthermore, neonatal death has been linked to the maternal use of the plant. In cardiology, the concomitant administration of ginseng with warfarin has the potential to reduce prothrombin time [73].

A number of studies have emphasized that *P. quinquefolius* has a multiplicity of pharmacological effects on the cardiovascular and central nervous systems, antidiabetic effects, antitumour activities and immunomodulatory effects similar to those of *P. ginseng.* In comparison to *P. ginseng*, ginsenosides are also its major biologically active constituents. In a study involving 20 healthy individuals it was found that *P. quinquefolius* reduced the anticoagulant effect of warfarin after 14 days of its administration [59]. Similarly, in another study, a dose of 2 g per day for 14 to 28 days of American ginseng caused a decrease in the AUC of warfarin [36].

P. ginseng is a medicinal herb documented with diverse biological effects, including immune function enhancement and anti-aging, anti-diabetic, anti-tumor, anti-apoptotic, and anti-oxidative effects. Indeed, a wealth of literature suggests that it has diverse pharmacological activities, including effects on the central nervous system, antineoplastic effects and immunomodulatory effects. Many of ginseng's medicinal effects are attributed to triterpene glycosides, which are known as the ginsenosides. Indeed, 38 ginsenosides have been found to bear the potential of exerting distinct effects on the endothelial cells, prevention of programmed cell death, regulation of angiogenesis, and stabilizing blood pressure. Intriguingly, it is reported that ginsenosides can enhance endothelial function [29, 47]. Additionally it is also reported that *P. ginseng* can induce the activity of the enzymes of the CYP450 family and as a consequence lower the bioavailability of a number of drugs including warfarin [26]. A number of reports have also concluded that *P. ginseng* bears the same effect as anticoagulant drugs in where it reduces platelet adhesiveness and binding as well as delays the time required for blood to clot. When administered concurrently with warfarin it has the potential to lower the drug's level during metabolism where reduced levels of the drug lowers it INR (international normalized ratio) [62, 94]. Nonetheless, even with these set of findings it has not been possible to fully understand the mechanism underlying these consequences. It is only known that the herb has no effect on the activity of CYP1A2 and CYP3A4 but induces CYP2C9 the enzyme primarily responsible for S-warfarin metabolism but nothing has been yet confirmed for other isoenzymes of the cytochrome family [22].

Hypericum perforatum L. (Hyperiacea) - St John's Wort

Hypericum perforatum remains one of the most ancient and popular herbs in the United States [39]. It is mainly advocated against depression, anxiety, sleep disorders, the common cold, herpes, and the human immunodeficiency virus. Furthermore, it is used as a topical analgesic, and is administered as an enema for the treatment of ulcerative colitis. Scientific investigations have identified numerous pharmacologically active compounds in the plant including; naphthodianthrones for example hypericin and pseudohypericin, phloroglucinols for example hyperforin and adhyperforin, flavonoids for example quercetin, quercitrin and 13, 118-biapigenin [65].

H. perforatum has been identified as an inducer of the CYP450 system, particularly of the main drug metabolizing enzyme CYP3A4. Ultimately it results in decreased levels of various drugs metabolized by this enzyme system such as; ethinyl estradiol, indinavir, and cyclosporine with the potential of reducing their levels up to 50 % as happened in an organ transplant patient under cyclosporine treatment resulting in tissue rejection. Given the

potential of the herb to result in serious adverse effects such as arrhythmia, hypertension, or other undesirable effects its co-administration with drugs metabolized by CYP3A4 system should be prohibited [13].

It has also been found that the concomitant use of warfarin with *H. perforatum* decreases blood clotting time hence resulting in sub-therapeutic anticoagulation and increased risk of thromboembolism [92]. Indeed, patients under warfarin treatment and who have a history of stroke, thrombosis, atrial fibrillation, or prosthetic cardiac valves should avoid the use of St John's Wort. Sub-therapeutic levels of statins may potentiate the risk of cardiovascular events. The herb can also induce the multidrug resistance gene product P-gly, which may reduce the blood levels and efficacy of drugs such as digoxin [8, 27]. Additionally, it has been reported that the herb can induce the activity of CYP2C9 as well and result in decreased levels of drugs metabolized by this enzyme. Indeed, the inability of warfarin and phenprocoumon to exert their therapeutic potential as a consequence of depleted blood levels has been reported and is considered a confirmed interaction with the herb. Therefore, the UK Medicines and Healthcare Regulatory Agency forbids CVD patients from using the herb [81]. Additionally it is reported that the levels of drugs used for the management of cardiovascular drugs such as amiodarone, amlodipine, diltiazem, felodipine, lidocaine, losartan, lovastatin, nifedipine, propafenone, simvastatin, and verapamil are severely reduced during concurrent use of the herb hence preventing the desired response from these drugs. The concomitant use of these herbs with drugs can hence exacerbate conditions like arrhythmia, angina pectoris, or hypertension [8]. Table 2 summarise the major classes of drug and the Cytochrome enzyme/transport protein involved during the adverse event.

Leonurus cardiaca- Linn. (Lamiaceae)-Motherwort

Motherwort has a long standing use in orthodox medicine particularly among the European and Asian traditional systems. Its use as a sedative and antispasmodic started earlier than the 15th century. The origin of its name emanates from its use by Greeks for the relief of anxiety among pregnant women. Its potential against cardiovascular ailments is also well documented where it can assuage cardiac arrhythmias, tachycardia as well as heart palpitations. Its main metabolites elucidated till date are the phenylpropanoid glycosides and contribute to the purported pharmacological effects. Studies in rats have depicted that a phenylpropanoid, lavandulifolioside isolated from the herb has the potential to extend PR, QRS, and QT intervals. It is also validated that the activity of the herb can be compared to that of class 3 antiarrhythmic agents. Despite considerable research on this herb there is a dearth in evidence regarding its safe and effective use in the management of palpitations and cardiac arrhythmias in humans. Additionally data related to the metabolism of its active constituents by the CYP450 family is scarce. In line with the results of studies involving this herb, it is suggested that its use must be monitored carefully in patients who are under drug treatment bearing narrow therapeutic windows as well as metabolized by the cytochrome isoenzymes. Additionally, an intravenous infusion of the herb has antiplatelet and antithrombotic effects as well as depletes fibrinogen levels. Due to these effects its concomitant use with antiplatelet or anticoagulant agents is strongly interdicted [8, 73].

Table 2 Summary of major classes of drug and the Cytochrome enzyme/transport protein involved during adverse events

Drug/class	Cytochrome enzyme/transport protein involved	Effect of interaction
Digoxin/cardiac glycoside	P-gp	Decreases drug AUC by 25-30 %
Nifedipine/calcium channel blocker	CYP3A4, P-gp	Decreases drug AUC by 45 %
Simvastatin/ antihyperlipidemic	CYP3A4	Decreases drug AUC by 50 %
Warfarin/ anticoagulant	CYP2C9	Loss of efficacy due to decrease in INR

Adapted from [23]

Stephania tetrandra - S. Moore (Menispermaceae)

Stephania tetrandra is recommended for hypertension and angina in TCM. One of the major metabolites of the plant responsible for blood pressure lowering effect is the alkaloid tetrandrine which acts as a T and L calcium channel antagonist similar to verapamil and hence when taken concomitantly competes with the drug and other calcium channel blockers for the same effect. Animal studies in rats have demonstrated that a parenteral infusion of dose 15 mg/kg has the potential to lower the mean, systolic, and diastolic blood pressures for more than half an hour. Nonetheless, a higher dose of the infusion (40 mg/kg) caused death of the rats by myocardial depression. Moreover in dogs an orally administered dose of 40 mg/kg 24 times at regular intervals for 60 days caused necrotic liver cell death while the same experiment at a lower dose of the tetrandrine (20 mg/kg) caused reversible injury to liver cells. The use of the herb is not recommended due to underlying risks of hepatotoxicity and renal failure unless more extensive studies establish safe and effective doses of the alkaloid [15, 73].

Miscellaneous plants and CVD

A summary of some herb-drug interactions and other herbal products documented to have adverse effects is presented in Tables 3 and 4.

Table 3 Mechanism of herb-drug interactions

Scientific/vernacular name	Ethnopharmacological use	Suggested mechanism	Likely nature of effect	Reference
Aesculushippocastanum/horse chestnut	Venous insufficiency	SM aesculin a hydroxycoumarin; ↑ anticoagulants.	A, I	[2]
Aloe barbadensis/aloe vera	Laxative, hypercholesterolemia	Laxative; causes hypokalemia: ↑ cardiac glycosides and antiarrhythmic drugs.	I	[82]
Ammi visnaga/khella	Muscle spasms	SM khellin; inhibits cytochrome P 450 enzymes: anticoagulants ↑, calcium channel blockers.	Not known	[85]
Angelica sinensis/angelica	Antitumour, antiinflammatory, analgesic, antispasmodic, dyspepsia, infection	Decreases prothrombin time ↑; anticoagulants, calcium channel blockers.	A	[88]
Cassia senna/senna	Laxative	Causes hypokalemia; ↑ cardiac glycosides + antiarrhythmic drugs and calcium channel blockers.	I	[84]
Chondrus crispus/irish moss	Ulcers, gastritis	Exerts anti-thrombin activity similar to heparin; ↑ anticoagulants and antihypertensives.	Not known	[58]
*Cimifuga racemosa/*black cohosh	Gynaecological ailments and premenstrual tension	Inhibits CYP3A4	Not known	[42, 76]
Glycyrrhiza glabra/licorice	Gastric ulcers	Causes hypokalemia reduces water and sodium excretion ↑; cardiac glycosides, ↓ thiazide and loop diuretics.	A, I	[86]
Hapagophytum Procumbens/ devil's claw	Anti-inflammatory	Inhibits cytochrome P 450 enzymes mainly CYP1A2 and CYP2D6; ↑ anticoagulants, statins and antihypertensives.	A	[55]
*Hydrastis Canadensis/*golden seal	Antiinflammatory, antimicrobial	Inhibits cytochrome P 450 enzymes mostly CYP3A4 and CYP2D6; ↑ antihypertensives, calcium channel blockers and digoxin	Anta, A	[56]
Oleum Oenotherae Biennis/ evening primrose oil	Menopausal symptoms	Inhibits platelet activating factor; anticoagulants	Unknown	[87]
Zingiber officinalis/ginger	Antiemetic	Inhibits thromboxane synthase, acts as a prostacyclin agonist and large doses enhance hypothrombinaemia ↑; platelet inhibitors, anticoagulants and antihypertensives.	A	[89]

Key:↑; Induces effect of ↓; Suppresses effect of, *A* agonism, *SM* secondary metabolite, *I* inhibition, *Anta* antagonism

Case-reports

It is imperative that information on the risks associated with the use of herbal products is systematically collected and analysed in order to protect public health. A number of cases of herbs interacting with cardiovascular drugs have been reported [10].

Camellia sinensis (L.) kuntze (Theaceae) -Green tea

The consumption of *Camellia sinensis* as a medicinal herb began almost 5000 years back. Today, it is one of the most popular beverages worldwide. Plethora of chemical components have been isolated from the plant including chiefly polyphenols, catechins, caffeine, amino acids, and flavonoids and reported to have anti-oxidant properties having many beneficial effects. Interestingly, tea flavonoids have been reported to reduce inflammation, possess antimicrobial effects and prevent tooth decay. Furthermore the consumption of *C. sinensis* may have diuretic effects due to the caffeine present. Theophylline, a licensed medicine for the treatment of respiratory diseases such as asthma is one of the components of the *C. sinensis* [64]. There is mounting evidence about the benefits of *C. sinensis* in maintaining endothelial function and vascular homeostasis and an associated reduction in atherogenesis and CVD risk. *C. sinensis* catechins have been suggested to improve vascular function from epidemiological, human intervention and animal studies [48]. Nonetheless, it is reported that a 44 year old male patient with an artificial heart valve having recourse to one gallon of green tea daily and under warfarin treatment had a reduced response to the drug and when examined it was found that the INR of the drug was reduced from 3.79 to 1.37 [18].

Citrus aurantium (L.) (Rutaceae)-Bitter orange

Citrus aurantium is also commonly known as *Aurantii pericarpium,* Kijitsu, Shangzhou zhiqiao, Zhi qiao, Zhi shi, and Seville orange. *C. aurantium* extract and its primary protoalkaloidal constituent *p*-synephrine are extensively used in weight management products and as thermogenic agents [21]. Other widely known uses are enhancing stamina in athletes. *C. aurantium* extract is widely known as *C. aurantium* extract, a product that is derived from the immature green fruits of the Seville orange. *C. aurantium* is a small citrus tree, about 5 m tall, with scented white flowers. *C. aurantium* is too sour to be popular for eating, but the ripe fruit is eaten in Iran

Table 4 Summary of common herbs used in CVD with possible adverse events

Scientific/vernacular name	Ethnopharmacological use	Possible adverse event	Likely nature of effect	***Reference***
Capsicum annuum/capsicum	Shingles, trigeminal and diabetic neuralgia	Blood pressure increased with mono-amine oxidase inhibitors	Not known	[17]
Capsicum spp./chilli pepper	Analgesic	May interfere with antihypertensives	I	[12]
Convallaria majalis/ lilly of the valley	CHF	β-blockers + calcium channel blockers + digitalis + quinidine + steroids	Not known	[17]
Cucurbita pepo/pumpkin seed	Benign prostatic hyperplasia	Diuretics	A	[12]
Fumaria officinalis/fumitory	Infection, edema, hypertension, constipation	β–blockers + calcium channel blockers + cardiac glycosides ↑		[17]
Gossipyum hirsutum/gossypol	Male contraceptive	Diuretics ↑, Hypokalemia	Not known	[17]
Laminariales/kelp	Cancer, obesity	Antihypertensives and anticoagulants ↑	Not known	[17]
Medicago sativa/alfafa	Arthritis, asthma, dyspepsia, hyperlipidemia, diabetes	Warfarin ↑	Not known	[12]
Aetheroleum Menthae piperitae/ peppermint oil	Irritable bowel syndrome	Cardiac glycosides ↑	A	[17]
Selenicereus grandiflorus/night blooming cereus	CHF	Angiotension-converting enzyme inhibitors + antiarrhythmics + β-blockers + calcium channel blockers + cardiac glycosides ↑	Not known	[17]
Storphantus preussi/strophanthus	CHF	Cardiac glycosides ↑	Not known	[17]
Tanacetum parthenium/feverfew	Prevention of migraine	Platelet inhibitors + anticoagulants ↑	A	[12]
Taraxacum officinale/dandelion	Laxative, diuretic	Antihypertensives + diuretics ↑	A	[12]
Trigonella Foenum-graecum/ fenugreek	Hypercholesterolemia	anticoagulants + lipid-lowering drugs ↑	A, I	[12]
Urtica dioica/nettle	Diuretic, analgetic	Diuretics + antihypertensives	A	[12]
Vaccinium myrtillus/bilberry	Disturbed night vision, local inflammation, skin conditions, diarrhea, arthritis	Anticoagulants ↑	A	[17]
Vitex agnus castus/chaste tree	Menstrual symptoms	Beta-blockers + Antihypertensives ↑	A	[12]

Key:↑; effect induced; ↓ effect suppressed; *A* agonism, *Anta* antagonism, *I* inhibition, *CHF* chronic congestive heart failure patients

and in Mexico and fresh fruits are sometimes eaten with salt and chili paste.

The most active components in *C. aurantium* fruit are synephrine (also called *p*-synephrine or oxedrine) and octopamine. It is the substituent for ephedra in many ephedra free products after the latter has been banned from the market. Interestingly, at the suggested dose *C. aurantium* can increase heart rate in healthy subjects by more than 10 beats per minute. In a study over 18 months its combined use with caffeine increased the systolic and diastolic blood pressure of healthy subjects increased by 10 mmHg and 9 mmHg [70]. Additionally, health authorities from Canada recorded 15 reports of adverse cardiovascular events by *C. aurantium* out of which were serious and one even included a case of myocardial infarction [12].

Matricaria recutita L. (Asteraceae) - Chamomille

Matricaria recutita is one of the most ancient medicinal herbs known to mankind. It bears a rich diversity of metabolites. In fact, the dried flowers of *M. recutita* contain many terpenoids, coumarins and flavonoids contributing to its medicinal properties. *M. recutita* preparations are commonly used for a number of ailments such as hay fever, inflammation, muscle spasms, menstrual disorders, insomnia, ulcers, wounds, gastrointestinal disorders, rheumatic pain, and hemorrhoids. Furthermore, essential oils of *M. recutita* are used extensively in cosmetics and aromatherapy. Multiple preparations of *M. recutita* have been developed, the most popular of which is in the form of herbal tea consumed more than one million cups per day [68]. A number of reports tend to suggest that regular use of flavonoids consumed in food may reduce mortality from coronary heart disease in elderly men. A study assessed the flavonoid intake of 805 men aged 65–84 years who were followed up for 5 years. It was found that flavonoid intake was significantly lowered the mortality from coronary heart disease and showed an inverse relation with incidence of myocardial infarction [19]. A reported case of *M. recutita* interaction with cardiovascular drug was brought in a recent study where a 70 year old female patient having a mechanical mitral valve and previous episode of atrial fibrillation and under amiodarone, digoxin, synthroid, alendronate, metoprolol

and warfarin treatment experienced major bleeding due to an increased INR of 7.9. This effect was induced due to the high coumarin content which is believed to have anticoagulant potentials as warfarin [18].

Salvia miltiorrhiza Bunge- (Lamiaceae)-Danshen

Salvia miltiorrhiza, a relative of the Western sage *S. officinalis*, is native to China. In TCM, the root of *S. miltiorrhiza* has a long standing use as a circulatory stimulant, sedative, and cooling agent. It is reported that dihydrotanshinone present in the root of the plant can inhibit the uptake of calcium ions in vascular smooth muscle cells and hence exert vasorelaxant effect [52]. Additionally, *in vitro* studies have concluded that varying doses of *S. miltiorrhiza* can interfere with platelet adhesion. Interestingly, *S. miltiorrhiza* appears to have benefits in ischemic myocardium, enhancing the recovery of contractile force upon reoxygenation. Moreover, *S. miltiorrhiza* has been reported to interfere with the elimination of warfarin hence increasing its blood levels as well as inhibits cyclic adenosine monophosphate phosphodiesterase. The result is an increase in the INR of warfarin as well as prolongs prothrombin time hence increasing the risks of profound bleeding [32]. It is also established that the intake of danshen with digoxin can interfere with the digoxin metabolism which has a small therapeutic window and hence result in drug toxicity [73].

A number of case reports emanating from the use cardiovascular drugs and the herb show that this practice is not safe. Indeed a 62 year old (y/o) male who was administered a daily dose of 5 mg of warfarin and who was having recourse to an extract of danshen as well for 14 days had to be admitted due to pleural and pericardial effusion and showed an elevated warfarin INR of more than 8.4. Moreover, in a 48 (y/o) woman having a daily dose of 4 mg of warfarin and concurrently taking danshen every other day had an INR of 5.6 which is higher than normal and which was stabilized to the therapeutic level after danshen withdrawal. Similarly in a 66 y/o male under a 2.5 mg daily intake of warfarin was hospitalized due to a bleeding gastric carcinoma and when examined had an elevated INR of 5.5. Clinical trials will be necessary to further evaluate the use of the herb among cardiovascular patients since a number of case reports have questioned its safety and efficacy [35].

Vaccinium microcarpum (Ericaceae) - Cranberry

Vaccinium microcarpum juice is a rich source of polyphenolic compounds, particularly anthocyanins. A number of studies have proposed that *V. microcarpum* consumption might have cardioprotective effects by reducing inflammation and serum lipids. Interestingly, postprandial studies have shown increased plasma antioxidant capacity following cranberry juice consumption in healthy volunteers. An intervention trial ranging from 2 to 16 weeks have reported *V. microcarpum* to improve oxidative stress, postprandial glycemic response, dyslipidemia, and atherosclerotic markers in healthy volunteers and in patients with type 2 diabetes mellitus. Another trial involving two 12-weeks interventions in type 2 diabetics consuming *V. microcarpum* juice concentrate powder or *V. microcarpum* extract powder showed a significant decrease in serum insulin or in total and LDL-cholesterol levels [34, 46, 50, 61, 79]. It has been reported from a study a patient in the 70's under warfarin treatment for poor appetite died from gastrointestinal and pericardial hemorrhage. Nonetheless, mechanisms pertaining to such events remain unclear [18].

Discussion

Despite widespread use of herbal remedies, herb-drug interactions are a stark reality today. The number of cases reported for the emerging herb-drug interactions is thriving worldwide and it is of no denying that there is a lacuna of up-to-date documentation of herb-drug interactions for CVDs. Furthermore, herb-drug interaction events reporting amongst cardiovascular patients are considered to be a key factor to help promote patient health and hence ensuring successful conventional drug therapy. It is a frequent practice for patients to judge herbal products as safe or with minimal side effects as they are considered to be natural and with a long history of use. Nonetheless, there is no denying to the fact that herbs are considered as drugs and when administered inappropriately they can have serious adverse effects which can even lead to mortality. In this endeavor, it is the duty of clinicians to implement strategies that will enable their patients to express themselves freely on any herbal products they could be using concomitantly with conventional drugs.

Furthermore, it is suggested that patients must be treated as a partner in ensuring successful therapy. The clinician must not be judgmental of the patient's traditional or cultural beliefs and must be ready to offer appropriate guidance to avert the risks of adverse events [81]. Since physicians are most of the time the first healthcare professionals likely to encounter patients employing herbal remedies, they need to be aware of the plausible effects of such products as well as deleterious effects due to interactions with drugs. They should also be ready to use pharmacovigilance tools to document such effects [72].

Nonetheless, in many cases the herb-drug interactions may increase toxicity or even be fatal. This is supported by a number of documentations where today some mechanisms are believed to be better understood [25]. There is evidence that taking herbal preparations can result in pharmacokinetic or pharmacodynamic

interactions that represent a potential risk to patients on conventional medicines. All pharmacokinetic interactions identified so far point to the fact that herbs affect Cytochrome enzymes and P-glycoproteins. Interactions where herbal products can significantly increase the bioavailability of the administered drug are more frequent with antihypertensives, anti-coagulants, β-blockers, diuretics and cardiac glycosides. Plausible cases of herb-drug interactions include bleeding when warfarin is combined with *Ginkgo biloba*, *A. sativum* or *Salvia miltiorrhiza*; and decreased bioavailability of digoxin, theophylline and cyclosporine when these drugs are combined with St John's Wort [5, 74]. Patients receiving warfarin therapy should be discouraged from using herbal products and other dietary supplements. Raising the concentrations of such drugs with narrow therapeutic window has been lethal in more than one case. Indeed, it is becoming increasingly evident that herbal interactions with warfarin remains the most common case and more precautionary measures must be undertaken by clinicians when prescribing this drug. Having a complete list of the patient's medical history together with discussion about any home remedy he could be taking is also an imperative consideration. Herbs that act in synergy with warfarin aggravate bleeding risks while other herbs that result in its sub-therapeutic concentrations promote thromboembolic events [26, 91].

The possibility of interactions is directly related to the amount of herb being consumed and the frequency of consumption. It is suggested that a small amount of *A. sativum* as culinary uses may not be having any clinical relevance, whereas the regular consumption of large and therapeutic amounts of fresh *A. sativum* could interfere to a considerable extent in patients under anticoagulant therapy. The most harmful effects of interactions of herbs with drugs arise when the latter have a narrow therapeutic window and hence likely to produce an acute clinical consequence. Therefore, it is imperative that clinical studies are performed on documented herbs to evaluate safe amounts and dose. It is also recommended that when adverse reactions are experienced with drug therapy, patients must always be queried and encourage to report of any concomitant intake of herbal products [44].

Conclusion and future perspectives

The present review has aimed to emphasize on the potential effects of herbs on CVD and cardiovascular drug interactions. The documentation, monitoring and reporting of evidence-based data is a critical baseline step in proper prescribing and adequate counseling for patients. Ignorance of the fact that herbal products have effects analogous to conventional drugs can have severe implications and may also result in morbidity and mortality amongst patients. Considering the present lack of understanding and dearth of data on herb-drug interactions, proper reporting of cases, pharmacovigilance techniques, evidence-based appraisal and regular updated systematic reviews are imperative approaches to promote the efficiency of drug regimens and meet therapeutic targets successfully in patients. Therefore, it is fundamental to perform rigorous clinical studies in compliance with clinical safety standards to validate therapeutic use of such herbal products in CVD patients.

It is recommended that doctor-patient communication and education be enhanced and that clinicians should be more cooperative with patients to enable the reporting of cases and should routinely inquirer about such use. Additionally, it also important when addressing adverse drug reactions, question patients about possible herbal products use and not to discount long-term use of herbs as causing side effects. Such cases should be reported to appropriate authorities and pharmacovigilance centers. Clinicians must also accept the fact that they should update their knowledge on such kind of practice and must be provided with adequate herb-drug interactions related training so that they can effectively counsel their patients of any danger related to the concomitant use of both. Consequently, due to these prevailing circumstances the American Herbal Products Association advices consumers to report to their treating physician the concomitant use of herbs so that physicians are sufficiently informed and can provide valuable advice [5]. It is also suggested that herbal product(s) manufacturers should warn their patients by incorporating into their product label its potential to interfere with the patient's drug metabolism systems such as the Cytochrome P450 enzyme family. Labels in the form of cautions that prohibit the use of the product in specific disease conditions are also proposed. In addition, companies should focus on supplying standardized extracts following intensive quality control and/or rigorous double-blind clinical trials.

On the other hand, once the active constituents in a herbal product and the mechanism via which they act are defined, a standardized quality extract must be prepared for evaluating their pharmacological potentials clinically. Therapeutic investigations must be performed through well-designed, randomized, double-blinded, placebo-controlled clinical trials involving a significant number of subjects. It may be better to study effects via clinical trials following good clinical practice to increase the yield of quality results rather than to rely on clinical studies that may bear methodological weaknesses.

It is also recommended to study the varying phenotypes and genotypes of CYP alleles in various populations, ethnic groups, different environmental conditions

and the effect of dietary and social habits on CYP activity as well as understanding the metabolism of natural products and the impact of these natural products on the CYP enzyme activities. Studying such factors in the cytochrome P450 family will enable understanding mechanisms clearly and this will help to better monitor the adverse drug events of herbals in patients.

The use of *in silico* protein–drug interactions studies and computer aided drug designing approach and quantum mechanical calculations will allow predicting the mechanism of interaction of P450 with herbal constituents. Wherever possible, computer aided approaches can also be employed to explore and better describe the effects of multi-item and polyherbal prescriptions. Last but not least, it is important to encourage scientific meetings and lectures regarding herb-drug interactions worldwide to inform and educate clinicians and patients.

Competing interests

SS and FM declare no competing interests. Neither author has any commercial associations that might create a conflict of interest in connection with this article.

Authors' contributions

SS and FM contributed equally in the design of the study. Both authors read and approved the final manuscript.

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