Herbs have served as medicine throughout human history. Since the passage of the Dietary Supplement Health and Education Act (DSHEA), inconsistent regulatory practices have resulted in widespread, indiscriminate use of herbal supplements. Available data indicate that cancer patients use these products (along with standard treatments) more often than the general population. The reasons cited for such use include improving health, reducing the risk of recurrence, and reducing the side effects of cancer treatments. Herbs, however, contain biologically active compounds and can potentially interact with prescription medications, including chemotherapy drugs. We describe the mechanisms via which these interactions may occur, as divided into pharmacokinetics and pharmacodynamics. We highlight four popular herbs and a medicinal mushroom commonly used by cancer patients-turmeric, green tea, ginger, ashwagandha, and reishi mushroom-along with reports of their interactions with standard drugs. We conclude by emphasizing the need to inform patients and physicians about herb-drug interactions and how to advise patients on appropriate use of herbal supplements to minimize the risk for interactions.

Herb-drug interaction related morbidity is thus an emerging serious public health issue with broad implications for clinicians, pharmaceutical industries and health authorities. Nonetheless, despite increasing recognition of herb-drug interaction, a standard system for interaction prediction and evaluation is still nonexistent. This review article discusses the herb-drug interactions related hepatotoxicity and underlying mechanisms, including drug metabolizing enzymes and their regulation.

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. Plausible cases of herb-drug interactions include: bleeding when warfarin is combined with ginkgo (Ginkgo biloba), garlic (Allium sativum), dong quai (Angelica sinensis), or danshen (Salvia miltiorrhiza); mild serotonin syndrome in patients who mix St John's wort (Hypericum perforatum) with serotonin-reuptake inhibitors; decreased bioavailability of digoxin, theophylline, cyclosporin, and phenprocoumon when these drugs are combined with St John's wort; induction of mania in depressed patients who mix antidepressants and Panax ginseng; exacerbation of extrapyramidal effects with neuroleptic drugs and betel nut (Areca catechu); increased risk of hypertension when tricyclic antidepressants are combined with yohimbine (Pausinystalia yohimbe); potentiation of oral and topical corticosteroids by liquorice (Glycyrrhiza glabra); decreased blood concentrations of prednisolone when taken with the Chinese herbal product xaio chai hu tang (sho-salko-to); and decreased concentrations of phenytoin when combined with the Ayurvedic syrup shankhapushpi. Anthranoid-containing plants (including senna [Cassia senna] and cascara [Rhamnus purshiana]) and soluble fibres (including guar gum and psyllium) can decrease the absorption of drugs. Many reports of herb-drug interactions are sketchy and lack laboratory analysis of suspect preparations. Health-care practitioners should caution patients against mixing herbs and pharmaceutical drugs.

Herbs are often administered in combination with therapeutic drugs, raising the potential of herb-drug interactions. An extensive review of the literature identified reported herb-drug interactions with clinical significance, many of which are from case reports and limited clinical observations. Cases have been published reporting enhanced anticoagulation and bleeding when patients on long-term warfarin therapy also took Salvia miltiorrhiza (danshen). Allium sativum (garlic) decreased the area under the plasma concentration-time curve (AUC) and maximum plasma concentration of saquinavir, but not ritonavir and paracetamol (acetaminophen), in volunteers. A. sativum increased the clotting time and international normalised ratio of warfarin and caused hypoglycaemia when taken with chlorpropamide. Ginkgo biloba (ginkgo) caused bleeding when combined with warfarin or aspirin (acetylsalicylic acid), raised blood pressure when combined with a thiazide diuretic and even caused coma when combined with trazodone in patients. Panax ginseng (ginseng) reduced the blood concentrations of alcohol (ethanol) and warfarin, and induced mania when used concomitantly with phenelzine, but ginseng increased the efficacy of influenza vaccination. Scutellaria baicalensis (huangqin) ameliorated irinotecan-induced gastrointestinal toxicity in

cancer patients.Piper methysticum (kava) increased the 'off' periods in patients with parkinsonism taking levodopa and induced a semicomatose state when given concomitantly with alprazolam. Kava enhanced the hypnotic effect of alcohol in mice, but this was not observed in humans. Silybum marianum (milk thistle) decreased the trough concentrations of indinavir in humans. Piperine from black (Piper nigrum Linn) and long (P. longum Linn) peppers increased the AUC of phenytoin, propranolol and theophylline in healthy volunteers and plasma concentrations of rifamipicin (rifampin) in patients with pulmonary tuberculosis. Eleutheroccus senticosus (Siberian ginseng) increased the serum concentration of digoxin, but did not alter the pharmacokinetics of dextromethorphan and alprazolam in humans. Hypericum perforatum (hypericum; St John's wort) decreased the blood concentrations of ciclosporin (cyclosporin), midazolam, tacrolimus, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline, but did not alter the pharmacokinetics of carbamazepine, pravastatin, mycophenolate mofetil and dextromethorphan. Cases have been reported where decreased ciclosporin concentrations led to organ rejection. Hypericum also caused breakthrough bleeding and unplanned pregnancies when used concomitantly with oral contraceptives. It also caused serotonin syndrome when used in combination with selective serotonin reuptake inhibitors (e.g. sertraline and paroxetine). In conclusion, interactions between herbal medicines and prescribed drugs can occur and may lead to serious clinical consequences. There are other theoretical interactions indicated by preclinical data. Both pharmacokinetic and/or pharmacodynamic mechanisms have been considered to play a role in these interactions, although the underlying mechanisms for the altered drug effects and/or concentrations by concomitant herbal medicines are yet to be determined. The clinical importance of herb-drug interactions depends on many factors associated with the particular herb, drug and patient. Herbs should be appropriately labeled to alert consumers to potential interactions when concomitantly used with drugs, and to recommend a consultation with their general practitioners and other medical carers.

Nearly 25% of U.S. adults report concurrently taking a prescription medication with a dietary supplement. Some supplements, such as St. John's wort and goldenseal, are known to cause clinically important drug interactions and should be avoided by most patients receiving any pharmacologic therapy. However, many other supplements are predicted to cause interactions based only on in vitro studies that have not been confirmed or have been refuted in human clinical trials. Some supplements may cause interactions with a few medications but are likely to be safe with other medications (e.g., curcumin, echinacea, garlic, Asian ginseng, green tea extract, kava kava). Some supplements have a low likelihood of drug interactions and, with certain caveats, can safely be taken with most medications (e.g., black cohosh, cranberry, ginkgo, milk thistle, American ginseng, saw palmetto, valerian). Clinicians should consult reliable dietary supplement resources, or clinical pharmacists or pharmacologists, to help assess the safety of specific herbal supplement-drug combinations. Because most patients do not disclose supplement use to clinicians, the most important strategy for detecting herb-drug interactions is to develop a trusting relationship that encourages patients to discuss their dietary supplement use.

The aim of this overview of systematic reviews (SRs) is to evaluate critically the evidence regarding interactions between herbal medicinal products (HMPs) and synthetic drugs.

Today it is very common for patients to take many medications simultaneously. This is particularly true for elderly patients who frequently take ten and more medications. With multiple prescribed medications, there are numerous potential drug interactions that are often unpredictable. However, the scenario gets even more complicated in cases of cotreatment with herbal drug products that are often poorly defined with variable ingredients. Detection of these interactions is further hindered by the fact that many patients do not disclose the use of herbal products to their physicians and pharmacists.The current issue of Planta Medica is a dedicated summary of articles dealing with various aspects of herb-drug interactions. The first two articles address the regulatory implication for drug approval and labeling, both in the US and in Europe. Both the

FDA and EMA recently released updated guidance documents for the Pharmaceutical Industry on studying and reporting drug-drug interactions. Unfortunately, herb-drug interactions are addressed with little detail in these documents and the articles presented in this issue help fill this gap.

This review updates our knowledge on clinical food-drug interactions with emphasis on mechanism and clinical implications. Results obtained from literature search identified interactions with selected foods/herbs generated from in vivo and in vitro studies. For example, interaction studies in humans revealed a reduction in the bioavailability of mercaptopurine when taken concurrently with substances containing xanthine oxidase (eg, cow milk); a reduction in the bioavailability of quinine with Garcinia kola; increased bioavailability/toxicity of felodipine, nifedipine, saquinavir, sildenafil with grape juice; increased bioavailability of felodipine, cisapride with red wine and diminished bioavailability of fexofenadine with apple. Pharmacokinetic and/or pharmacodynamic mechanisms are implicated in many of these interactions. By evaluating the dietary patterns of patients and use of prescribed medications, health professionals will be well informed of potential interactions and associated adverse effects.

The first clinically relevant reports of preparations of St. John's wort (SJW), a herbal medicine with anti-depressant effects, interacting with other drugs, altering their bioavailability and efficacy, were published about 20 years ago. In 2000, a pharmacokinetic interaction between SJW and cyclosporine caused acute rejection in two heart transplant patients. Since then, subsequent research has shown that SJW altered the pharmacokinetics of drugs such as digoxin, tacrolimus, indinavir, warfarin, alprazolam, simvastatin, or oral contraceptives. These interactions were caused by pregnane-X-receptor (PXR) activation. Preparations of SJW are potent activators of PXR and hence inducers of cytochrome P450 enzymes (most importantly CYP3A4) and P-glycoprotein. The degree of CYP3A4 induction correlates significantly with the hyperforin content in the preparation. Twenty years after the first occurrence of clinically relevant pharmacokinetic drug interactions with SJW, this review revisits the current knowledge of the mechanisms of action and on how pharmacokinetic drug interactions with SJW could be avoided.

Apigenin, a natural flavone, is widely distributed in plants such as celery, parsley and chamomile. It is present principally as glycosylated in nature. Higher intake of apigenin could reduce the risk of chronic diseases. It has gained particular interest in recent years as a beneficial, health-promoting agent with low intrinsic toxicity. Areas covered: This review summarizes and the absorption, distribution, metabolism and excretion (ADME) properties of apigenin, and drug-drug interaction of apigenin. Expert opinion: Since apigenin is a bioactive plant flavone and is widely distributed in common food, its consumption through the diet is recommended. Apigenin-enriched drugs are better for some chronic diseases, but may affect animal and human health if present in the daily diet. Dietary or therapeutic apigenin has value as a good cellular regulator in cancer, especially cancers of the gastrointestinal tract. Due to apigenin's limitations on absorption and bioavailability, novel carriers would need to be developed to enhance the oral bioavailability of apigenin. Further research about its ADME properties and drug-drug interactions are needed before apigenin can be brought to clinical trials.

Ginkgo biloba leaf extracts (GLEs) are popular herbal remedies for the treatment of Alzheimer's dementia, tinnitus, vertigo and peripheral arterial disease. As GLEs are taken regularly by older people who are likely to also use multiple other drugs for the treatment of, e.g. hypertension, diabetes, rheumatism or heart failure, potential herb-drug interactions are of interest. Preclinical studies of high doses/concentrations of GLEs of varying quality and standardization hinted at both an inhibition and induction of metabolic enzymes and transporters. However, in humans, positive in vitro-findings could not be replicated in vivo. At maximum recommended doses of 240 mg/day, a clinically relevant interaction potential of the standardized GLE EGb 761 could not be shown. GLE doses higher than the recommended ones led to a weak induction of the

CYP2C19-mediated omeprazole 5-hydroxylation, and a weak inhibition of the CYP3A4-mediated midazolam 1'-hydroxylation, respectively. Also, the regular intake of a poorly characterized GLE at a dose of 360 mg/day slightly increased the bioavailability of talinolol, a substrate of P-glycoprotein and various organic anion-transporting polypeptides. Thus, regarding pharmacokinetic herb-drug interactions, the intake of the standardized GLE, EGb 761, together with synthetic drugs appears to be safe as long as daily doses up to 240 mg are consumed. If this applies to other extracts prepared according to the European Pharmacopoeia remains uncertain. Also, a relevant potential for drug interactions cannot be excluded for poorly standardized GLEs used in many food supplements.

With more and more popular use of traditional herbal medicines, in particular Chinese herbal medicines, herb-drug interactions have become a more and more important safety issue in the clinical applications of the conventional drugs. Researches in this area are increasing very rapidly. Herb-drug interactions are complicated due to the fact that multiple chemical components are involved, and these compounds may possess diverse pharmacological activities. Interactions can be in both pharmacokinetics and pharmacodynamics. Abundant studies focused on pharmacokinetic interactions of herbs and drugs. Herbs may affect the behavior of the concomitantly used drugs by changing their absorption, distribution, metabolism, and excretion. Studies on pharmacodynamics interactions of herbs and drugs are still very limited. Herb-drug interactions are potentially causing changes in drug levels and drug activities and leading to either therapeutic failure or toxicities. Sometime it can be fatal. The exposures to drugs, lacking of knowledge in the potential adverse herb-drug interactions, will put big risk to patients' safety in medical services. On the contrary, some interactions may be therapeutically beneficial. It may be used to help develop new therapeutic strategies in the future. This chapter is trying to review the development in the area of herb-drug interactions based on the recently published research findings. Information on the potential interactions among the commonly used Chinese medicinal herbs and conventional drugs is summarized in this chapter.

The herbal remedies referred to as "ginseng" are derived from the roots of several plants. One of the most commonly used and researched of the ginsengs is Panax ginseng, also called Asian or Korean ginseng. The main active components of Panax ginseng are ginsenosides, which have been shown to have a variety of beneficial effects, including anti-inflammatory, antioxidant, and anticancer effects. Results of clinical research studies demonstrate that Panax ginseng may improve psychologic function, immune function, and conditions associated with diabetes. Overall, Panax ginseng appears to be well tolerated, although caution is advised about concomitant use with some pharmaceuticals, such as warfarin, oral hypoglycemic agents, insulin, and phenelzine. Panax ginseng does not appear to enhance physical performance. Products with a standardized ginsenoside concentration are available.

The global increase in the popularity of alternative medicines has raised renewed concerns regarding herb–drug interactions. These interactions are especially important for drugs with narrow therapeutic indices and may either be pharmacodynamic or pharmacokinetic in nature.Pharmacokinetic interactions which may exist between herbs and drugs, and the mechanisms of these interactions with appropriate examples based on primary and secondary data in publications are discussed. The mechanisms covered include those that affect oral drug absorption (e.g., modulation of efflux and uptake transporters, complex formation, gastrointestinal motility and pH) and drug biotransformation (e.g., inhibition or induction of enzymes).

Systematic reviews and meta-analyses represent the uppermost ladders in the hierarchy of evidence. Systematic reviews/meta-analyses suggest preliminary or satisfactory clinical evidence for agnus castus (Vitex agnus castus) for premenstrual complaints, flaxseed (Linum usitatissimum) for hypertension, feverfew (Tanacetum partenium) for migraine prevention, ginger (Zingiber officinalis) for pregnancy-induced nausea, ginseng (Panax ginseng) for improving fasting glucose levels as well as phytoestrogens

and St John's wort (Hypericum perforatum) for the relief of some symptoms in menopause. However, firm conclusions of efficacy cannot be generally drawn. On the other hand, inconclusive evidence of efficacy or contradictory results have been reported for Aloe vera in the treatment of psoriasis, cranberry (Vaccinium macrocarpon) in cystitis prevention, ginkgo (Ginkgo biloba) for tinnitus and intermittent claudication, echinacea (Echinacea spp.) for the prevention of common cold and pomegranate (Punica granatum) for the prevention/treatment of cardiovascular diseases. A critical evaluation of the clinical data regarding the adverse effects has shown that herbal remedies are generally better tolerated than synthetic medications. Nevertheless, potentially serious adverse events, including herb-drug interactions, have been described.

Herbal medicines are often used in combination with conventional drugs, and this may give rise to the potential of harmful herb-drug interactions. This paper updates our knowledge on clinical herb-drug interactions with an emphasis of the mechanistic and clinical consideration. In silico, in vitro, animal and human studies are often used to predict and/or identify drug interactions with herbal remedies. To date, a number of clinically important herb-drug interactions have been reported, but many of them are from case reports and limited clinical observations. Common herbal medicines that interact with drugs include St John's wort (Hypericum perforatum), ginkgo (Ginkgo biloba), ginger (Zingiber officinale), ginseng (Panax ginseng), and garlic (Allium sativum). For example, St John's wort significantly reduced the area under the plasma concentration-time curve (AUC) and blood concentrations of cyclosporine, midazolam, tacrolimus, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline. The common drugs that interact with herbal medicines include warfarin, midazolam, digoxin, amitriptyline, indinavir, cyclosporine, tacrolimus and irinotecan. Herbal medicines may interact with drugs at the intestine, liver, kidneys, and targets of action. Importantly, many of these drugs have very narrow therapeutic indices. Most of them are substrates for cytochrome P450s (CYPs) and/or P-glycoprotein (P-gp). The underlying mechanisms for most reported herb-drug interactions are not fully understood, and pharmacokinetic and/or pharmacodynamic mechanisms are implicated in many of these interactions. In particular, enzyme induction and inhibition may play an important role in the occurrence of some herbdrug interactions. Because herb-drug interactions can significantly affect circulating levels of drug and, hence, alter the clinical outcome, the identification of herb-drug interactions has important implications.

In healthy volunteers, the probe drug method is widely practised to assess the pharmacokinetic mediated herb-drug interactions (HDI). We analyzed the clinical evidence of CYP3 A4 probe drug, Midazolam.

Psoraleae Fructus (the dried fruits of Psoralea corylifolia), one of the most frequently used Chinese herbs in Asian countries, has a variety of biological activities. In clinical settings, Psoraleae Fructus or Psoraleae Fructus-related herbal medicines frequently have been used in combination with a number of therapeutic drugs for the treatment of various human diseases, such as leukoderma, rheumatism and dysentery. The use of Psoraleae Fructus in combination with drugs has aroused concern of the potential risks of herb-drug interactions (HDI) or herb-endobiotic interactions (HEI). This article reviews the interactions between human drug-metabolizing enzymes and the constituents of Psoraleae Fructus; the major constituents in Psoraleae Fructus, along with their chemical structures and metabolic pathways are summarized, and the inhibitory and inductive effects of the constituents in Psoraleae Fructus on human drug-metabolizing enzymes (DMEs), including target enzyme(s), its modulatory potency, and mechanisms of action are presented. Collectively, this review summarizes current knowledge of the interactions between the Chinese herb Psoraleae Fructus and therapeutic drugs in an effort to facilitate its rational use in clinical settings, and especially to avoid the potential risks of HDI or HEI through human DMEs.

Co-medication with herbs can result in changes in pharmacological effects of many drugs. This review describes the assessment of single-ingredient herbs, crude herb extracts, and herbal formulae. When choosing a research method to investigate herb-drug interactions, the properties of the drugs and herbs should be considered.

While most food, herbs and supplements can be safely taken in moderation, healthcare professionals should be aware of the increased risk of bleeding when taking several food and herbs. These include Chinese wolfberry, chamomile tea, cannabis, cranberry, chitosan, green tea, Ginkgo biloba, ginger, spinach, St. John's Wort, sushi and smoking tobacco. Patients should be counselled to continue to seek advice from their healthcare professionals when starting any new herbs, food or supplement.

Medicinal herbs have been a part of human medicine for thousands of years. The herb-drug interaction is an extension of drug-drug interaction, in which the consumptions of herbs cause alterations in the metabolism of drugs the patients happen to take at the same time. The pregnane X receptor (PXR) has been established as one of the most important transcriptional factors that regulate the expression of phase I enzymes, phase II enzymes, and drug transporters in the xenobiotic responses. Since its initial discovery, PXR has been implicated in multiple herb-drug interactions that can lead to alterations of the drug's pharmacokinetic properties and cause fluctuating therapeutic efficacies, possibly leading to complications. Regions of the world that heavily incorporate herbalism into their primary health care and people turning to alternative medicines as a personal choice could be at risk for adverse reactions or unintended results from these interactions. This article is intended to highlight our understanding of the PXR-mediated herb-drug interactions.

Herbal and dietary supplements are commonly used throughout the World. There is a tendency for underreporting their ingestion by patients and the magnitude of their use is underrecognised by Physicians. Herbal hepatotoxicity is not uncommonly encountered, but the precise incidence and manifestations have not been well characterised.

Widespread usage of herbs as supplements or medicines raises the potential of herb-drug interactions (HDIs). Basically, HDIs occur by pharmacokinetic and/or pharmacodynamic pathways. Nuclear receptors (NRs) are a class of transcription factors whose role in drug interactions has been defined. A large number of herbs activate NRs, resulting in HDIs. NR-mediated HDIs are similar to drug-drug interactions, but are more complicated because of the presence of multiple compounds in herbs. Dosage and therapeutic sequence as well as various other factors, including the patient's gender, age, and genetic makeup, may affect outcomes of NR-mediated HDIs.

Everolimus is a widely used oral mTOR inhibitor that has the potential for drug interactions that may affect therapeutic outcomes, produce toxicities, or both. This article provides a review of evidence-based literature, along with the prescribing information, to educate clinicians on the significance of these drug interactions and their impact on management with everolimus.

Pharmacokinetic interactions often occur as a result of activity changes of drug-metabolizing and transporting proteins, especially cytochrome P450 (CYP) isoenzymes and P-glycoprotein (P-gp). The activity of these enzymes and drug transporters can be enhanced or inhibited by synthetic drugs as well as by natural products. Since the number of herb-drug interactions has increased in recent years, systematic in vitro screenings and more clinical studies to identify such interactions were proposed for herbal medicinal products. However, previous results regarding this issue are not only contradictory but also of less predictability. One reason for the discrepancies could be the lack of validation of the recommended in vitro tests. Furthermore, it has to be considered that pharmacokinetic drug interactions are not only mediated by herbal medicines but also by several foods, beverages and life-style products. Since herbal medicines are considered to have a broad therapeutic range, a preventive risk assessment for pharmacokinetic drug interactions should first be realized for synthetic drugs with a narrow therapeutic index. Efforts to identify all possible interactions will lead to limitless investigations and to inconsistent decisions.

Herbal therapeutics are increasingly associated with herb drug interactions. The vast majority of the purported cases is unsubstantiated and misinterpreted. Pharmacological and clinical studies should only be

demanded in cases of reliable evidence. First steps to be taken by manufacturers of herbal drugs should be in vitro studies with metabolizing systems like CYP and P-gp. Manufacturers of drugs that are metabolized by modulated systems should be requested to conduct drug specific interaction studies as necessary.

Herbal drugs are being used worldwide in a variety of debilitating neurological and psychiatric disorders such as cerebrovascular accident, Alzheimer's disease, Parkinson's disease and schizophrenia. However, unlike drugs of modern medicine, herbal drugs are complex products containing multiple pharmacologically active constituents. The nature and relative amounts of these constituents vary due to diverse factors such as but not limited to source of the plant(s), local environmental conditions, parts of the plant used, storage, method of extract preparation, accidental contamination or intentional adulteration. Further, they are handled by the human body like modern drugs and subjected to the processes of absorption, distribution, metabolism and excretion. In each of these processes, they can potentially interact with modern drugs due to sharing of similar transport proteins, metabolizing cytochrome P450 (CYP450) enzymes and uptake ,efflux pumps. Moreover, herbal drugs can also inhibit or induce CYP450 enzymes or inactivate transporters leading to Herb-Drug interactions (HDIs).

Whilst the popular use of herbal medicine globally, it poses challenges in managing potential drug-herb interaction. There are two folds of the drug-herb interaction, a beneficial interaction that may improve therapeutic outcome and minimise the toxicity of drug desirably; by contrast, negative interaction may evoke unwanted clinical consequences, especially with drugs of narrow therapeutic index. Scutellaria baicalensis Georgi is one of the most popular medicinal plants used in Asian countries. It has been widely used for treating various diseases and conditions such as cancer, diabetes, inflammation, and oxidative stress. Studies on its extract and bioactive compounds have shown pharmacodynamic and pharmacokinetic interactions with a wide range of pharmaceutical drugs as evidenced by plenty of in vitro, in vivo and clinical studies. Notably, S. baicalensis and its bioactives including baicalein, baicalin and wogonin exhibited synergistic interactions with many pharmaceutical drugs to enhance their efficacy, reduce toxicity or overcome drug resistance to combat complex diseases such as cancer, diabetes and infectious diseases. On the other hand, S. baicalensis and its bioactives also affected the pharmacokinetic profile of many drugs in absorption, distribution, metabolism and elimination via the regulatory actions of the efflux pumps and cytochrome P450 enzymes. This review provides comprehensive references of the observed pharmacodynamic and pharmacokinetic drug interactions of Scutellaria baicalensis and its bioactives. We have elucidated the interaction with detailed mechanistic actions, identified the knowledge gaps for future research and potential clinical implications. Such knowledge is important for the practice of both conventional and complementary medicines, and it is essential to ensure the safe use of related herbal medicines. The review may be of great interest to practitioners, consumers, clinicians who require comprehensive information on the possible drug interactions with S. baicalensis and its bioactives.

The concomitant use of herbal medicines and pharmacotherapy is wide spread. We have reviewed the literature to determine the possible interactions between seven popular herbal medicines (ginkgo, St John's wort, ginseng, garlic, echinacea, saw palmetto and kava) and conventional drugs. Literature searches were performed using MEDLINE, Cochrane Library and EMBASE and we identified 128 case reports or case series, and 80 clinical trials. Clinical trials indicate that St John's wort (Hypericum perforatum), via cytochrome P450 (CYP) and/or P-glycoprotein induction, reduces the plasma concentrations (and/or increases the clearance) of alprazolam, amitriptyline, atorvastatin, chlorzoxazone, ciclosporin, debrisoquine, digoxin, erythromycin, fexofenadine, gliclazide, imatinib, indinavir, irinotecan, ivabradine, mephenytoin, methadone, midazolam, nifedipine, omeprazole, oral contraceptives, quazepam, simvastatin, tacrolimus, talinolol, verapamil, voriconazole and warfarin. Case reports or case series suggest interactions of St John's wort with adrenergic vasopressors, anaesthetics, bupropion, buspirone, ciclosporin, eletriptan, loperamide, nefazodone, nevirapine, oral contraceptives, paroxetine, phenprocoumon, prednisone, sertraline, tacrolimus, theophylline, tibolone, tryptophan, venlafaxine and warfarin. Ginkgo (Ginkgo biloba) decreases the plasma concentrations of omeprazole, ritonavir and tolbutamide. Clinical cases

indicate interactions of ginkgo with antiepileptics, aspirin (acetylsalicylic acid), diuretics, ibuprofen, risperidone, rofecoxib, trazodone and warfarin. Ginseng (Panax ginseng) may interact with phenelzine and warfarin. Kava (Piper methysticum) increases the clearance of chlorzoxazone (a CYP2E1 substrate) and may interact with alprazolam, levodopa and paroxetine. Garlic (Allium sativum) interacts with chlorpropamide, fluindione, ritonavir and warfarin; it also reduces plasma concentrations of chlorzoxazone (a CYP2E1 probe). Echinacea might affect the clearance of caffeine (a CYP1A2 probe) and midazolam (a CYP3A4 probe). No interactions have been reported for saw palmetto (Serenoa repens). Numerous interactions between herbal medicines and conventional drugs have been documented. While the significance of many interactions is uncertain, several interactions, particularly those with St John's wort, may have serious clinical consequences.

Herbal products, spices and/or fruits are perceived as inherently healthy; for instance, St. John's wort (SJW) is marketed as a natural antidepressant and patients often self-administer it concomitantly with oncology medications. However, food constituents/herbs can interfere with drug pharmacokinetics, with risk of altering pharmacodynamics and efficacy. The objective of this work was to develop a strategy to prioritize herb- or food constituent-drug interactions (FC-DIs) to better assess oncology drug clinical risk.

For healthcare professionals, the volume of literature available on herb-drug interactions often makes it difficult to separate experimental/potential interactions from those deemed clinically relevant. There is a need for concise and conclusive information to guide pharmacotherapy in HIV/AIDS. In this review, the bases for potential interaction of medicinal herbs with specific antiretroviral drugs are presented, and several botanicals are discussed for which clinically relevant interactions in humans are established. Such studies have provided, in most cases, sufficient ground to warrant the avoidance of concurrent administration of antiretroviral (ARVs) drugs with St John's wort (Hypericum perforatum), black pepper (Piper species) and grapefruit juice. Other botanicals that require caution in the use with antiretrovirals include African potato (Hypoxis hemerocallidea), ginkgo (Ginkgo biloba), ginseng (Panax species), garlic (Allium sativum), goldenseal (Hydrastis canadensis) and kava kava (Piper methysticum). The knowledge of clinically significant herb-drug interaction will be important in order to avoid herb-induced risk of sub-therapeutic exposure to ARVs (which can lead to viral resistance) or the precipitation of toxicity (which may lead to poor compliance and/or discontinuation of antiretroviral therapy).

Herbal medicines are currently in high demand, and their popularity is steadily increasing. Because of their perceived effectiveness, fewer side effects and relatively low cost, they are being used for the management of numerous medical conditions. However, they are capable of affecting the pharmacokinetics and pharmacodynamics of coadministered conventional drugs. These interactions are particularly of clinically relevance when metabolizing enzymes and xenobiotic transporters, which are responsible for the fate of many drugs, are induced or inhibited, sometimes resulting in unexpected outcomes. This article discusses the general use of herbal medicines in the management of several ailments, their concurrent use with conventional therapy, mechanisms underlying herb-drug interactions (HDIs) as well as the drawbacks of herbal remedy use. The authors also suggest means of surveillance and safety monitoring of herbal medicines. Contrary to popular belief that "herbal medicines are totally safe," we are of the view that they are capable of causing significant toxic effects and altered pharmaceutical outcomes when coadministered with conventional medicines. Due to the paucity of information as well as sometimes conflicting reports on HDIs, much more research in this field is needed. The authors further suggest the need to standardize and better regulate herbal medicines in order to ensure their safety and efficacy when used alone or in combination with conventional drugs.

Healthcare practitioners are deeply concerned about drug-herb interactions and how concurrent administration may affect both the safety and effectiveness of prescribed drugs. Interactions between botanical medicines and synthetic drugs can be clinically relevant and it is important to understand what kinds of interactions are possible. Better knowledge in this area will help avoid negative interactions and

may also help enable synergistic interactions.Includes articles related to the investigation of Western botanicals or whole herbal extracts in human subjects, investigating either the impact on Cytochrome P450 isoenzymes or an assessment of specific drug-herb interactions within a clinical trial. Searches were conducted in both Pubmed and EMBASE

Global diabetes epidemic is the major cause of fatality and lethality. As per IDF 2019 report, diabetes caused 4.2 million deaths, approximately 463 million people are living with diabetes and by 2045, this will rise to 700 million. Nowadays, the physicians and common people in both developed and developing countries are using medicinal plants and their formulations to treat diseases with the postulation that organic commodities are safe for consumption. These plants may act as inhibitors or inducers of the Cytochrome P450 or transport and efflux proteins or both and may alter gastrointestinal, renal functions leading to Herb-Drug Interactions. This review intends to focus on the frequently employed medicinal plants, their traditional uses, their Cytochrome P450 inhibition or induction activity, phytochemical, and pharmacological effects, established HDI with the help of in vitro tools, in vivo pharmacokinetics and pharmacodynamics studies to understand the impact of herbs on ADME of the drug and whether it is beneficial, harmful or has no effect respectively. This review will help the physicians and other health care professionals as a reference guide to update their knowledge and expertise about HDI. However, more quality research in this area is needed to evaluate the efficacy of many herbal medicines, thereby reducing side effects and improving the safety of patients.

In India, traditional herbal medicines have been an essential part of therapy for the last centuries. However, a large portion of the general populace is using these therapies in combination with allopathy lacking a proper understanding of possible interactions (synergistic or antagonistic) between the herbal product and the allopathic drug. This is based on the assumption that herbal drugs are relatively safe, i.e. without side effects. We have established a comprehensive understanding of the possible herb-drug interactions and identified interaction patterns between the most common herbs and drugs currently in use in the Indian market. For this purpose, we listed common interactors (herbs and allopathic drugs) using available scientific literature. Drugs were then categorized into therapeutic classes and aligned to produce a recognizable pattern present only if interactions were observed between a drug class and herb in the scientific literature. Interestingly, the top three categories (with highest interactors), antibiotics, oral hypoglycemics, and anticonvulsants, displayed synergistic interactions only. Another major interactor category was CYP450 enzymes, a natural component of our metabolism. Both activation and inhibition of CYP450 enzymes were observed. As many allopathic drugs are known CYP substrates, inhibitors or inducers, ingestion of an interacting herb could result in interaction with the co-administered drug. This information is largely unavailable for the Indian population and should be studied in greater detail to avoid such interactions. Although this information is not absolute, the systematic literature review proves the existence of herb-drug interactions in the literature and studies where no interaction was detected are equally important.

This is a patient case exploring the importance of evaluating herbal and dietary supplements and how they may impact drug-drug and drug-gene implications based on pharmacogenomics test results. Even though herbal supplements are considered natural by many patients, which is often the reason for starting them, herbal supplements may still be metabolized by the same pathways as other medications, potentially contributing to drug-drug, drug-herb, and drug-gene interactions, and therefore, potentially impacting a patient's response to medications.

Potential herb-drug interactions (pHDIs) often go unrecognized, and little is known about the prevalence of pHDIs in older adults.

The use of herbal medicinal products (HMPs) is common among older adults; however, little is known about concurrent use with prescription drugs, as well as potential interactions associated with such combinations.

An increasing number of cancer patients are using complementary and alternative medicines (CAM) in combination with their conventional chemotherapeutic treatment. Considering the narrow therapeutic window of oncolytic drugs, this CAM use increases the risk of clinically relevant herb-anticancer drug interactions. Such a relevant interaction is that of St. John's wort with the anticancer drugs irinotecan and imatinib. It is, however, estimated that CAM-anticancer drug interactions are responsible for substantially more unexpected toxicities of chemotherapeutic drugs and possible undertreatment seen in cancer patients. Induction of drug-metabolizing enzymes and ATP-binding cassette drug transporters can be one of the mechanisms behind CAM-anticancer drug interactions. Induction will often lead to therapeutic failure because of lower plasma levels of the anticancer drugs, and will easily go unrecognized in cancer treatment, where therapeutic failure is common. Recently identified nuclear receptors, such as the pregnane X receptor, the constitutive androstane receptor, and the vitamin D-binding receptor, play an important role in the induction of metabolizing enzymes and drug transporters. This knowledge has already been an aid in the identification of some CAM probably capable of causing interactions with anticancer drugs: kava-kava, vitamin E, quercetin, ginseng, garlic, beta-carotene, and echinacea. Evidently, more research is necessary to prevent therapeutic failure and toxicity in cancer patients and to establish guidelines for CAM use.

The increasing use of herbal medicinal products (HMPs) in the community where people are also receiving prescription medicines suggests that adverse herb-drug interactions may be of significant public health consequence. The evidence available to guide practitioners in decision making is complex and consists of a range of sources including adverse event database entries, spontaneous or case reports, in vivo and in vitro drug metabolism studies, and in vivo drug interaction studies in healthy subjects and patients. In the absence of further rigorous studies to assess the clinical significance of herb-drug interactions, an evidence-based appraisal of the current literature is essential to guide practitioners involved in patient care.

Patients over age 50 typically present with one chronic disease per decade. Each chronic disease typically requires long-term drug therapy, meaning most older patients require several drugs to maintain health. Simultaneously, use of complementary and alternative medicine (CAM) has increased in the United States in the last 20 years, reaching 36% in 2002; herbal medicine use accounts for approximately 22% of all CAM use. Older adults often add herbal medicines to prescription medications, yet do not always inform their physicians. The drug metabolizing enzyme systems process all compounds foreign to the body, including prescription and herbal medications. Therefore use of both medicinals simultaneously has a potential for adverse interactions. This review, which discusses saw palmetto, is the last in a series covering the documented interactions among the top 5 efficacious herbal medicines and prescription drugs.

The effectiveness of warfarin, an oral anticoagulant originally derived from a plant, is strongly affected by patient's characteristics such as the age, presence of comorbidities, and concomitant use of another drug. Warfarin has the potential to interact with many drugs, medicinal plants, and food, which increases the risk of adverse events. A critical analysis of scientific literature was conducted to assess the interferences of medicinal plants with blood haemostasis and then with warfarin anticoagulation. We found 58 different plants that may alter the blood haemostasis and anticoagulation with warfarin. The herbs that showed the greatest potential to interact with warfarin include garlic, ginger, ginkgo, St. John's wort, and ginseng, i.e. plants normally consumed as food and also used for therapeutic purposes. The interactions between drugs and herbs are varied because of the complex chemical matrix of plants. Mainly coumarins, quinones, xanthones, terpenes, lignans, and vitamin K showed significant influence on warfarin treatment. In general, these plants can potentiate the effect of warfarin by stimulating anticoagulation in multiple ways, and the clinical outcome associated with this interaction is the increase of bleeding risk. Moreover, potential

interactions between herbal products and drugs are a safety concern, especially for drugs with a narrow therapeutic index or for patients receiving drug treatment for chronic diseases, and both of these apply to warfarin pharmacotherapy. Therefore, this review article summarises the data on the influence of medicinal plants on warfarin treatment and analyses this information in view of the interaction targets. The relevant plants were categorised according to their target, and their effects are discussed in order to organise the isolated information and to highlight the need of further discussion and new studies on the safety of herbal medicines and warfarin.

The aim of this review was to assess the severity of adverse drug reactions (ADRs) due to herb-drug interactions (HDI) in patients taking herbs and prescribed medications based on published evidence. Electronic databases of PubMed, the Cochrane Library, Medline and Scopus were searched for randomized or nonrandomized clinical studies, case-control and case reports of HDI. The data were extracted and the causal relationship of ADRs as consequences of HDI assessed using Horn's drug interaction probability scale or Roussel Uclaf Causality Assessment Method scoring systems. The mechanism of interaction was ascertained using Stockley's herbal medicine interaction companion. Forty-nine case reports and two observational studies with 15 cases of ADRs were recorded. The majority of the patients were diagnosed with cardiovascular diseases (30.60%), cancer (22.45%) and renal transplants (16.32%) receiving mostly warfarin, alkylating agents and cyclosporine, respectively. HDI occurred in patients resulting in clinical ADRs with different severity. Patients may poorly respond to therapeutic agents or develop toxicity due to severe HDI, which in either scenario may increase the cost of treatment and/or lead to or prolong patient hospitalization. It is warranted to increase patient awareness of the potential interaction between herbs and prescribed medicines and their consequences to curb HDI as a potential health problem.

The use of complementary and alternative medicine at least once during or after cancer treatment has increased over the past years from an estimated 25% in the 1970s and 1980s to more than 32% in the 1990s and to 49% after 2000. The risk of herb-drug interaction is therefore increasingly recognized as a public health problem. To the best of our knowledge, we report here the first case of interaction between ginger and anticancer drug, with serious consequences for the patient. There is an urgent need regarding complementary and alternative medicine: Both clinicians and patients should be aware of the potential interactions between herbs and prescribed drugs.

Herbal medicine is one of most popular choices of complementary therapies for women, particularly as an alternative treatment for menopausal symptoms. The most commonly used herbal medicines for the menopause is probably black cohosh (Actaea/Cimcifuga racemosa); other preparations used include red clover (Trifolium pratense), dong quai (Angelica sinesis) and evening primrose (Oenothera biennis). Some of these herbal medicines have a very good safety profile with little or no suggestion of interaction with conventional drugs. For others, there are many and significant drug-herb interactions. This article outlines the major known and theoretical drug-herb interactions of herbal medicines thought to be of benefit for menopausal symptoms, as well as discussing the implications for the medical profession.

Geriatric patients typically present with one chronic disease per decade over age 50. Each chronic disease typically requires long-term drug therapy, meaning most older patients require several drugs to control their conditions and/or maintain their health. Simultaneously, the use of complementary and alternative medications (CAM) has increased in the United States over the last 20 years, reaching 36% in 2002; herbal medicine use accounts for approximately 22% of all CAM use. Older adults often add herbal medicines to the medications prescribed by their physicians, yet do not always inform their physicians. The drug metabolizing enzyme systems process all compounds foreign to the body, including prescription drugs and herbal medications. Therefore, use of both medicinals simultaneously has a potential for interactions of an adverse nature. This review, which will discuss ginkgo biloba, is the first of a continuing series covering the documented interactions between herbal medicines with proven efficacy and prescription drugs.

There is a continued predisposition of concurrent use of drugs and botanical products. Consumers often self-administer botanical products without informing their health care providers. The perceived safety of botanical products with lack of knowledge of the interaction potential poses a challenge for providers and both efficacy and safety concerns for patients. Botanical-drug combinations can produce untoward effects when botanical constituents modulate drug metabolizing enzymes and/or transporters impacting the systemic or tissue exposure of concomitant drugs. Examples of pertinent scientific literature evaluating the interaction potential of commonly used botanicals in the US are discussed. Current methodologies that can be applied to advance our efforts in predicting drug interaction liability is presented. This review also highlights the regulatory science viewpoint on botanical-drug interactions and labeling implications.

Over the years studies have shown the high prevalence rate in the use of herbal drugs among patients, doctors and health workers as such there is a need to take care of any health consequences associated with herbal drugs administrations. Herbal drugs are made of pharmacologically effective constituents, that can interact with anesthesia drugs that risk the life of the patients in question. In addition, pharmacokinetics and pharmacodynamics of herbal drugs are yet to be fully understood thus still needs more study. In view of this anesthesiologist should take a thorough history of the patient in question, taking into full consideration earlier use of herbal medicine/drugs by the patient. The aim of this article is to provide a mini-review on herb-anesthesia drug interactions.

Herbals in the form of medicine are employed extensively around the world. Herbal and conventional medicine combination is a potentially dangerous practice mainly in comorbid, hepato insufficient and frail patients leading to perilous herb-drug interactions (HDI) and toxicity. This study features potential HDI of 15 globally famous plant species through data mining and computational methods. Several plant species were found to mimic warfarin. Phytochemicals from M. charantia induced hypoglycemica. M. chamomila and G. biloba possessed anticoagulant activities. S. hispanica reduces postprandial glycemia. R. officinalis has been reported to inhibit the efflux of anticancer substrates while A. sativum can boost the clearance of anticancer agents. P. ginseng can alter blood coagulation. A cross link of the biological and in silico data revealed that a plethora of herbal metabolites such as ursolic and rosmarinic acid among others are possible/probable inhibitors of specific CYP450 enzymes. Consequently, plant species/metabolites with a given pharmacological property/metabolizing enzyme should not be mixed with drugs having the same pharmacological property/metabolizing enzyme. Even if combined with drugs, herbal medicines must be used at low doses for a short period of time and under the supervision of a healthcare professional to avoid potential adverse and toxic effects.

Herbal usage remains popular as an alternative or complementary form of treatment, especially in Africa. However, the misconception that herbal remedies are safe due to their "natural" origins jeopardizes human safety, as many different interactions can occur with concomitant use with other pharmaceuticals on top of potential inherent toxicity. Cytochrome P450 enzymes are highly polymorphic, and pose a problem for pharmaceutical drug tailoring to meet an individual's specific metabolic activity. The influence of herbal remedies further complicates this. The plants included in this review have been mainly researched for determining their effect on cytochrome P450 enzymes and P-glycoprotein drug transporters. Usage of herbal remedies, such as Hypoxis hemerocallidea, Sutherlandia frutescens and Harpagophytum procumbensis popular in Africa. The literature suggests that there is a potential for drug-herb interactions, which could occur through alterations in metabolism and transportation of drugs. Research has primarily been conducted in vitro, whereas in vivo data are lacking. Research concerning the effect of African herbals on drug metabolism should also be approached, as specific plants are especially popular in conjunction with certain treatments. Although these interactions can be beneficial, the harm they pose is just as great.

CBZ/GR treatment may reduce the auto-induction of CBZ over 2 weeks. While the reduction of auto-induction could enhance the therapeutic effects of CBZ, it could also lead to an increase in neurological

side effects and non-neurological adverse effects. Our results provided preclinical evidence of herb-drug interaction, which may have implications for epilepsy patients treated with GR.

Drugs have the potential to interact with nutrients potentially leading to reduced therapeutic efficacy of the drug, nutritional risk or increased adverse effects of the drug. Despite significant interest in such interactions going back to over more than 40 years, the occurrence and clinical significance of many drug-nutrient interactions remains unclear. However, interactions involving drugs with a narrow therapeutic margin such as theophylline and digoxin and those that require careful blood monitoring such as warfarin are likely to be those of clinical significance. Drugs can affect nutrition as a result of changes in appetite and taste as well as having an influence on absorption or metabolism of nutrients. Moreover, foods and supplements can also interact with drugs, of which grapefruit juice and St John's wort are key examples. Significant numbers of people take both supplements and medication and are potentially at risk from interactions. Professionals, such as pharmacists, dietitians, nurses and doctors, responsible for the care of patients should therefore check whether supplements are being taken, while for researchers this is an area worthy of significant further study, particularly in the context of increasingly complex drug regimens and the plethora of new drugs.

Serious drug-drug interactions have contributed to recent U.S. market withdrawals and also recent nonapprovals of a few new molecular entities. Many of these interactions involved the inhibition or induction of metabolizing enzymes and efflux transporters, resulting in altered systemic exposure and adverse drug reactions or loss of efficacy. In addition to drug-drug interactions, drug-dietary supplement and drug-citrus fruit interactions, among others, could also cause adverse drug reactions or loss of efficacy and are important issues to consider in the evaluation of new drug candidates. This commentary reviews (1). the current understanding of the mechanistic basis of these interactions, (2). issues to consider in the interpretation of study results, and (3). recent labeling examples to illustrate the translation of study results to information useful for patients and health care providers.

Rising rates of obesity across the globe have been associated with an increase in the use of herbal preparations for weight control. However, the mechanisms of action for these substances are often not known, as is the potential for interaction with other herbal preparations or prescription pharmaceutical drugs. To investigate the reported efficacy and safety of herbal weight loss preparations, we conducted a review of the literature focusing on herbs that are most commonly used in weight loss preparations, specifically, Garcinia cambogia, Camellia sinensis, Hoodia gordonii, Citrus aurantium and Coleus forskohlii. There was no clear evidence that the above herbal preparations would cause sustained long-term weight loss in humans in the long term. Serious illness and even death have occasionally resulted from the use of herbal weight loss preparations. Few clinical trials have been undertaken to evaluate the efficacy and/or safety of herbal weight loss preparations. In addition, potential issues of herb-herb and herb-drug interactions are often not considered. Regulation of these products is much less rigorous than for prescription medications, despite documented cases of associated hepatotoxicity.

Herbal products have grown steadily across the globe and have increasingly been incorporated into western medicine for healthcare aims, thereby causing potential pharmacokinetic Herb-drug Interactions (HDIs) through the inhibition or induction of drug-metabolizing enzymes and transporters. Human Carboxylesterases 1 (CES1) and 2 (CES2) metabolize endogenous and exogenous chemicals including many important therapeutic medications. The growing number of CES substrate drugs also underscores the importance of the enzymes. Herein, we summarized those potential inhibitors and inducers coming from herbal constituents toward CES1 and CES2. We also reviewed the reported HDI studies focusing on herbal products and therapeutic agents metabolized by CES1 or CES2.

Danshen, the dried root and rhizome of Salvia miltiorrhiza Bunge, is a widely used medicinal plant for the treatment of cardiovascular diseases in China and a complementary medicine in the West. Danshen is indexed in the 2010 Chinese Pharmacopoeia, with more than 35 formulations and concoctions containing Danshen water-extracts, ethanolic extracts or their combination, which are rich in phenolic acids and different levels of tanshinones. There are rare reports on the adverse effects of Danshen preparations. It is, however, well-known that Danshen leads the anticoagulation failure of warfarin. The Danshen-warfarin interaction may be mediated via both pharmacodynamic and pharmacokinetic mechanisms. This review does not summarize recent progress, but the effects of Danshen and its active ingredients on the interactions of cytochrome P450 (CYP450) and drug transporters, as well as the analysis of ingredients, and the metabolism and pharmacokinetics that are related to these interactions. Tanshinones play significant roles in the inhibition and induction of several CYP450 isozymes. It can be concluded that precautions should be taken when using Danshen preparations rich in tanshinones for CYP-related herb-drug interactions.

The concomitant use of conventional and herbal medicines can lead to clinically relevant herb-drug interactions. Clinical risk management offers a systematic approach to minimize the untoward consequences of these interactions by paying attention to: (i) risk identification and assessment; (ii) development and execution of risk reduction strategies; and (iii) evaluation of risk reduction strategies. This paper reviews which steps should be explored or taken in these domains to improve the clinical risk management of adverse herb-drug interactions.

The use of herbal medicines (HM) is on the rise among the global population. Although the safety profile of many herbal medicines is promising, accumulated data show evidence of significant interactions with medications, which can place individual patients at great risk. A range of electronic databases have been reviewed for articles published in this field: Medline, Allied and Complementary Medicine Database, HealthSTAR, AMBASE, CINHAL, Cochrane Library, as well as Internet documents and manually searched references in medical journals. In this review, we examined the literature from 1966 to 2006 and focused on the importance of the risk of drug interactions and potential side effects when HM are involved. We discuss these in light of the documented findings. A review of the problematic issues is given and recommendations are made in order to encourage the setting up of clinical trials on HM and herb-drug interactions.

he novel algorithm allows to transparently generate and dynamically display herb-drug interaction risks based on the available evidence from clinical and laboratory pharmacologic studies. It provides health professionals with readily available and easy updatable information about the risk of pharmacokinetic interactions between herbs and oncologic drugs.

Herbal medicines have been widely used for thousands of years, and now are gaining continued popularity worldwide as a complementary or alternative treatment for a variety of diseases, rehabilitation and health care. Since herbal medicines contain more than one pharmacologically active ingredient and are commonly used with many prescribed drugs, there are potential herb-drug interactions. A variety of reported herb-drug interactions are of pharmacokinetic origin, arising from the effects of herbal medicines on metabolic enzymes and/or transporters. Such an alteration in metabolism or transport can result in changes in absorption, distribution, metabolism, and excretion (e.g., induction or inhibition of metabolic enzymes, and modulation of uptake and efflux transporters), leading to changed pharmacokinetics of the concomitantly prescribed drugs. Pharmacokinetic herb-drug interactions have more clinical significance as pharmacokinetic parameters such as the area under the plasma concentration-time curve (AUC), the maximum plasma concentration (Cmax) or the elimination half-life (t1/2) of the concomitant drug alter. This review summarizes the mechanism underlying herb-drug interactions and the approaches to identify the interactions, and discusses pharmacokinetic interactions of eight widely used herbal medicines (Ginkgo biloba, ginseng, garlic, black cohosh, Echinacea, milk thistle, kava, and St. John's wort) with conventional drugs, using various in vitro, animal in vivo, and clinical studies. The increasing understanding of pharmacokinetic herb-drug interactions will make health care professionals and patients pay more attention to the potential interactions.

Herbal supplements are often used concomitantly with conventional medications resulting in considerable potential for herb-drug interactions. These interactions, which are generally through interfering with pharmacokinetic and/or pharmacodynamic pathways, may result in beneficial effects or more often adverse reactions such as toxicity or treatment failure and may be influenced by multiple environmental and/or genetic factors. The pharmacogenetic approach may help to identify some interactions which may be more pronounced or only occur in specific groups of subjects although the complex nature of the herbal medicines may limit the discovery of such an interaction. Preclinical studies such as gene expression profiling in rodent liver may help to define metabolic pathways influenced by herbal medicines and facilitate more accurate targeting of human in vivo studies. This review discusses the mechanisms of herb-drugs interaction and the potential influence of genetic variation on herb-drug interactions based on available clinical evidence.

Every time a drug is administered to the animal to treat an ailment, no matter whether it is acute or chronic manifestation, it usually goes together with some other prescription medicine, OTC (Over the counter)

formulation, herbs or even food. All the xenobiotics such as drugs, toxins and food components as well as the endogenous compound that are formed in the animal body as a routine phenomenon exert a stimulatory or inhibitory effect on the different physiological and biochemical processes going in the body. These effects may alter the normal metabolism and/or drug transport or its efficacy drastically and thus expose the man and animals to the risk of a potentially dangerous interaction. The present review discusses these potential reactions and their mechanisms that help in navigating the hazardous combinations of drugs with other medicines, food, herbs, vitamins and minerals with confidence.

Interactions between herbal medicines and conventional drugs have recently been reported; the most significant herb with such drug interactions is Saint John's wort, an inducer of cytochrome P450 3A3/4, an enzyme responsible for clearance of many clinically important drugs from the body. Foods (especially grapefruit) and habits or lifestyle factors such as smoking or alcohol consumption may also alter the metabolism of drugs through effects on the cytochrome P450 system. The authors review here the functioning of the drug-metabolizing enzymes and discuss their particular significance in cancer chemotherapy treatment. They then present the herbal medicines, foods, and lifestyle factors that induce or inhibit drug-metabolizing enzymes that are important for both cancer chemotherapy drugs and drugs used adjunctively in cancer treatment. It is notable that no actual herb-drug interactions have been reported clinically in cancer treatment, and their potential for interaction still must be regarded as theoretical. Although some chemotherapy patients may be interested in taking herbal medicines that could potentially interact with cancer chemotherapy agents, it may be wise to counsel them to use other means of addressing the problems for which they use specific herbs during the time they receive chemotherapy.

Until reports of interactions between St John's wort and drugs such as digoxin, warfarin, protease inhibitors and oral contraceptives began to appear, very few herb-drug interactions were documented. These are now becoming more common, although still rare compared with drug-drug interactions. In the absence of hard data, potential interactions are being highlighted, and this review attempts to distinguish between the speculative and the proven. The subject is approached from a therapeutic point of view since in most cases the patient is already taking one or more prescription drugs, and the question is whether or not it is safe for a particular herb to be added to the regimen. Although many of the examples of herb-drug interactions are minor or theoretical at present, the fact remains that some are serious and life threatening, and these almost exclusively concern cyclosporin, anticoagulants, digoxin, antidepressants and protease inhibitors, taken with the herb St John's wort. Ginkgo and ginseng are implicated in a number of reports, but many of these are unsubstantiated. To date, the cardiovascular, central nervous and immune systems are the most common therapeutic categories cited in the literature and other than those, examples are very limited. Although many herbal drugs have good safety profiles, it must be borne in mind that herbal supplements are intended to be taken over an extended period of time, which provides the opportunity for enzyme induction and other mechanisms of interaction to take effect.

Rhizoma coptidis shows various pharmacological activities attributed to its alkaloid constituents. To guide the pharmacological studies, the candidate drug research and development and the clinic applications of these compounds, a review on their pharmacokinetic behavior and toxicity should be beneficial.

Inhibition of CYP enzymes is thought to be the most common cause of drug-drug and/or herb-drug interactions. To characterize the inhibition of CYP enzymes activities by chemicals, enzyme inhibition kinetic experiments are usually carried out. The purpose of this letter is to call attention to evaluate the enzyme inhibition kinetics in drug-drug interactions.

Cancer patients are increasingly using herbal supplements for relief of symptoms. However, there is a great potential for interactions with concurrent use of herbs and chemotherapy agents. Physicians should be aware of such interactions and encourage patients to discuss supplement use.

An HERB–Drug Interaction (HDI) database is a structured data collection method for HDI information extracted from scattered literatures for quick retrieval. Our review summarized the ten currently available HDI databases, including those databases comprising HDI on the market. A detailed comparison on the scope of monographs, including the nature of content extracted from the original literature and user interfaces of these databases, was performed, and the number of references of fifty popular herbs in each HDI database was counted and presented in a heatmap to give users an intuitive understanding of the focuses of different HDI databases. Since it is well known that the development and maintenance of databases need continuous investment of capital and manpower, the sustainability of these databases was also reviewed and compared. Recently, artificial intelligence (AI) technologies, especially Natural Language Processing (NLP), have been applied to screen specific topics from massive articles and automatically identify the names of drugs and herbs in the literature. However, its application on the labor-intensive extraction and evaluation of HDI-related experimental conditions and results from literature remains limited due to the scarcity of these HDI data and the lack of well-established annotated datasets for these specific NLP recognition tasks. In view of the difficulties faced by current HDI databases and potential expansion of AI application in HDI database development, we propose a standardized format for data reporting and use of Concept Unique Identifier (CUI) for medical terms in the literature to accelerate the structured data collection.

The aim of this study was to find the prevalence of potential drug-herb interactions in patients with chronic diseases and identify factors associated with these interactions if present.

Increasing numbers of adults and children around the world are using natural health products (NHPs) to promote wellbeing or alleviate illness. Although often considered safe due to their natural origin, NHPs are potentially pharmacologically active and, therefore may cause harm. Limited data suggest that NHPs can interact with other NHPs as well as with prescription medication and foods. Although some common NHP-drug interactions have been identified and studied, in general, the epidemiology of NHP-drug interactions is not well-understood, in part because these harms are often underreported. Users rarely disclose NHP use to their physicians, and physicians rarely enquire about such use. Even if physicians become aware of a potential NHP-drug interaction, passive surveillance systems mean that it is left to the physician's discretion whether or not to report it to the proper authority. It is likely that active surveillance of NHP-drug interactions would result in increased reporting of NHP-related harms as well as better quality reports. Subsequent lab investigation would determine if adulteration, contamination, species misidentification, or misuse was responsible for the harm, or if a pharmacokinetic or pharmacodynamic NHP-drug interaction occurred. This kind of thorough detection and investigation of potential NHP-drug interactions is necessary to ensure the safe use of NHPs.

The combination of herbs and drugs is one of the most important approaches in the prevention and treatment of diseases in the integrated traditional and Western medicine (ITWM). While most medical practices have proved that the combination of herbs and drugs led to a clinical efficacy that was often superior to merely using only one of them; results from some studies have triggered adverse reactions to such an approach. Since few herb-drug interaction studies were carried out during treatments combining herbs and drugs, it really restricts the development of treatment and treatment theory of the combination of herbs and drugs. Given that herb-drug interactions may occur through the main pathway of cytochrome P450 enzymes and transporters; then to exhaustively study the role and impact of herbs in drug metabolism, as well as to establish a corresponding database, is of great significance for guiding the rational combination of herbs

and drugs. When the herb-drug interaction information platform is implemented, we would get at ease a reasonable herb-drug prescription to achieve a better outcome, reduce dosage of some expensive drugs preserving the same efficacy, or even reduce some side effects of particular drugs; which might also promote the dynamic combination of Chinese and Western medicine, and accelerate the theory development of ITWM.

Herb-drug interactions undoubtedly do occur and may put individuals at risk. However our present knowledge is incomplete and more research is urgently needed.

The Caco-2 model is employed in pre-clinical investigations to predict the likely gastrointestinal permeability of drugs because it expresses cytochrome P450 enzymes, transporters, microvilli and enterocytes of identical characteristics to the human small intestine. The FDA recommends this model as integral component of the Biopharmaceutics Classification System (BCS). Most dedicated laboratories use the Caco-2 cell line to screen new chemical entities through prediction of its solubility, bioavailability and the possibility of drug-drug or herb-drug interactions in the gut lumen. However, challenges in the inherent characteristics of Caco-2 cell and inter-laboratory protocol variations have resulted to generation of irreproducible data. These limitations affect the extrapolation of data from pre-clinical research to clinical studies involving drug-drug and herb-drug interactions. This review addresses some of these caveats and enumerates the plausible current and future approaches to reduce the anomalies associated with Caco-2 cell line investigations focusing on its application in herb-drug interactions.

Drug disposition in the human body is strongly influenced by transporters and metabolizing enzymes expressed in key organs including intestine, liver and kidney. Since drugs and chemicals present in foods such as fruit juices and herb-based products are substrates of the above-mentioned proteins, there is a high probability of pharmacokinetic interactions. Findings from preclinical and clinical studies helped to characterize the mechanisms by which the components of fruit juices and herbs act as perpetrators of pharmacokinetic interactions. The aim of this review is to provide an overview of pharmacokinetic fruit juice- and herb-drug interactions that could be relevant in the clinical setting.

In summary, herbs are commonly used, and it is the physician's responsibility to have better documentation of this practice by encouraging patients to report use of herbs, and to look for any unusual side effects that can occur in terms of herb-drug or herb-herb interactions

Many Americans use complementary and alternative medicine (CAM) to prevent or alleviate common illnesses, and these medicines are commonly used by individuals with cancer.These medicines or botanicals share the same metabolic and transport proteins, including cytochrome P450 enzymes (CYP), glucuronosyltransferases (UGTs), and P-glycoprotein (Pgp), with over-the-counter and prescription medicines increasing the likelihood of drug-botanical interactions.This review provides a brief description of the different proteins, such as CYPs, UGTs, and Pgp.The potential effects of drug-botanical interactions on the pharmacokinetics and pharmacodynamics of the drug or botanical and a summary of the more common models used to study drug metabolism are described.The remaining portion of this review summarizes the data extracted from several laboratory, animal, and clinical studies that describe the metabolism, transport, and potential interactions of 8 selected botanicals. The 8 botanicals include black cohosh, Echinacea, garlic, Gingko biloba, green tea, kava, milk thistle, and St John's wort; these botanicals are among some of the more common botanicals taken by individuals with cancer.These examples are included to demonstrate how to interpret the different studies and how to use these data to predict the likelihood of a clinically significant drug-botanical interaction.

Although HDS-drug interactions and contraindications primarily concerned a relatively small subset of commonly used medications and HDS entities, this review provides the summary to identify patients, HDS

products, and medications that are more susceptible to HDS-drug interactions and contraindications. The findings would facilitate the health-care professionals to communicate these documented interactions and contraindications to their patients and/or caregivers thereby preventing serious adverse events and improving desired therapeutic outcomes.

The purpose of this article was to gather data to cater an evidence-based discussion and information for providing complete knowledge to existing patients and consumers regarding herbal drug-drug interactions, would also help them a brief knowledge that what can go wrong in case of herbal-drug interaction, in conclusion, we also found that there is still no basic guideline defining the drug-drug interactions.

Prevention of adverse events from food-herb-drug interactions requires clinical monitoring in high-risk regimens and populations. Nutritional status has an important impact on the quality of life as well as appropriate responses to drug therapy. Both diet-drug histories and counseling are needed. As new foods and drugs emerge and more self-medication is promoted, research in the prevention of food-drug interactions is needed.

Herbal medicines and dietary supplements are commonly taken by patients with cancer, leading to concern over interactions with conventional medicines. A literature search was carried out to identify published studies exploring supplement use by patients with a cancer diagnosis. A total of 818 articles were retrieved using the key words, but only 41 are judged to be relevant based on title. Following the review of the abstracts, ten papers were considered to be potentially relevant, but of these, only two met the selection criteria, and three additional papers were identified from published reviews. Of 806 patients surveyed, 433 (53.7%) were reported to be taking combinations of supplements and drugs, and 167 incidents of risk were identified, affecting 60 patients (13.9%). The interactions identified were mainly theoretical and not supported by clinical data. No studies reported any adverse events associated with these combinations; most did not record the actual drug combinations taken, and the risk potential of some supplements appears to have been over-estimated. More effort should be made to investigate supplement use in this vulnerable patient group, based on sound evidence of plausible interaction, not only to avoid harm but also to provide reassurance where appropriate if the patient wishes to take a particular supplement.

Due to the rapidly increasing global interest in the use of herbs, phytomedicines and other natural products as medical or complementary remedies, concerns about the clinical medication safety have drawn much attention worldwide. Particularly, many natural ingredients exhibit inhibitory effects on cytochrome P450 (CYP) enzymes, which are the most important Phase I metabolism enzymes in liver. CYP2C9 is one of the most abundant CYP enzymes and responsible for the metabolism of over 15% clinical drugs, including oral sulfonylurea hypoglycemics, nonsteroidal anti-inflammatory agents, selective cyclooxygenase-2 inhibitors, antiepileptics, angiotensin II receptor inhibitors and anticoagulants. Diclofenac (4'-hydroxylase) and tolbutamide (methylhydroxylation) are widely used as probe substrates for CYP2C9. To date, numerous natural products have been reported to have the capabilities of inhibiting the catalytic activity of CYP2C9 and further influencing the pharmacokinetic and pharmacodynamic behaviors of drugs that are mainly metabolized by CYP2C9, leading to potential herb-drug interactions. Moreover, some fatal adverse interactions may occur for drugs with a narrow therapeutic window when they are coadministered with a CYP2C9 inhibitor, especially irreversible inactivators. For the purpose of better understanding the interactions of natural products with CYP2C9, we comprehensively reviewed the characteristics of CYP2C9, the natural ingredients that inhibit CYP2C9, the related research approaches and strategies, the types of inhibition and the underlying mechanisms.

Detection of drug-drug interactions is essential during the early stages of drug discovery and development, and the understanding of drug-botanical interactions is important for the safe use of botanical dietary

supplements. Among the different forms of drug interactions that are known, inhibition of cytochrome P450 (P450) enzymes is the most common cause of drug-drug or drug-botanical interactions. Therefore, a rapid and comprehensive mass spectrometry-based in vitro high-throughput P450 cocktail inhibition assay was developed that uses 10 substrates simultaneously against nine CYP isoforms. Including probe substrates for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and two probes targeting different binding sites of CYP3A4/5, this cocktail simultaneously assesses at least as many P450 enzymes as previous assays while remaining among the fastest due to short incubation times and rapid analysis using ultrahigh pressure liquid chromatography-tandem mass spectrometry. The method was validated using known inhibitors of each P450 enzyme and then shown to be useful not only for single-compound testing but also for the evaluation of potential drug-botanical interactions using the botanical dietary supplement licorice (Glycyrrhiza glabra) as an example.

Herbs, vitamins, and other dietary supplements may augment or antagonize the actions of prescription and nonprescription drugs. St. John's wort is the supplement that has the most documented interactions with drugs. As with many drug-drug interactions, the information for many dietary supplements is deficient and sometimes supported only by case reports. Deleterious effects are most pronounced with anticoagulants, cardiovascular medications, oral hypoglycemics, and antiretrovirals. Case reports have shown a reduction in International Normalized Ratio in patients taking St. John's wort and warfarin. Other studies have shown reduced levels of verapamil, statins, digoxin, and antiretrovirals in patients taking St. John's wort. Physicians should routinely ask patients about their use of dietary supplements when starting or stopping a prescription drug, or if unexpected reactions occur.

It is concluded that a basic assessment of certain pharmacokinetic HDI is needed to settle on educated choices in regard to patient safety. The expanding comprehension of HDPKI will direct more attention to potential interactions.

Medicinal plants are gaining in popularity due to the various advantages they offer, such as fewer side-effects, better patient compliance, relatively low cost and high accessibility as well as their high acceptability due to a long history of use. There is a widespread belief among the general public that herbal preparations are "good for humans" as they are "all natural". However, the increasing use of herbal medicinal products in the community where people are also receiving prescription medicines suggests that adverse herb-drug interactions may be have significant public health consequences. There is little understanding or appreciation of the fact that these "all natural" preparations are actually a combination of potentially biologically active compounds already existing in marketed products in unknown quantities. Among the most popular herbal products used worldwide is Ginkgo biloba, used for the treatment of cerebral insufficiency, peripheral vascular diseases, and frequently taken for the enhancement of memory function. Although the safety of Ginkgo biloba is promising, accumulated data show evidence of significant interactions with medications, which can place individual patients at great risk. In this review, we examined the literature from 2000 to 2008 and focused on the importance of the risk of drug interactions and potential side effects when Ginkgo biloba is involved. The aim of this systematic review is to assess the clinical evidence on interactions between Ginkgo biloba and drugs.

UDP-glucuronosyltransferases (UGTs) play important roles in the disposition of many drugs and xenobiotics. Herbal medicine, an important group of multicomponent therapeutics, is widely and increasingly used. Drug metabolism of herbal medicine mediated by cytochrome P450s has been extensively studied; however, herbal medicine metabolism mediated by UGTs has not been adequately investigated. Thus, it is necessary to evaluate current evidence on the glucuronidation of herbal medicines by UGTs. In this review, the research advances of the potential for commonly used herbal medicines as

UGT substrate and modulator are summarized. In addition, the herb-drug interactions associated with UGTs are also discussed.

P-Glycoprotein (P-gp), the most extensively studied ATP-binding cassette transporter, functions as a biological barrier by extruding toxic substances and xenobiotics out of cells. Drug efflux pumps such as P-gp play a functional role in determining the pharmacokinetics of drugs administered by oral and parenteral routes. Determining the activity of drug efflux transport proteins has important implications in the identification of substrates and/or inhibitors. The significant role of the small intestine in reducing the oral bioavailability of drugs is due to metabolic enzymes and efflux transporters. The role of cytochrome P-450 3A (CYP3A) and P-gp in intestinal drug disposition has been highlighted. This review examines the structure, localisation and functional role of P-gp, the mechanism of drug efflux and drug-herb interactions.

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.

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.

Recognition of the adverse effects of medicinal herbs is not routine and the reports on such effects are even less frequent in clinical practice. Potential herb-drug interactions are of a major safety concern, especially for drugs with narrow therapeutic indices like warfarin, which can lead to severe adverse reactions that are sometimes life-threatening. The interactions between warfarin and medicinal herbs described in the literature have been summarized in this paper relying on Medline database (via PubMed) using the key words: warfarin, herbal supplements and interactions. The references on the analyzed literature have been investigated in order to collect the existing data. The case reports with severe adverse effects such as spontaneous postoperative bleeding, formation of hematomas, hematemesis, melena, thrombosis, subarachnoid hemorrhage and/or subdural hematomas after concomitant use of warfarin and the medicinal herbs: Panax ginseng, Hypericum perforatum, Salvia milthiorizza, Gingko biloba, Serenoa repens, Angelica sinensis, Vaccinium species, Allium sativum, Zingiber officinale, Tanacetum parthenium, Lucium barbarum, Matricaria chamomilla, Boswellia serrata and Camellia sinensis have been estimated. Some of the interactions between warfarin and medicinal herbs have been well assessed proving that they are closely-dependent. The interactions between warfarin and medicinal herbs, not generally reported in previous reviews, are presented in our review. The health professionals who are involved in treating the patients are expected to be fully informed about the interactions between warfarin and medicinal herbs in order to minimize the health risks of the patients.

The fact that many cancer patients take herbal medicine, including Chinese herbal medicine, together with chemotherapy is well known. The potential for side effects resulting from concurrent use of these two different treatment modalities requires physicians to be aware of the potential risks and benefits that might arise. This study searched available evidence for herb-drug interaction in cancer therapy and identified 168 articles. Little direct evidence for such interaction could be found, whereas there is some indirect evidence for benefit. Hence, most of the concern about herb-drug interaction in chemotherapy appears to be theoretical. To resolve this discrepancy, evidence-based studies should be undertaken to document the positive and/or negative effects of the concomitant use of herbs with anticancer chemotherapeutic drugs. As evidence accumulates, it would be helpful to set up an internationally accessible database to document the use of Chinese medicine herbs with anticancer drugs. Once this information is collected, efforts should be made to educate health care professionals and patients about the use of Chinese herbal medicine together with Western drugs in treating cancer.

An HERB-Drug Interaction (HDI) database is a structured data collection method for HDI information extracted from scattered literatures for quick retrieval. Our review summarized the ten currently available HDI databases, including those databases comprising HDI on the market. A detailed comparison on the scope of monographs, including the nature of content extracted from the original literature and user interfaces of these databases, was performed, and the number of references of fifty popular herbs in each HDI database was counted and presented in a heatmap to give users an intuitive understanding of the focuses of different HDI databases. Since it is well known that the development and maintenance of databases need continuous investment of capital and manpower, the sustainability of these databases was also reviewed and compared. Recently, artificial intelligence (AI) technologies, especially Natural Language Processing (NLP), have been applied to screen specific topics from massive articles and automatically identify the names of drugs and herbs in the literature. However, its application on the labor-intensive extraction and evaluation of HDI-related experimental conditions and results from literature remains limited due to the scarcity of these HDI data and the lack of well-established annotated datasets for these specific NLP recognition tasks. In view of the difficulties faced by current HDI databases and

potential expansion of AI application in HDI database development, we propose a standardized format for data reporting and use of Concept Unique Identifier (CUI) for medical terms in the literature to accelerate the structured data collection. SIGNIFICANCE STATEMENT: The worldwide popularity of botanical and/or traditional medicine products has raised safety concerns due to potential HDI. However, the publicly available HDI databases are mostly outdated or incomplete. Through our review of the currently available HDI databases, a clear understanding of the key issues could be obtained and possible solutions to overcome the labour-intensive extraction as well as professional evaluation of information in HDI database development are proposed.

Jingyin granules, a marketed antiviral herbal medicine, have been recommended for treating H1N1 influenza A virus infection and Coronavirus disease 2019 (COVID-19) in China. To fight viral diseases in a more efficient way, Jingyin granules are frequently co-administered in clinical settings with a variety of therapeutic agents, including antiviral drugs, anti-inflammatory drugs, and other Western medicines. However, it is unclear whether Jingyin granules modulate the pharmacokinetics of Western drugs or trigger clinically significant herb-drug interactions. This study aims to assess the inhibitory potency of the herbal extract of Jingyin granules (HEJG) against human drug-metabolizing enzymes and to clarify whether HEJG can modulate the pharmacokinetic profiles of Western drug(s) in vivo. The results clearly demonstrated that HEJG dose-dependently inhibited human CES1A, CES2A, CYPs1A, 2A6, 2C8, 2C9, 2D6, and 2E1; this herbal medicine also time- and NADPH-dependently inhibited human CYP2C19 and CYP3A. In vivo tests showed that HEJG significantly increased the plasma exposure of lopinavir (a CYP3A-substrate drug) by 2.43-fold and strongly prolonged its half-life by 1.91-fold when HEJG (3 g/kg) was co-administered with lopinavir to rats. Further investigation revealed licochalcone A, licochalcone B, licochalcone C and echinatin in Radix Glycyrrhizae, as well as quercetin and kaempferol in Folium Llicis Purpureae, to be time-dependent CYP3A inhibitors. Collectively, our findings reveal that HEJG modulates the pharmacokinetics of CYP substrate-drug(s) by inactivating CYP3A, providing key information for both clinicians and patients to use herb-drug combinations for antiviral therapy in a scientific and reasonable way.

Herb-drug interactions have turned out not to be a major issue in the European regulatory landscape. For a minority of herbal preparations, herb-drug interactions are clinically relevant, e.g., between high-dose St.John's wort extracts and a number of chemical substances. The inclusion of adequate information on such interactions into the package leaflet is important for the safe use of the products. Information on potential interactions is also part of the official HMPC monographs. However, only for some herbal preparations described in these monographs, such a potential is known. Thus, in accordance with the relevant European guidance documents, potential interactions should be assessed critically for their clinical relevance, and a balanced assessment is required when regulatory documents are established or regulatory measures are implemented.

P-glycoprotein (Pgp) is a 170 kDa phosphorylated glycoprotein encoded by human MDR1 gene. It is responsible for the systemic disposition of numerous structurally and pharmacologically unrelated lipophilic and amphipathic drugs, carcinogens, toxins, and other xenobiotics in many organs, such as the intestine, liver, kidney, and brain. Like cytochrome P450s (CYP3A4), Pgp is vulnerable to inhibition, activation, or induction by herbal constituents. This was demonstrated by using an ATPase assay, purified Pgp protein or intact Pgp-expressing cells, and proper probe substrates and inhibitors. Curcumin, ginsenosides, piperine, some catechins from green tea, and silymarin from milk thistle were found to be inhibitors of Pgp, while some catechins from green tea increased Pgp-mediated drug transport by heterotropic allosteric mechanism, and St. John's wort induced the intestinal expression of Pgp in vitro and in vivo. Some components (e.g., bergamottin and quercetin) from grapefruit juice were reported to modulate

Pgp activity. Many of these herbal constituents, in particular flavonoids, were reported to modulate Pgp by directly interacting with the vicinal ATP-binding site, the steroid-binding site, or the substrate-binding site. Some herbal constituents (e.g., hyperforin and kava) were shown to activate pregnane X receptor, an orphan nuclear receptor acting as a key regulator of MDR1 and many other genes. The inhibition of Pgp by herbal constituents may provide a novel approach for reversing multidrug resistance in tumor cells, whereas the stimulation of Pgp expression or activity has implication for chemoprotective enhancement by herbal medicines. Certain natural flavonols (e.g., kaempferol, quercetin, and galangin) are potent stimulators of the Pgp-mediated efflux of 7,12-dimethylbenz(a)-anthracene (a carcinogen). The modulation of Pgp activity and expression by these herb constituents may result in altered absorption and bioavailability of drugs that are Pgp substrates. This is exemplified by increased oral bioavailability of phenytoin and rifampin by piperine and decreased bioavailability of indinavir, tacrolimus, cyclosporine, digoxin, and fexofenadine by coadministered St. John's wort. However, many of these drugs are also substrates of CYP3A4. Thus, the modulation of intestinal Pgp and CYP3A4 represents an important mechanism for many clinically important herb-drug interactions. Further studies are needed to explore the relative role of Pgp and CYP3A4 modulation by herbs and the mechanism for the interplay of these two important proteins in herb-drug interactions.

To ensure good patient care, it is important that healthcare professionals are aware of possible health complications associated with the concomitant use of herbs and medications.

These results demonstrate that most HDI studies so far have examined PK interactions and have been limited to very few conventional drugs and herbal drugs. This suggests that more studies focusing on PD are necessary to understand interactions between commonly used herbal and conventional drugs.

In addition to conventional medicine, many patients regularly use complementary and alternative therapies. And yet, communication between patients and providers about CAM use is not consistent. There is a demand for interventions in health care that provide timely, integrative communication support. Delivering the herb-drug-disease alerts through multiple channels could help meet critical patient information needs.

There is appropriate concern about the potential risk for hepatotoxicity from herbal products because they are unregulated and therefore not standardized with regard to their contents. This is particularly the case for the crude herbals that are commonly formulated as a mixture, so that their ingredients may be ambiguous and even contain harmful contaminants. Presented here is an overview of the more commonly recognized herbal products that have been reported to be associated with liver injury. Although many of them are clearly implicated, there are some, particularly those identified solely through an occasional case report, for which the relationship is uncertain.

The ethanol extract of E. koreanum is not likely to cause HDI via inducing the major human CYPs. But the potential for interactions between E. koreanum extract and substrates of CYP1A2 or 2B6 cannot be overlooked.

Deoxyshikonin, a natural shikonin derivative, is the major component of Lithospermum erythrorhizon and exhibits various pharmacological effects such as lymphangiogenetic, antibacterial, wound healing, and anticancer effects. To investigate the herb-drug interaction potential associated with deoxyshikonin, the inhibitory effects of deoxyshikonin on eight major cytochrome P450 (CYP) enzymes were examined using cocktail substrate-incubated human liver microsomes. Deoxyshikonin strongly inhibited CYP2B6-catalyzed bupropion hydroxylation, with a K_i value of 3.5 μM, and the inhibition was confirmed using purified human CYP2B6. The inhibition was reversible because the inhibitory effect of deoxyshikonin was not dependent on the preincubation time. The results indicated that deoxyshikonin-induced drug-drug

interaction should be considered when any herb containing deoxyshikonin is used for conventional medications.

Some cases have reported that TCMs may increase the bleeding risk or has no effect on coagulation when anticoagulant/antiplatelet drugs are concurrently used. However, pharmacokinetic studies have presented either consistent or slightly varying results. So it is difficult to ascertain whether the concurrent use of TCM may increase or reduce the pharmacologic effects of anticoagulant/antiplatelet drugs with adverse reactions. Therefore, herb-drug interactions of TCM and anticoagulant/antiplatelet drugs should be further explored and defined.

Reported utilisation of prescription drug use concurrently with herbal or vitamin products have increased, placing an estimated 15 million patients at risk of potential drug-supplement interactions. This systematic review aims to consolidate relevant herb and supplement interactions data available for some of the more common classes of interactions experienced by clinicians. These classes include: hypoglycaemic/hyperglycaemics; hypotensive/hypertensives, diuretics, sedatives, cardiac glycosides, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, laxatives, immunomodulators, agents that may increase the risk of bleeding or clotting, agents that may be hepatotoxic, agents that may have hormonal properties, and agents with cytochrome P450 enzyme activity. The format is designed to promote use as a decision support tool for healthcare providers.

Combined use of Chinese medicine and western medicine is one of the hot spots in the domestic medical and academic fields for many years. There are lots of involved reports and studies on interaction problems due to combined used of Chinese medicine and western medicine, however, framework understanding is still rarely seen, affecting the clinical rationality of drug combinations. Actually, the inference ideas of drug interactions in clinical practice are more extensive and practical, and the overall viewpoint and pragmatic idea are the important factors in evaluating the rationality of clinical drug combinations. Based on above points, this paper systemically analyzed the existing information and examples, deeply discuss the embryology background (environment and action mechanism of interactions), and principally divided the interactions into three important and independent categories. Among the three categories, the first category (Iapproach) was defined as the physical/chemical reactions after direct contact in vivo or in vitro, such as the combination of Chinese medicine injections and western medicine injections (in vitro), combination of bromide and Chinese medicines containing cinnabar (in vivo). The evaluation method for such interactions may be generalized theory of Acid-Base reaction. The second category (II approach) was defined as the interactions through the pharmacokinetic process including absorption (such as the combination of aspirin and Huowei capsule), distribution (such as the combination of artosin and medicinal herbs containing coumarin), metabolism (such as the combination of phenobarbital and glycyrrhiza) and excretion (such as the combination of furadantin and Crataegi Fructus). The existing pharmacokinetic theory can act as the evaluation method for this type of interaction. The third category (III approach) was defined as the synergy/antagonism interactions by pharmacological effects or biological pathways. The combination of warfarin and Salvia miltiorrhiza is an example for synergy interaction, while the combination of guanethidine and ephedra is an example for anatagonism interaction. The repeated application of Chinese and western medicine compound preparations and same type of western medicine also belongs to this approach. The receptor competition theory under the view of the overall pathways might act as the evaluation method for this type of interactions. Above all, the research framework on interactions between Chinese medicine and western medicine was proposed, providing overall thinking and support for the essential study on combined application of Chinese medicine and western medicine.

Populations using herbs and herbal preparations are widespread and growing. As many herbal ingredients exert actions on psychotropic drug targets, psychiatrists should be well informed and aware of potential

drug-drug interactions in clinical practice. Reliable and clinically useful information in this area, however, is fragmented, if not deficient. This paper reviewed the clinical aspects of herb-drug interactions, focusing in particular on the monoamine oxidase enzyme and P450 cytochrome enzyme-inhibitory properties of herbs and their potential interference with psychotropic drug actions and clinical judgement.

Risk of drug interactions in seniors might be high, but few interactions are clinically significant. Only 1 found in our study carried a recommendation for avoidance. The on-line program reported all significant interactions, but the high proportion of insignificant interactions (6 : 1) also reported could lead physicians to override computer-generated alerts.

People mistakenly think that all herbs are safe, because of the fact that they are natural, and the use of herbal medication is growing. Aspects of the efficacy, safety, and quality of herbal or natural products are the subjects of on-going debates. Concurrent administration of herbs may interfere with the effect of drugs. Lack of knowledge of the interaction potential together with an underreporting of herbal use poses a challenge for health care providers and a safety concern for patients. A good understanding of the mechanisms of herb-drug interactions is also essential for assessing and minimizing clinical risks. Examples of herbal medicine-pharmaceutical drug interactions of commonly used herbs are presented. The potential pharmacokinetic and pharmacodynamic basis of such interactions is discussed, as well as the challenges associated with the identification and prediction of herb-drug interactions.

Interactions between natural health products (NHP) and prescription medications are of increasing concern. This paper aims to identify all clinical trials of NHP-drug interactions. To determine the prevalence and outcomes of clinical investigations of NHP-drug pharmacokinetic interactions, electronic databases were searched from inception through March 2004, as well as reference lists from published reports and experts in the field for unpublished studies. Eligible studies were clinical investigations of the interaction between a NHP and the metabolism of a regulated medication in humans. Studies were excluded that only investigated the metabolism of an NHP or examined food-drug or NHP-NHP interactions. Two reviewers selected studies for inclusion and independently extracted data. Forty-seven trials were identified, studying an average of 14 participants/study (95% confidence interval [CI] 11-18), examined drug interactions with 19 different herbal preparations. All trials were pharmacokinetic studies, 41 of healthy volunteers and 6 of patients. Ten different herbal medicines as well as 5 different traditional herbal concoctions were studied. Potentially clinically significant drug interactions were observed with St. John wort (16/24 studies), garlic (2/5 studies), and American ginseng (1 study). Research on NHP-drug interactions is limited in number and scope. With the exception of St. John wort, clinicians and the public do not have information that permits strong inferences about interactions between NHPs and conventional medications.

A resurgence in the use of medical herbs in the Western world, and the co-use of modern and traditional therapies is becoming more common. Thus there is the potential for both pharmacokinetic and pharmacodynamic herb-drug interactions. For example, systems such as the cytochrome P450 (CYP) may be particularly vulnerable to modulation by the multiple active constituents of herbs, as it is well known that the CYPs are subject to induction and inhibition by exposure to a wide variety of xenobiotics. Using in vitro, in silico, and in vivo approaches, many herbs and natural compounds isolated from herbs have been identified as substrates, inhibitors, and/or inducers of various CYP enzymes. For example, St. John's wort is a potent inducer of CYP3A4, which is mediated by activating the orphan pregnane X receptor. It also contains ingredients that inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Many other common medicinal herbs also exhibited inducing or inhibiting effects on the CYP system, with the latter being competitive, noncompetitive, or mechanism-based. It appears that the regulation of CYPs by herbal products complex, depending on the herb type, their administration dose and route, the target organ and species. Due to the difficulties in identifying the active constituents responsible for the modulation of CYP

enzymes, prediction of herb-drug metabolic interactions is difficult. However, herb-CYP interactions may have important clinical and toxicological consequences. For example, induction of CYP3A4 by St. John's wort may partly provide an explanation for the enhanced plasma clearance of a number of drugs, such as cyclosporine and innadivir, which are known substrates of CYP3A4, although other mechanisms including modulation of gastric absorption and drug transporters cannot be ruled out. In contrast, many organosulfur compounds, such as diallyl sulfide from garlic, are potent inhibitors of CYP2E1; this may provide an explanation for garlic's chemoproventive effects, as many mutagens require activation by CYP2E1. Therefore, known or potential herb-CYP interactions exist, and further studies on their clinical and toxicological roles are warranted. Given that increasing numbers of people are exposed to a number of herbal preparations that contain many constituents with potential of CYP modulation, high-throughput screening assays should be developed to explore herb-CYP interactions.

Provided that patients are not taking ginkgo, St. John's wort, evening primrose or valerian, oral health care providers can prescribe or administer any of the medications used commonly in dentistry without concern about possible dietary supplement-drug interactions.

Understanding the potential for adverse drug reactions (ADRs), from herb-drug interactions, is a key aspect of medicinal plant safety, with particular relevance for public health in countries where medicinal plant use is highly prevalent. We undertook an in-depth assessment of extracts of Hyptis verticillata Jacq., via its impact on activities of key cytochrome P450 (CYP) enzymes (CYPs 1A1, 1A2, 1B1, 3A4 and 2D6), its antioxidant properties (determined by DPPH assays) and chemical characterisation (using LC-MS). The dried plant aqueous extract demonstrated potent inhibition of the activities of CYPs 1A1 (7.6 μg/mL), 1A2 (1.9 μg/mL), 1B1 (9.4 μg/mL) and 3A4 (6.8 μg/mL). Further analysis of other crude extracts demonstrated potent inhibition of CYP1A2 activity for a dried plant ethanol extract (1.5 μg/mL), fresh plant ethanol extract (3.9 μg/mL), and moderate activity for a fresh plant aqueous extract (27.8 μg/mL). All four extracts demonstrated strong antioxidant activity, compared to the positive control (ascorbic acid, 1.3 μg/mL), with the dried plant ethanol extract being the most potent (1.6 μg/mL). Analysis of the dried plant aqueous extract confirmed the identity of seven phytochemicals, five lignans and two triterpenes. Individual screening of these phytochemicals against the activity of CYP1A2 identified yatein as a moderate inhibitor (71.9 μM), likely to contribute to the plant extract's potent bioactivity. Further analysis on the impact of this plant on key drug metabolizing enzymes in vivo appears warranted for likely ADRs, as well as furthering development as a potential chemopreventive agent.

Warfarin and ginseng have been widely used in the treatment of cardiovascular diseases. However, the clinical safety and effectiveness of herb-drug combination treatment are still controversial. Therefore, it is very essential to probe the interaction between warfarin and ginseng. In this study, in vitro and in vivo study was carried out to demonstrate that whether there is an interaction between warfarin and ginsenosides (GS), which is the main component of ginseng. In vitro study showed that the adhesion ability between endothelial cells and matrigel/platelets was enhanced due to the up-regulating expression of intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1) proteins by treatment of warfarin+GS combination compared to warfarin/GS treatment alone. Moreover, GS could weaken the anticoagulation effect of warfarin in hyperlipemia rats owning to the increased expression levels of coagulation factors and hepatic cytochrome P450 enzymes in plasma after long-term co-administration of warfarin with GS. The results of both in vitro and in vivo study demonstrated that there is a serious interaction between warfarin and ginseng, which may deteriorate atherosclerosis and thrombosis after combined use of warfarin and GS.

Herbal medicinals are being used by an increasing number of patients who typically do not advise their clinicians of concomitant use. Known or potential drug-herb interactions exist and should be screened for. If used beyond 8 weeks, Echinacea could cause hepatotoxicity and therefore should not be used with other

known hepatoxic drugs, such as anabolic steroids, amiodarone, methotrexate, and ketoconazole. However, Echinacea lacks the 1,2 saturated necrine ring associated with hepatoxicity of pyrrolizidine alkaloids. Nonsteroidal anti-inflammatory drugs may negate the usefulness of feverfew in the treatment of migraine headaches. Feverfew, garlic, Ginkgo, ginger, and ginseng may alter bleeding time and should not be used concomitantly with warfarin sodium. Additionally, ginseng may cause headache, tremulousness, and manic episodes in patients treated with phenelzine sulfate. Ginseng should also not be used with estrogens or corticosteroids because of possible additive effects. Since the mechanism of action of St John wort is uncertain, concomitant use with monoamine oxidase inhibitors and selective serotonin reuptake inhibitors is ill advised. Valerian should not be used concomitantly with barbiturates because excessive sedation may occur. Kyushin, licorice, plantain, uzara root, hawthorn, and ginseng may interfere with either digoxin pharmacodynamically or with digoxin monitoring. Evening primrose oil and borage should not be used with anticonvulsants because they may lower the seizure threshold. Shankapulshpi, an Ayurvedic preparation, may decrease phenytoin levels as well as diminish drug efficacy. Kava when used with alprazolam has resulted in coma. Immunostimulants (eg, Echinacea and zinc) should not be given with immunosuppressants (eg, corticosteroids and cyclosporine). Tannic acids present in some herbs (eg, St John wort and saw palmetto) may inhibit the absorption of iron. Kelp as a source of iodine may interfere with thyroid replacement therapies. Licorice can offset the pharmacological effect of spironolactone. Numerous herbs (eg, karela and ginseng) may affect blood glucose levels and should not be used in patients with diabetes mellitus.

Lexicomp is the best available tool for screening herb-drug interaction, and Medscape is the best free alternative; however, the sensitivity and performance for detecting herb-drug interaction was far lower than for drug-drug interactions, and overall quite poor. Further research is needed to improve herb-drug interaction screening performance.

Traditional Chinese medicine (TCM) is a holistic approach to health that attempts to bring the body, mind and spirit into harmony. TCM is an essential part of the healthcare system in several Asian countries, and is considered a complementary or alternative medical system in most Western countries. An integration of the traditional Chinese and Western systems of medicine has begun in multiple medical centers internationally, and there is increasing evidence that several herbs and combinations of herbs used in TCM impart important pharmacological effects. The number of databases and compilations of herbs, herbal formulations, phytochemical constituents and molecular targets is increasing, primarily because of the widespread use of TCM in combination with Western drugs. The continued popularity of herbal remedies worldwide suggests that evidence-based research in this field, as well as information regarding the potential efficacy and safety of phytochemical constituents in herbs and TCM formulations, are essential, particularly when TCM is used in combination with other drugs. Herb-drug interactions are similar to drug-drug interactions in terms of their effects on ADME properties. Improvements in the knowledge of the molecular targets and metabolic pathways, as well as of the synergistic and inhibitory effects associated with important phytochemicals from herbs and herbal formulations, will lead to the development of rational approaches for the safe combination of healthcare systems from different cultures.

Herbal supplements are used extensively worldwide without much awareness regarding their safety and efficacy. Extensive research to determine the safety, utility, and level of research support for commonly used herbs has culminated in an easily accessible summary chart for NP providers.

Botanicals fall under different regulations in different countries and are mostly consumed without the consultation of the healthcare professional. Over the last decade, utilization of herbal therapies has been extensively documented. The findings indicate the possibility of potential herb-drug interactions due to the concomitant administration of herbal extracts and prescription/over-the-counter drugs. Simultaneously,

with the increasing public awareness and search for safer herbal remedies, the study on herbal-drug interactions has gained momentum through the study of drug metabolizing enzymes. Cytochrome P450 (CYP) inhibition or induction is probably the most common mechanism for the pharmacokinetic interactions of herbs and drugs. Any inhibition of CYP enzymes by herbal extracts may result in enhanced plasma and tissue concentration of drugs, leading to toxicity, while induction results in reduced drug concentration leading to decreased drug efficacy and treatment failure. Considering the rapidly growing herbal markets, these types of clinical interactions remain under-reported and unclear. With the increasing consumption of herbal extracts along with prescription medicines, the safety of herbs has become a concern. This article reviews the potential for drug interactions by herbal extracts through drug metabolizing enzymes.

Herbal medicines are widely used. Almost one-third of current users of herbal medicines were at risk of a herb-drug interaction. The most common potential herb-drug interaction was between ginkgo and aspirin. This finding has important potential implications because both of these products are regularly used by older people. Physicians and other healthcare providers should be aware of potential herb-drug interactions and should monitor and inform their patients accordingly.

Herbal medicines have enormous presence world wide. Herbs are listed under the "supplement" category by the food and Drug Administration in the USA. The Dietary Supplement and Health Education Act signed into law in October 1994, requires no proof of efficacy, no demonstration of safety, and sets no standards for quality control for the products labeled as "supplements" thereby increasing the risk of adverse effects as quantities of active agents are unregulated. The United States has experienced an epidemic of over-the-counter "natural" products over the last two decades; but there is little motivation for the manufacturers to conduct randomized, placebo-controlled, double-blinded clinical trials to unequivocally prove the safety and efficacy of these drugs. Physicians must enquire and be aware of herbal/drug interactions. In addition, patient education of the potential interactions should be a routine component of preoperative assessment. The American Society of Anesthesiologists (ASA) recommends that all herbal medications should be discontinued 2-3 weeks prior to an elective surgical procedure. If the patient is not sure of the contents of the herbal medicine, he/she should be urged to bring the container so that an attempt can be made to review the contents of the preparation. While such an action holds some promise in the elective setting, emergency care should be based on a thorough drug-intake history from the patient or a relative, if possible. Medical research and medical literature in general has not addressed this new group of health supplements, despite the fact that many of these herbs have the potential to cause serious health problems and drug interactions. There is a need to conduct scientific clinical trials to study the anesthetic drug responses to commonly used neutraceutical agents.

Complementary medicine (CM) is used by one third to one half of cancer patients throughout the world. The objective of this study was to describe the prevalence of CM use and the potential for interactions with cancer treatments in an academic oncology centre. A cross-sectional study was conducted among patients undergoing current cancer treatment. Among 132 included patients, 56% had used CM since their cancer diagnosis and 45% were using CM during cancer treatment at the time of the survey. The main CM used were green tea (35%), herbal tea (35%), homeopathy (27%), dietary supplements (27%), and herbal medicines (27%). A small majority of patients (58%) spontaneously mentioned the use of CM to their oncologist. Of 42 identified combinations of concomitant use of biologically based CM and anticancer agents among the study patients, the potential for pharmacokinetic interactions of clinical relevance was not expected in 17 combinations (40%), hypothetical and deemed unlikely in 23 (55%), and of probable low clinical relevance in 2 (5%). Considering the high prevalence of CM use, active enquiries should be

made by healthcare professionals to detect symptoms that may relate to CM tolerance and effects or that suggest interactions between CM and cancer treatments.

Complementary medicine (CM) is used by one third to one half of cancer patients throughout the world. The objective of this study was to describe the prevalence of CM use and the potential for interactions with cancer treatments in an academic oncology centre. A cross-sectional study was conducted among patients undergoing current cancer treatment. Among 132 included patients, 56% had used CM since their cancer diagnosis and 45% were using CM during cancer treatment at the time of the survey. The main CM used were green tea (35%), herbal tea (35%), homeopathy (27%), dietary supplements (27%), and herbal medicines (27%). A small majority of patients (58%) spontaneously mentioned the use of CM to their oncologist. Of 42 identified combinations of concomitant use of biologically based CM and anticancer agents among the study patients, the potential for pharmacokinetic interactions of clinical relevance was not expected in 17 combinations (40%), hypothetical and deemed unlikely in 23 (55%), and of probable low clinical relevance in 2 (5%). Considering the high prevalence of CM use, active enquiries should be made by healthcare professionals to detect symptoms that may relate to CM tolerance and effects or that suggest interactions between CM and cancer treatments.

To date, several clinically important drugs have been identified that interact with commonly used herbs. These drugs include (among others) warfarin, midazolam, digoxin, amitriptyline, indinavir, cyclosporine, tacrolimus and irinotecan. Importantly, many of these drugs have very narrow therapeutic indices. Most of them are substrates for cytochrome P450s (CYPs) and/or P-glycoprotein (P-gp). Because drug-herb interactions can significantly affect circulating levels of drug and, hence, alter the clinical outcome, the identification of drugs that interact with commonly used herbal medicines has important implications in drug development. In silico, in vitro, animal and human studies are often used to identify drug interactions with herbs. We propose that drug-herb and herb-CYP interaction studies should be incorporated into drug development.

Health care providers are being increasingly confronted with the use of herbal medications by their patients. It is imperative that patients be questioned regarding herbal preparation use and that health care providers become familiar with these agents. Research into the active components and mechanisms of action of various herbals is ongoing [350]. Long-range studies need to be performed to follow patients for efficacy or toxicity in chronic use [351,352]. Adverse reactions to herbal remedies should be reported to the FDA

Ginseng is often prescribed together with cisplatin for treatment of cancer, but the interaction between ginseng and cisplatin is still unknown. This study employed ginsenoside Rb1 (Rb1), one of the major components in ginseng, to explore the effects and involved mechanisms of cisplatin on the pharmacokinetics of ginseng. The effects of cisplatin on the pharmacokinetics of Rb1 and its bioactive metabolites Rd, Rg3, and F2 were investigated by using A549-bearing mice with and without cisplatin intervention. Our data showed that cisplatin could significantly decrease the $AUC_{(0-t)}$ and C_{max} of Rd, Rg3, and F2, except Rb1. To evaluate the involved mechanisms, feces and intestinal mucosa were collected to explore the effects of cisplatin on the gut metabolism of Rb1 in vitro; meanwhile, Caco-2 cell model and small intestine histological characters were examined to evaluate the effects of cisplatin on the gut absorptive areas and permeability. The mechanisms involved may be mainly related to the comprehensive contributions of inhibited intestinal bacteria and mucosa metabolisms, narrowed intestinal absorptive area, increased efflux ratio of intestinal absorption and enhanced intestinal permeability. All these findings suggested that the dosage of ginseng traditionally used for health protection should be adjusted when it was prescribed together with cisplatin in the treatment of cancer.

Curcumin, a yellow pigment in Asian spice, is a natural polyphenol component of Curcuma longa rhizome. Curcuminoid components include curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). Previous studies established curcumin as a safe agent based on preclinical and clinical evaluations and curcuminoids have been approved by the US Food and Drug Administration (FDA) as "Generally Recognized as Safe" (GRAS). The present review collects and summarizes clinical and preclinical studies of curcumin interactions, with an emphasis on the effect of curcumin and curcumin analogs on the mRNA and protein levels of microsomal CYP450 enzymes (phase I metabolism) and their interactions with toxicants, drugs and drug probes. The literature search was conducted using keywords in various scientific databases, including Web of Science, Scopus, PubMed, and Google Scholar. Studies concerning the impact of curcumin and curcumin analogs on microsomal enzyme activity are reviewed and include oral, topical, and systemic treatment in humans and experimental animals, as well as studies from in vitro research. When taken together, the data identified some inconsistent results between various studies. The findings showed significant inhibition of CYP450 enzymes by curcumin and its analogs. However, such effects are often differed when curcumin and curcumin analogs were coadministered with toxicant and other drugs and drug probes. We conclude from this review that herb-drug interactions should be considered when curcumin and curcumin analogs are consumed.

A recent series of deaths in previously healthy dogs in Victoria, Australia associated with the ingestion of raw meat contaminated by indospicine derived from native Australian plants of the Indigofera species draws attention to the potential that exists for herbal toxicity in domestic animals. Although the efficacy of herbal remedies generally remains unproven in domestic animals, herbal preparations are being increasingly used as supplements and treatments. Issues with incorrect ingredients, inadequate processing, faulty, incomplete or inaccurate product labelling, contamination with toxins, adulteration with undeclared pharmaceutical agents and herb-herb interactions are well recognized as causes of adverse effects in humans. However, apart from of the effects of noxious weed species, the literature on herbal toxicity in domestic animals is sparse. Thus, the forensic evaluation of cases of suspected poisoning in domestic animals should also encompass an accurate description the type and dose of any herbal preparations that may have been recently administered.

The metabolism of a drug can be altered by another drug or foreign chemical, and such interactions can often be clinically significant. Cytochrome P450 (CYP) enzymes, a superfamily of enzymes found mainly in the liver, are involved in the metabolism of a plethora of xenobiotics and have been shown to be involved in numerous interactions between drugs and food, herbs and other drugs. The observed induction and inhibition of CYP enzymes by natural products in the presence of a prescribed drug has (among other reasons) led to the general acceptance that natural therapies can have adverse effects, contrary to the popular beliefs in countries where there is an active practice of ethnomedicine. Herbal medicines such as St. John's wort, garlic, piperine, ginseng, and gingko, which are freely available over the counter, have given rise to serious clinical interactions when co-administered with prescription medicines. Such adversities have spurred various pre-clinical and in vitro investigations on a series of other herbal remedies, with their clinical relevance remaining to be established. Although the presence of numerous active ingredients in herbal medicines, foods and dietary supplements complicate experimentation, the observable interactions with CYP enzymes warrant systematic studies, so that metabolism-based interactions can be predicted and avoided more readily. This article highlights the involvement of CYP enzymes in metabolism-related drug-herb interactions and the importance of gaining a mechanism-based understanding to avoid potential adverse drug reactions, in addition to outlining other contributory factors, such as pharmacogenetics and recreational habits that may compound this important health issue.

Africa is a continent of rich plant biodiversity with many indigenous plants having a long history of being used for medicinal purposes. A considerable number of patients consult traditional healers in African countries for their primary health-care needs. As Western medicines become more available through governmental programmes to treat diseases such as infections with HIV/AIDS, patients are faced with an increased potential of herb-drug interactions.

The current study provides a website platform and 80 sets of validated bilingual HDIs involving ginseng, ginkgo and dong quai in an online database. A search of HDI monographs related to these three herbs can be performed with this bilingual, easy-to-use query website, which is feasible for professionals and the general public. The identified reliability level for each HDI may assist readers' decisions regarding whether taking Western medications concomitant with one of three herbal medicinal foods is safe or whether caution is required due to potentially serious outcomes.

This study aimed to investigate the liver microsomal inhibitory effects of silybin, silychristin, andrographolide, and curcumin by using morphine as an in vitro UGT2B7 probe substrate, and predict the magnitude of the herb-drug interaction arising from these herbal constituents' inhibition in vivo. Studies were performed in the incubation with and without bovine serum albumin (BSA). Andrographolide and curcumin showed a marked inhibition on morphine 3- and 6-glucuronidation with IC_{50} of 50&87 and 96&111 μM, respectively. In the presence of 2%BSA, andrographolide also showed a strong inhibition on morphine 3- and 6-glucuronidation (IC_{50} 4.4&21.6 μM) whereas curcumin showed moderate inhibition (IC_{50} 338&333 μM). In the absence and presence of 2%BSA, morphine 3- and 6-glucuronidation was moderately inhibited by silybin (IC_{50} 583&862 and 1252&1421 μM, respectively), however was weakly inhibited by silychristin (IC_{50} 3527&3504 and 1124&1530 μM, respectively). The K_i of andrographolide, curcumin and silybin on morphine 3- and 6-glucuronidation were 7.1&9.5, 72.7&65.2, and 224.5&159.7 μM, respectively, while the respective values generated from the system containing 2%BSA were 2.4&3.1, 96.4&108.8, and 366.3&394.5 μM. Using the in vitro and in vivo extrapolation approach, andrographolide was herbal component that may have had a potential interaction in vivo when it was co-administered with morphine.

This survey provides evidence to suggest that pharmacists encounter reportable NHP-drug interactions, yet rarely choose to report these events. The current lack of available data on NHP AEs makes it difficult to provide patients and healthcare providers with useful strategies for managing AEs and drug interactions. Changes to the current system of monitoring AEs due to NHPs and further education of healthcare professionals regarding NHP-drug interactions is required.

The use of herbal supplements has increased steadily over the last decade. Recent surveys show that many people who take herbal supplements also take prescription and nonprescription drugs, increasing the risk for potential herb-drug interactions. While cytochrome P450-mediated herb-drug interactions have been extensively characterized, the effects of herbal extracts and constituents on UDP-glucuronosyl transferase (UGT) enzymes have not been adequately studied. Thus, the purpose of this review is to evaluate current evidence on the glucuronidation of phytochemicals and the potential for UGT-mediated herb-drug interactions with the top-selling herbal supplements in the United States and Europe. IN VITRO and animal studies indicate that cranberry, GINKGO BILOBA, grape seed, green tea, hawthorn, milk thistle, noni, soy, St. John's wort, and valerian are rich in phytochemicals that can modulate UGT enzymes. However, the IN VIVO consequences of these interactions are not well understood. Only three clinical studies have investigated the effects of herbal supplements on drugs cleared primarily through UGT enzymes. Evidence on the potential for commonly used herbal supplements to modulate UGT-mediated drug metabolism is summarized. Moreover, the need for further research to determine the clinical consequences of the described interactions is highlighted.

The increased use of herbal supplements as complementary or alternative medicines has become a clinical conundrum due to the potential for herb-drug interactions. This is exacerbated by an increased supply of new herbal supplements in the market claiming various health advantages. These herbal supplements are available as over-the-counter self-medications. Herbal supplements are generally perceived as efficacious without side effects commonly associated with conventional drugs. However, despite regulations, claims related to their therapeutic effects are mostly unsupported by scientific evidence. These products often lack suitable product quality controls, labelled inadequately and with batch to batch variations, potentially compromising the safety of the consumer. Amongst health practitioners, the greatest concern is related to the lack of chemical characterization of the active compounds of the herbal supplements. The interaction between these different active components and their concomitant effects on other conventional drugs is generally not known. This review will focus on herbal supplements with the potential to effect pharmacokinetic and pharmacodynamic properties of oestrogen-based oral contraceptives. The use of herbal supplements for weight management, depression, and immune boosting benefits were selected as likely herbal supplements to be used concomitantly by women on oral contraceptives.

Herbs are often administered in combination with therapeutic drugs, raising the possibility for herb-drug interactions (HDIs). Furoquinoline alkaloids are found in Rutaceae plants, which are structurally similar and have many medicinal properties. This study aims to investigate the inhibition of four furoquinoline alkaloids on the activity of UDP-glucuronosyltransferases (UGTs).The recombinant UGTs-catalyzed glucuronidation metabolism of 4-methylumbelliferone (4-MU) was utilized to investigate the inhibition potential. Inhibition type and parameters were determined, and *in silico* docking was employed to elucidate the inhibition difference of furoquinoline alkaloids towards UGTs.Dictamine, haplopine, γ-fagarine and skimmianine strongly inhibited UGT1A3, UGT1A7, UGT1A9 and UGT2B4, respectively. Among them, dictamnine inhibited more than 70% of the four UGTs. Inhibition kinetics determination showed that they all exerted competitive inhibition, and the inhibition kinetic constant (K_i) was determined to be 8.3, 7.2, 3.7 and 33.9 μM, respectively. *In vitro-in vivo* extrapolation (IVIVE) was employed to demonstrate the inhibition possibility for four alkaloids. Skimmianine was proved to be more suitable for clinical application. *In silico* docking study indicated that the hydrophobic interactions played a key role in the inhibition of furoquinoline alkaloids towards three of the four UGTs. In conclusion, monitoring the interactions between furoquinoline alkaloids and drugs mainly undergoing UGTs-catalyzed metabolism is necessary.

This article provides an overview of the clinical evidence of interactions between herbal and conventional medicines. Herbs involved in drug interactions--or that have been evaluated in pharmacokinetic trials--are discussed in this review. While many of the interactions reported are of limited clinical significance and many herbal products (e.g. black cohosh, saw palmetto, echinacea, hawthorn and valerian) seem to expose patients to minor risk under conventional pharmacotherapy, a few herbs, notably St. John's wort, may provoke adverse events sufficiently serious to endanger the patients' health. Healthcare professionals should remain vigilant for potential interactions between herbal medicines and prescribed drugs, especially when drugs with a narrow therapeutic index are used.

Traditional Chinese medicine (TCM) formulas with fixed combinations rely on "sovereign, minister, assistant and guide" and fuzzy mathematical quantitative law, leading to greater challenges for the identification of active ingredients. Transformation and metabolic studies involving the Phase I drug-metabolizing enzyme cytochrome P450 (CYP) might potentially solve some of these challenges. The pharmacological effects can not be attributed to one active ingredient in TCMs, but integrated effects resulting from the combined actions of multiple ingredients. However, it is only after long-term administration that most ingredients exert their actions, which can result in prolonged exposure to herbs in

vivo. Therefore, interactions between herbal compounds and CYPs appear to be inevitable. Yet unlike Western drugs, experimental determination of the absorption and disposition properties is not commonly carried out for TCMs. Moreover, the use of TCM as injections is an innovation aimed to improve efficiency in extensive clinical use in Mainland China. Therefore, in recent years, cases of adverse drug reactions (ADR) mainly concerning allergic reactions involving TCMs such as ShenMai injection and QingKaiLing injection have been reported, which have attracted attention with regard to the legal responsibilities for TCM approval. The lack of information on the ADME characteristics, especially the metabolic stability and interaction potential between CYPs and herbs, increases ADR occurrence due to TCMs. In this article, we review the most common herbs used in TCM prescriptions and fixed combinations of their usable frequency, and summarize the current understanding of the ability of phytochemical ingredients to act as substrates, inhibitors or inducers of human CYP enzymes, through which the key role of CYP enzymes on the herb disposition and toxicity is highlighted. The potential interaction between herbal phytochemicals and CYP enzymes dominates the target exposure, which further helps to elucidate the herbal pharmacological basis, assess the individual toxic risk of herbal remedies and gain mechanistic insight into herb-drug interactions (HDIs).

formulation with Curcuma longa Linn (Turmeric, Haridra, Nisha in Sanskrit; Family: Zingiberaceae) and Phyllanthus emblica Linn (Indian gooseberry, Amlaki in Sanskrit; Family: Phyllanthaceae) which is described for various diseases including diabetes in ayurvedic texts and Nighantus. The aim of the present study was to assess the pharmacokinetic (PK) and pharmacodynamic (PD) interactions of chemically standardized NA and Curcuminoids (CE) with metformin (MET) in normal and diabetic animals. Oral administration of NA (200 mg/kg) and CE (30 mg/kg) was carried out for seven days followed by co-administration of MET till fifteen days. MET plasma PK parameters including C_{max}, $AUC_{0-\infty}$, $t_{1/2}$, CL and V_d were measured on the eighth day. PD parameters including plasma glucose AUC followed by oral glucose tolerance test, high-density lipoproteins (HDL), total cholesterol (TC) and triglycerides (TG) were measured on the fifteenth day. In normal animals, co-administration of NA + MET and CE + MET resulted in significant increase ($p < 0.05$) in C_{max}, $AUC_{0-\infty}$, $t_{1/2,}$ and reduction of CL and V_d. We report that co-administration of NA + MET and CE + MET significantly ($p < 0.01$, $p < 0.001$) reduced plasma glucose level, HDL level while a notable reduction in TG and TC level was observed. Interestingly, in diabetic condition, co-administration of NA + MET and CE + MET indicated a significant decrease ($p < 0.05$) in C_{max}, $AUC_{0-\infty}$, $t_{1/2}$ and enhanced CL and $V_{d.}$ Hence, to conclude, co-administration of NA + MET and CE + MET resulted in beneficial PK and PD interactions leading to antihyperglycemic and antihyperlipidemic effects in both conditions. However, PK interaction was drastically different in diabetic and normal conditions.

A substantial percentage of potential drug-herbal interactions were found among patients with chronic diseases. Healthcare providers are encouraged to discuss the safety and efficacy of herbal products with their patients.

Herb-drug interaction strongly limits the clinical application of herbs and drugs, and the inhibition of herbal components towards important drug-metabolizing enzymes (DMEs) has been regarded as one of the most important reasons. The present study aims to investigate the inhibition potential of andrographolide derivatives towards one of the most important phase II DMEs UDP-glucuronosyltransferases (UGTs). Recombinant UGT isoforms (except UGT1A4)-catalyzed 4-methylumbelliferone (4-MU) glucuronidation reaction and UGT1A4-catalyzed trifluoperazine (TFP) glucuronidation were employed to firstly screen the andrographolide derivatives' inhibition potential. High specific inhibition of andrographolide derivatives towards UGT2B7 was observed. The inhibition type and parameters (Ki) were determined for the compounds exhibiting strong inhibition capability towards UGT2B7, and human liver microsome (HLMs)-

catalyzed zidovudine (AZT) glucuronidation probe reaction was used to furtherly confirm the inhibition behavior. In combination of inhibition parameters (Ki) and in vivo concentration of andrographolide and dehydroandrographolide, the potential in vivo inhibition magnitude was predicted. Additionally, both the in vitro inhibition data and computational modeling results provide important information for the modification of andrographolide derivatives as selective inhibitors of UGT2B7. Taken together, data obtained from the present study indicated the potential herb-drug interaction between Andrographis paniculata and the drugs mainly undergoing UGT2B7-catalyzed metabolic elimination, and the andrographolide derivatives as potential candidates for the selective inhibitors of UGT2B7.

The aim of this open-label, fixed-sequence study was to investigate the potential of the botanical supplement Echinacea purpurea to interact with etravirine, a nonnucleoside reverse transcriptase inhibitor of HIV. Fifteen HIV-infected patients receiving antiretroviral therapy with etravirine (400 mg once daily) for at least 4 weeks were included. E. purpurea root/extract-containing capsules were added to the antiretroviral treatment (500 mg every 8 h) for 14 days. Etravirine concentrations in plasma were determined by high-performance liquid chromatography immediately before and 1, 2, 4, 6, 8, 10, 12, and 24 h after a morning dose of etravirine on day 0 and etravirine plus E. purpurea on day 14. Individual etravirine pharmacokinetic parameters were calculated by noncompartmental analysis and compared between days 0 and 14 by means of the geometric mean ratio (GMR) and its 90% confidence interval (CI). The median age was 46 years (interquartile range, 41 to 50), and the median body weight was 76 kg (interquartile range, 68 to 92). Echinacea was well tolerated, and all participants completed the study. The GMR for etravirine coadministered with E. purpurea relative to etravirine alone was 1.07 (90% CI, 0.81 to 1.42) for the maximum concentration, 1.04 (90% CI, 0.79 to 1.38) for the area under the concentration-time curve from 0 to 24 h, and 1.04 (90% CI, 0.74 to 1.44) for the concentration at the end of the dosing interval. In conclusion, the coadministration of E. purpurea with etravirine was safe and well tolerated in HIV-infected patients; our data suggest that no dose adjustment for etravirine is necessary.

Herb-drug interactions are subject to much interest at present, but for various reasons reports may be unreliable or unsubstantiated. Herbal medicines are variable in composition and quality, which may affect their interaction profile as well as the reliability of reports concerning them. In this review, clinical and experimental reports have been collated, evaluated and summarised, and the theoretical and clinical evidence presented. There is an explanation of the particular issues involved with herbal medicines as compared with conventional drugs, and reasons why comparisons may or may not be valid, which is intended for those without specialist experience in herbal products. It has become apparent that only a few herbal drugs have so far been cited in interaction reports, for example St John's Wort, Ginkgo biloba, Dan Shen, liquorice, Ma huang and garlic, and that the main drugs involved are those which are already susceptible to interactions with many other conventional drugs, such as warfarin, protease inhibitors and anti-cancer drugs. An attempt has been made to put the matter into perspective and recommendations have been given for health professionals to advise or develop strategies to safeguard patients, without resorting to speculation or scaremongering.

Complementary and alternative medicine (CAM) is presently not considered to be part of conventional medicine. Nevertheless, an estimated 51% of patients with gastrointestinal disorders have tried some from of CAM. Indeed, 10% of alternative medicines are being used for digestive symptoms. After prayer or spiritual healing, herbal medicine is the second most common CAM therapy. While herbal products make numerous health-related claims, those that have been systematically evaluated are unfortunately few. The modern gastroenterologist must be up to date with the regulations, side effects, and possible benefits of specific herbal products used in patients with gastrointestinal disorders.

The increasing use of herbal remedies by the general public presents several challenges to healthcare professionals who may be asked to give advice on the use of such products in conjunction with other medicines. In particular, the pharmacological properties and potential interactions of herbal products are often less well understood than those of conventional medicines, increasing the risk of adverse effects and drug interactions. In addition, good quality data on herbal medicines are often lacking. Here we highlight the problem of drug-herb interactions and consider the nature of the evidence supporting drug interactions with herbal products.

Herbal remedies, considered to be both safe and effective by most consumers, may interact with conventional drugs. Warfarin, a vitamin K antagonist originally derived from the sweet clover plant, has a narrow therapeutic window which can be monitored using prothrombin international normalized ratios (PT-INR). Many herbs can increase the risk for bleeding when combined with warfarin, either by augmenting the anticoagulant effects of the drug (with increased PT-INR levels) or through intrinsic anti-platelet properties (without altering PT-INR levels). The increased risk for bleeding among such patients may be difficult to predict, especially when formulas which contain many herbs are used. Further research into herb-drug interactions is warranted, as are guidelines for the use of herbal remedies by patients on chronic anticoagulation therapy.

These results suggest that when mechanism-based inhibitors from phytomedicine containing amine or furan heterocycle substructures are used alone or with other drugs, in vivo hepatotoxicity screening or its clinical implications for herb-drug interactions are needed to attention.

Food-drug interactions have been associated with clinically important pharmacokinetic and pharmacodynamic changes of a drug. The aim of this paper is to review the regulation of P-glycoprotein (P-gp) by dietary components and to correlate the changes in cellular P-gp function and expression with drug bioavailability. In summary, the published literature has provided extensive data supporting the modulation of drug bioavailability through P-gp regulation by components in food groups such as fruit juices, spices, herbs, cruciferous vegetables and green tea. Most of these data were, however, derived from in vitro cell models and, except for the St John's wort, the clinical significance of most reported interactions remains to be clarified. Studies on piperine and capsaicin have underscored an often poor correlation between in vivo and in vitro data, whereas experiments involving curcumin highlighted differences between acute and chronic consumption of a dietary component on P-gp function and expression in vivo. A better understanding of the pharmacokinetic and pharmacodynamic profiles of the dietary components will aid in addressing these knowledge gaps.

Medications are used concurrently with NHP in every fifth pediatric patient in the emergency department and many NHP users are receiving more than 1 NHP simultaneously. One quarter of all paired medication-NHP or NHP-NHP could potentially cause interactions. Although we can not confirm that these were true interactions resulting in clinical symptoms, parents and health care providers need to balance the potential benefit of concurrent NHP-medication use with its potential harms.

In the past two decades, there has been an exponential increase in the use of medicinal herbal products around the world. In various countries, these products are classified and promoted as foods, not pharmaceuticals, which facilitate their availability on the international market without requiring a medical prescription. Since older adults (OAs) are an important and growing sector of the population in many countries, it is important to know the prevalence of their herbal product use, since many OA take herbs along with diverse quantities of prescription and over the counter medications. For this reason, it is important to be aware of the possibilities of health complications due to the concomitant use of diverse medications and herbs. OA are an especially vulnerable population, since many of the human body's

physiological activities, such as renal and hepatic detoxification and clearance usually decrease with age. Additionally, information on certain herbal products is either misleading, or simply unavailable. These products may indeed be a therapeutic option, but some can be used properly only under the guidance of a health professional. Those OA taking combinations of various medications and herbal supplements are also more at risk to experience some sort of herb-drug interactions. This publication reviews selected articles related to the use of herbal products by OAs and mentions the various patterns of use and health implications of the concomitant use of herbal products and prescription medications. This topic is currently not fully understood and further research is warranted.

Diabetes mellitus is a chronic illness with a variety of causes and pathophysiology. For the management of diabetes, various synthetic antidiabetic drugs are available. Still, people prefer complementary and alternative therapies as well as traditional herbal home remedies because they are perceived to be free of side effects and generally recognized as safe due to their natural origin. Hence, worldwide, the majority of the population is consuming herbs and/or herbal products in their daily routine. It has been observed that individuals with diabetes also consume herbs/herbal products either with or without medical supervision. This co-consumption of antidiabetic medications and herb/herbal products may result in herb-drug interactions, which might be potentially beneficial or harmful or, in some cases, even fatal. Most of the times, these interactions remain unnoticed or undiagnosed due to lack of knowledge and awareness about them. In this review, the authors have summarized some important aspects related to the herb-drug interaction (HDI), which include methods for prediction and mechanism of HDI (pharmacokinetic and pharmacodynamic) and also the clinical and experimental literature on herb-drug interactions (HDI) in the treatment of diabetes. Authors have attempted to categorize the interactions between oral hypoglycemic agents and various herbs as beneficial or harmful based on the results reported in the original research work.

Despite their common use, it is not widely recognized that herbal medicines can alter the efficacy of coadministered prescription drugs. Constituents in herbs interact with nuclear receptors to enhance metabolizing enzyme and/or transporter activity leading to reduced drug concentrations. Although St John's wort was the first and most frequently reported source of induction-style herb-drug interactions, this knowledge has not yet changed its current availability. This type of interaction is likely to be relevant to other herbal products. Caregivers need to be aware of the issues and options for therapeutic management.

Complementary and alternative therapies are quickly gaining importance because they are perceived to be free of side effects due to their natural origin. However, herbal remedies are complex mixtures of bioactive entities, which may interact with prescription drugs through pharmacokinetic or pharmacodynamic mechanisms and sometimes result in life-threatening consequences. In particular, diabetes patients are often treated with multiple medications due to different comorbidities, and such patients use antidiabetic medications for their entire lives; thus, it is important to make the public aware of herb interactions with antidiabetic drugs. In this paper, we summarize the reports available on the interaction of herbal remedies with oral hypoglycemic agents and describe mechanisms, preclinical or clinical evidence, importance, and management strategies.

Herbal remedies are clearly a complementary and alternative modality used frequently by patients with hemato-oncological neoplasias during the course of their specific treatment. This review focuses on the potential safety and efficacy of herbs which are either used often or even on a daily basis by patients with hematological malignancies or indicated in the herbal pharmacopeias utilized by various traditional systems of medicine, in order to improve the well-being of patients with these cancers. Traditional medicine worldwide is a source for ongoing laboratory research related to the activity of herbs on cultured cell lines derived from patients with leukemia, lymphoma, and myeloma. Although the number of clinical studies in

the field of hemato-oncology is limited, there appears to be potential efficacy in studies of mistletoe (Viscum album), green tea, Indian and Middle-Eastern spices, and some traditional Chinese, American, and European herbs. In addition to the potential efficacy of herbs, safety issues are also reviewed here, particularly, the documented and potential side effects, herb-drug interactions, and matters of quality control. Based on the above issues, the authors suggest enhancing doctor-patient communication regarding herbal use by adopting a patient-centered attitude based on scientific perspective.

The clinical application of herbal medicines is increasing, but there is still a lack of comprehensive safety data and in-depth research into mechanisms of action. The composition of herbal medicines is complex, with each herb containing a variety of chemical components. Each of these components may affect the activity of metabolizing enzymes, which may lead to herb-drug interactions. It has been reported that the combined use of herbs and drugs can produce some unexpected interactions. Therefore, this study reviews the progress of research on safety issues caused by the effects of herbs on metabolizing enzymes with reference to six categories of drugs, including antithrombotic drugs, non-steroidal anti-inflammatory drugs, anti-diabetic drugs, statins lipid-lowering drugs, immunosuppressants, and antineoplastic drugs. Understanding the effects of herbs on the activity of metabolizing enzymes could help avoid the toxicity and adverse drug reactions resulting from the co-administration of herbs and drugs, and help doctors to reduce the risk of prescription incompatibility.

Isoflavones are the most widely consumed phytoestrogens. Besides being a dietary constituent, their consumption has been increasing in the form of herbal supplements and as promising alternatives to hormonal replacement therapy, in conjunction with prescription medicines. Isoflavones are extensively metabolized by phase I and II enzymes and are substrates of drug transporters. At high concentrations isoflavones may interact with drug metabolizing enzymes and drug transporters and modulate their activity, thus, altering the absorption, metabolism, distribution, excretion and toxicity profile of the co-administered drugs. This review summarizes the up-to-date literature of isoflavone-drug interactions giving insight into the possible mechanisms of interactions, in vitro-in vivo correlation and their implications on clinical outcomes.

Traditional Chinese medicines (TCMs) have a long history for safely treating human diseases. Unlike western medicine, TCMs usually contain multiple components synergistically and holistically acting on the diseases. It remains a big challenge to represent rationally the in vivo process of multiple components of TCMs for understanding the relationship between administration and therapeutic effects. For years, efforts were always made to face the challenge, and the achievements were obvious. Here, we give an comprehensive overview of the recent investigation progress (from 2015 to 2017, except the part of 'integrated pharmacokinetics of TCMs' from 2014 to 2017 and the part of 'reverse pharmacokinetics in drug discovery from natural medicines' in 2014) on pharmacokinetics of TCMs, mainly referring to the following six aspects: (1) classical pharmacokinetic studies on TCMs; (2) absorbed components and metabolites identification of TCMs; (3) pharmacokinetic herb-drug interactions and herb-herb interactions with TCMs; (4) integrated pharmacokinetics of TCMs; (5) pharmacokinetic and pharmacodynamic combination studies to dissect the action mechanisms of TCMs; and (6) reverse pharmacokinetics in drug discovery from natural medicines. Finally, based on the insights from the recent progress and our latest efforts, we propose new perspectives on the integrated pharmacokinetics of TCMs.

It is concluded that the widespread notion of HMPs being inherently safe is naive at best and dangerous at worst. More research is required to minimise the risk HMPs may pose to consumers' health.

The aim of this study was to assess the potential risks of interactions between biologically based complementary and alternative medication (BB-CAM) and conventional drugs during systemic therapy in breast and gynecological cancer patients by analyzing the actual CAM-drug combinations from individual patients' records.

Dibenzyl trisulfide (DTS) is the major active ingredient expressed in Petiveria alliacea L., a shrub widely used for a range of conditions, such as, arthritis, asthma and cancer. Given its use alone and concomitantly with prescription medicines, we undertook to investigate its impact on the activities of important drug metabolizing enzymes, the cytochromes P450 (CYP), a key family of enzymes involved in many adverse drug reactions. DTS and seven standardized extracts from the plant were assessed for their impact on the activities of CYPs 1A2, 2C19, 2C9, 2D6 and 3A4 on a fluorometric assay. DTS revealed significant impact against the activities of CYPs 1A2, 2C19 and 3A4 with IC50 values of 1.9, 4.0 and 3.2μM, respectively, which are equivalent to known standard inhibitors of these enzymes (furafylline, and tranylcypromine), and the most potent interaction with CYP1A2 displayed irreversible enzyme kinetics. The root extract, drawn with 96% ethanol (containing 2.4% DTS), displayed IC50 values of 5.6, 3.9 and 4.2μg/mL respectively, against the same isoforms, CYPs 1A2, 2C19 and 3A4. These investigations identify DTS as a valuable CYP inhibitor and P. alliacea as a candidate plant worthy of clinical trials to confirm the conclusions that extracts yielding high DTS may lead to clinically relevant drug interactions, whilst extracts yielding low levels of DTS, such as aqueous extracts, are unlikely to cause adverse herb-drug interactions.

Various studies reported conflicting results, with the results depending on the nature of the herb investigated (extracts or active constituents) and the biochemical tool (subcellular fractions, cells, or recombinant enzymes) and study system (in vitro/in vivo/ex vivo/clinical) applied. Each approach/system has its own advantages and disadvantages. Selecting the most appropriate approaches/systems allows us to extract the most meaningful and clinically relevant information on the metabolic pathways (the metabolites generated and the enzymes involved) and the potential drug interactions of herb-derived compounds for cancer therapy and prevention. Human primary hepatocytes are the best model that can be applied in any metabolic study. Human liver microsomes (HLMs) are a useful biochemical tool for preliminary drug metabolism studies. Recombinant microsomes that express specific enzymes and CYP-isoform-specific monoclonal antibodies are useful tools for enzyme inhibition studies.

There is high prevalence of herbal medicine use among elderly people. Most patients do not reveal their herbal use to their physicians and pharmacists. The authors describe some commonly used herbal remedies in terms of their potential benefits and known adverse effects. The review also highlights the potentially serious risk of herb-drug interactions and discusses communication issues and regulatory concerns associated with use of herbal medicines. Health practitioners should remember to include herbal use history in their routine drug histories and remain informed of the beneficial and harmful effects of these treatments.

We detected a high prevalence of MH consumption in CPC and interactions between herbs medicinal and drugs. Lack of knowledge of PC health professionals is important. It's necessary to record this consumption in the medical history and improve the knowledge of professionals about MH to detect possible interactions, reduce the associated risk and improve the quality of care.

Inpatient consumption of dietary and herbal supplements (DHS) has recently received research attention, particularly due to potential DHS-drug interactions. Nevertheless, DHS-DHS interactions have seldom been evaluated among hospitalized patients. We evaluated potential DHS-DHS interactions among inpatients. The study was a cross-sectional prospective study, conducted at Bnai Zion Medical Center (Haifa, Israel) in 2009-2014. A multi-disciplinary team of researchers constructed a questionnaire aimed at detecting DHS use among inpatients. The Natural Medicine Database was used to examine identified DHS

for potential DHS-DHS interactions. Then, medical files were reviewed to identify side effects potentially caused by such interactions and rate of documentation of DHS use. Univariate and multivariate logistic regression analyses were conducted to characterize potential risk factors for DHS-DHS interactions among hospitalized DHS users. Of 927 patients who agreed to answer the questionnaire, 458 (49.4 %) reported the use of 89 different DHS. Potential DHS-DHS interactions were identified in 12.9 % of DHS users. Three interactions were associated with the actual occurrence of adverse events. Patients at risk of DHS-DHS interactions included females ($p = 0.026$) and patients with greater numbers of concomitant medications ($p < 0.0001$) and of consumed DHS ($p < 0.0001$). In 88.9 % of DHS users, DHS use was not reported in medical files and only 18 % of the DHS involved in interactions were documented. Potential DHS-DHS interactions are common in inpatients, and may lead to hospitalization or worsen existing medical conditions. The causal relationship between potential interactions and actual adverse events requires further study.

The purpose of this paper is to explore the possibility that adverse reactions and drug interactions arising from the use of homeopathic and herbal medicines could lead to confusion when adverse reactions to conventional medicines are reported. An extensive literature review was conducted on the occurrence of adverse reactions and drug interactions following the use of homeopathic or herbal remedies, and the potential for these to confound adverse event reporting to conventional medicines considered. The survey demonstrates the potential for herbal remedies and homeopathic products, to produce adverse drug reactions or drug interactions, and shows the scope for potential for confusion with those arising from conventional medicines. There is a need for greater awareness that adverse reactions apparently due to a conventional medicine, might in reality be due to a herbal medicine or a drug interaction between a herbal medicine and a conventional drug, particularly when a health professional is unaware of the extent of a patient's self-medication with alternative therapies.

In the context of systems pharmacology, the DMPK knowledge base is expected to translate bench findings to clinical applications, as well as foster cardiovascular drug discovery and development.

In conclusion, andrographolide could increase the systemic exposure of warfarin in rats when andrographolide and warfarin were co-administered, and possibly by slowing down the metabolism of warfarin in rat liver by inhibiting the activity of CYP3A4 or CYP2C9

Liver injury due to prescription and nonprescription medications is a growing medical, scientific and public health problem. Drug-induced liver injury (DILI) is the single most common reason for regulatory actions, including failure of approval, removal from the marketplace and restriction of prescription. Worldwide, the estimated annual incidence rate of DILI is 13.9-24.0 per 100,000 inhabitants. At the same time, there is increasing concern about the potential risk for hepatotoxicity from complementary and alternative medicines (CAM) including herbal products because they are unregulated and not standardized with regard to their contents. Determining hepatotoxicity remains a major challenge in clinical practice due to a lack of reliable markers. The RUCAM/CIOMS scale have been proposed to establish a causal relationship between offending drug and liver injury. The efforts of Drug-Induced Liver Injury Network (DILIN, USA) directed toward the development of an abridged instrument in evaluating suspected drug-induced hepatotoxicity were presented at the National Institute of Health (NIH) Workshop, titled Drug-induced liver injury: Standardization of nomenclature and causality assessment, December, 2008. The main contents of the presentations and discussions at the NIH workshop are introduced in this article. This fine-tuned operations of RUCAM/CIOMS scale would enable a more confident assessment of causality and facilitate the collection of bona fide cases of drug-induced hepatotoxicity in Korea. Several demanding tasks for the near future in Korea are also proposed at the end.

Dietary supplement use may be prevalent among patients seeking dental care. While some dietary supplements may be effective and safe, their biological activity may interfere with treatment or medications in oral health care.

Ridayarishta formulation alone and cocktail with amlodipine besilate, atenolol, atorvastatin, metformin, glipizide, glimepiride had negligible or insignificant effect on CYP450 inhibition. It may be concluded that consumption of Ridayarishta along with selective cardio protective, antihypertensive and anti-diabetic conventional medicine is safe with negligible or without any significant CYP450 (CYP1A2, 2C19, 2D6 and 3A4) inhibition mediated HDI.

Complementary and alternative therapies, including herbal products, have become increasingly popular in the general population and among patients and physicians. Regulations and pharmacovigilance regarding herbal drugs are still incomplete and need to be improved. In fact, herbals are commonly marketed on the Internet, and in many countries they are sold as food supplements, which are beyond the control of drug regulatory agencies. In Europe and the U.S., reports of hepatotoxicity from these products, including those advertised for liver diseases, are accumulating. Many herbal drugs are also commonly used in children, and in women during pregnancy and lactation, because they are believed to be "natural" and, therefore, "harmless." One emerging problem is people preferring herbal-based slimming aids to conventional dietary and physical activity. In Italy, the use of non-conventional therapies has been reported for 13.6 % of the population, and 3.7 % freely use herbal drugs, unaware of the risks associated with a potential interaction with prescription drugs. In our review, we discuss the problem of the lack of standardization of herbal drugs, the lack of randomized clinical trials regarding the majority of these products, the unawareness of risks by the patients who buy and use them, and, further, the problem of underreporting. For the most commonly used herbal products and slimming aids, we describe their potential hepatotoxicity mechanisms, the causality assessment necessary for a correct diagnosis, and the clinical patterns for which these products seem to be responsible.

Radix Puerariae has been traditionally used for the treatment of diarrhea, acute dysentery, deafness and cardiovascular diseases. Yege (Gegen or Radix Puerariae lobatae), the dried root of Pueraria lobata (Wild.) Ohwi, has been widely used in China and, to a lesser extent, in Japan, Korea, and the United States. Although they have been classified into different categories in Chinese Pharmacopoeia, Yege is often used interchangeably in practice with Fenge (Radix Puerariae thomsonii), which is the dried root of Pueraria thomsonii Benth. Among various commercially available products of Radix Puerariae, injection of puerarin, the major isoflavone from Radix Puerariae, has been most widely used as a vasodilator for the treatment of angina and myocardial infarction. Considering the extensive clinical usage and recent alert of fatal herb-drug interaction of Radix Puerariae, the current review is proposed to cover its traditional applications, pharmacological activities, pharmacokinetics, clinical efficacy, and potential herb-drug interactions aiming to fill in the information gaps of this herb for frontline practitioners. Although various small, poorly designed clinical trials have demonstrated the safety, efficacy, and significant clinical benefits of Radix Puerariae, prospective randomized controlled clinical trials are needed to further establish its effective and safe use.

Grapefruit juice and Seville orange juice caused several clinically significant interactions with cytochrome P4503A (CYP3A). The OATP drug transporter was inhibited by grapefruit juice, orange juice, and apple juice. Other fruit juices also interacted with drug metabolizing enzymes and transporters in vitro, but more studies are needed to determine whether these interactions are clinically significant.

The potential for various natural products to perturb the metabolism and disposition of medications has been recognized for decades. There are numerous in vitro and in vivo methods available to screen botanical

products for drug interaction potential. Although many normal volunteer botanical-drug interaction studies have been performed, clearly, in vitro studies assessing the potential for drug interactions with various natural products represent the predominant type of published research performed to date. In addition to the recognized limitations of in vitro screening methodologies to assess conventional drug interactions, further difficulties emerge when examining botanical products. Primary challenges include assigning hepatic concentrations and accounting for bioavailability, distribution, first-pass metabolism and active metabolites. Additionally, variability in the chemical composition of commercially available botanical supplements, the lack of analytical standards and the inability to accurately screen the entities as mixtures add to complexities in experimental design. This mini-review is intended to address the particular problems and challenges in evaluating botanical supplements using in vitro methods, and review what can and cannot be learned from such investigations.

With the wide application of Chinese herbal medicine, herb-drug interaction (HDI) has become increasingly prominent. Metabolic enzymes and transporters are the main targets of HDI, because the changes in expression and function of enzymes and transporters can influence the disposition of drugs. Metabolic enzymes are responsible for the metabolic clearance of drugs, including cytochrome P450 (CYP), UDP-glucuronyl transferase (UGT) and sulfotransferases (SULT); transporters widely expressed in the intestine, kidney, liver and brain are involved in the oral absorption, distribution and excretion of drugs. Pueraria, ginkgo, ginseng, St. John's wort and other Chinese herbal medicine often induce a HDI because those herbal medicines combined with chemical medicine are widely used in clinic. The components of herb medicines mentioned above are prone to interact with enzymes and transporters, which often induce a HDI. This paper reviews the advances in the study of enzymes and transporters-mediated pharmacokinetic mechanism of HDI.

St. John's wort is an herb commonly used in Europe for decades and more recently the topic of scientific investigation in this country. St. John's wort has been found more effective than placebo and equally as effective as tricyclic antidepressants in the short-term management of mild-to-moderate depression. Comparisons to selective serotonin reuptake inhibitors have provided equivocal data. While it is generally well tolerated in clinical use, there is accumulating evidence of significant interactions with drugs. This evidence-based presentation of the literature includes a brief description of pharmacodynamics and clinical applications, followed by a systematic review of adverse effects, toxicity, and drug interactions.

The use of alternative medicines, including herbs, is common among HIV-positive patients, even in those on antiretroviral treatment. Equisetum arvense, known as "horsetail," is mainly used for its diuretic properties. There are limited data about the pharmacological properties of this compound and the potential drug-herb interactions. The authors report 2 cases in which a possible drug-herb interaction may have led to virological breakthrough in patients who were maintained on the same regimen for many years, including lamivudine (3TC)/zidovudine (ZDV)/efavirenz (EFV) and emtricitabine (FTC)/tenofovir (TDF)/EFV, respectively. Therefore, a drug-herb interaction may be expected when these agents are taken concurrently. Until additional data are available, the authors advise clinicians to avoid this combination when possible.

In 2000 an estimated pound sterling 335 x 106 was spent on food supplements and herbal remedies in the UK. Until recently, The Trades Description Act 1968, the Food Safety Act 1990 and The Food Labelling Regulations 1996 (amended 2004) were the only form of regulation available to protect the public. The medical community has been concerned about the risk to patients of inaccurate dosages and poor-quality products as well as drug-nutrient and nutrient-nutrient interactions. Following growing concern about the type and quality of food supplements and herbal remedies available in the EU, the European Commission has published directives regulating food supplements (2002/46/EC) and herbal remedies (2004/24/EC and 2004/27/EC) available within the EU. The directives came into force in 2005 and limit the number and

quality of permitted food supplements through the creation of a 'positive list' of approved supplements. In the present paper the new regulatory frameworks and the implications for the food supplement manufacturers, traditional and complementary therapists, the healthcare professions and patients will be examined. It would appear that there is considerable dissatisfaction with the regulations in their present form

Experimental evidence is accumulating to suggest that medicinal botanicals have anti-inflammatory and pain-alleviating properties and hold promise for treatment of endometriosis. Herein, we present a systematic review of clinical and experimental data on the use of medicinal herbs in the treatment of endometriosis. Although there is a general lack of evidence from clinical studies on the potential efficacy of medicinal herbs for the treatment of endometriosis-associated symptoms, our review highlights the anti-inflammatory and pain-alleviating mechanisms of action of herbal remedies. Medicinal herbs and their active components exhibit cytokine-suppressive, COX-2-inhibiting, antioxidant, sedative and pain-alleviating properties. Each of these mechanisms of action would be predicted to have salutary effects in endometriosis. Better understanding of the mechanisms of action, toxicity and herb-herb and herb-drug interactions permits the optimization of design and execution of complementary alternative medicine trials for endometriosis-associated pain. A potential benefit of herbal therapy is the likelihood of synergistic interactions within individual or combinations of plants. In this sense, phytotherapies may be analogous to nutraceuticals or whole food nutrition. We encourage the development of herbal analogues and establishment of special, simplified registration procedures for certain medicinal products, particularly herbal derivates with a long tradition of safe use.

Guanxin Shutong Capsule, an effective traditional Chinese medicine, is widely used for coronary heart disease clinically. Volatile components are one of its important bioactive constituents. To better understand the material basis for the therapeutic effects, the components of Guanxin Shutong Capsule absorbed into the blood and their metabolites were identified based on gas chromatography with mass spectrometry coupled with vortex-ultrasound-assisted dispersive liquid-liquid microextraction. As a result, three prototypes and 15 metabolites were identified or tentatively characterized in rat plasma. Subsequently, a pharmacokinetic study was carried out to monitor the concentrations of the main bioactive constituents and metabolites (isoborneol, borneol, eugenol, and camphor) by gas chromatography with mass spectrometry in rat plasma following oral administration of single herb extract and different combinations of herbs in this prescription. Compared to other groups, a statistically significant difference of the pharmacokinetic properties was obtained when the total complex prescription was administered, indicating possible drug-drug interactions among the complex ingredients of Guanxin Shutong Capsule. These findings provided an experimental basis concerning the clinical application and medicinal efficacy of Guanxin Shutong Capsule in the treatment of coronary heart disease.

A multi-billion dollar industry has evolved over the last decade based on herbal product sales with an underlying belief that herbals are natural and therefore safe. The herbal product industry is essentially unregulated and producers are not required to follow good manufacturing practices (GMP). Batch to batch product variation, heavy metal and pesticide contamination, and even therapeutic drug contamination are problematic. Compounding these manufacturing issues are drug to drug and drug to herbal interactions that can cause cytochrome induction or inhibition. It is important for physicians to query their patients on herbal use and educate them on the potential adverse reactions. Herbals have been used for thousands of years and undoubtedly have demonstrated health benefits. However, more research is needed to gain an understanding of the complexity issues from mechanism of action to interference with clinical laboratory testing.

Many patients with rheumatological conditions use herbal remedies as an adjunct to their conventional antirheumatic medication, often without seeking advice. Herbal remedies are exempt from the usual drug

safety requirements and may be a cause of both adverse effects and drug interactions. Data on interactions between herbal remedies and conventional antirheumatic medication is scarce. Reasons include a perception that herbal remedies are safe, a lack of reporting by patients and healthcare professionals and a lack of knowledge about the pharmacology and composition of herbal remedies, as well as adulteration. Interactions are likely between herbal remedies with antiplatelet or nephrotoxic effects and NSAIDs, hepatotoxic herbal remedies and disease-modifying antirheumatic medication, and between St. John's Wort and cyclosporin.

This review considers the potential of certain dietary supplements, including garlic, Ginkgo biloba, ginger, ginseng, fish oil, and vitamin E, to interfere with hemostasis. Dietary supplements are common components of the diet in the United States, with about half the US adult population taking some type of dietary supplement regularly. It has been suggested that some supplements could adversely affect coagulation when taken alone or in combination with antiplatelet medications. Supplements could alter hemostasis by a variety of mechanisms, such as reducing platelet aggregation or inhibiting arachidonic acid, a cellular signaling messenger and inflammatory intermediate. To conduct this review, multiple databases were searched using a variety of search terms to ensure relevant papers were located. Moderate to severe adverse events, such as spinal epidural hematoma, spontaneous intracerebral hemorrhage, retrobulbar hemorrhage, subarachnoid hemorrhage, spontaneous hyphema, and postoperative bleeding, have occasionally been anecdotally associated with consumption of dietary supplements. However, the number of controlled studies in the literature is too limited to demonstrate consistent anticoagulant effects of dietary supplements alone or in combination with drug therapy.

Tongmai Yangxin (TMYX) Pill is a traditional Chinese patent medicine, composed of eleven Chinese medicinal herbs. It has been used to treat coronary heart disease for several decades. In this study, six male Sprague-Dawley rats were dosed orally with TMYX methanol extract, and a serum pharmacochemistry technique was used to screen absorbed bioactive compounds by UPLC/Q-TOF-MS. By comparing MS spectra to the published literature data, 40 bioactive components were identified. The results indicated that almost 45% of the absorbed compounds were from Radix Glycyrrhizae (GC). Subsequently, a reliable HPLC method was used to determine the concentrations of liquiritin, liquiritigenin, isoliquiritigenin, glycyrrhizic acid, and glycyrrhetinic acid in rat plasma following oral administration of GC or the combination of GC and Ramulus Cinnamomi (GZ). The results showed that GZ enhanced the absorption of four bioactive components: liquiritigenin, isoliquiritigenin, glycyrrhizic acid, and glycyrrhetinic acid. The data demonstrate that herb combination in TMYX Pill exhibit a synergistic action.

Panax ginseng C. A. Meyer is a perennial herb native to Korea and China and has been used as an herbal remedy in eastern Asia for thousands of years. Modern therapeutic claims refer to vitality, immune function, cancer, cardiovascular diseases, improvement of cognitive and physical performance and sexual function. A recent systematic review of randomised controlled trials found that the efficacy of ginseng root extract could not be established beyond doubt for any of these indications. In order to obtain a balanced assessment of the therapeutic value of P. ginseng it is also necessary to consider the safety profile. In view of the extremely widespread use of P. ginseng it seems important to ask whether this herbal medicine involves health risks for the consumer. This review was conducted as a systematic attempt to document and evaluate all the available safety data on P. ginseng root extracts. Systematic searches were performed in five electronic databases and the reference lists of all papers located were checked for further relevant publications. All articles containing original data on adverse events and drug interactions with P. ginseng were included. Information was also requested from 12 manufacturers of ginseng preparations, the spontaneous reporting schemes of the WHO and national drug safety bodies. No language restrictions were imposed. Data from clinical trials suggest that the incidence of adverse events with ginseng

monopreparations is similar to that with placebo. The most commonly experienced adverse events are headache, sleep and gastrointestinal disorders. The possibility of more serious adverse events is indicated in isolated case reports and data from spontaneous reporting schemes; however, causality is often difficult to determine from the evidence provided. Combination products containing ginseng as one of several constituents have been associated with serious adverse events and even fatalities. Interpretation of these cases is difficult as ingredients other than P. ginseng may have caused the problems. Possible drug interactions have been reported between P. ginseng and warfarin, phenelzine and alcohol. Collectively, these data suggest that P. ginseng monopreparations are rarely associated with adverse events or drug interactions. The ones that are documented are usually mild and transient. Combined preparations are more often associated with such events but causal attribution is usually not possible.

Synergistic interactions are of vital importance in phytomedicines, to explain difficulties in always isolating a single active ingredient, and explain the efficacy of apparently low doses of active constituents in a herbal product. This concept, that a whole or partially purified extract of a plant offers advantages over a single isolated ingredient, also underpins the philosophy of herbal medicine. Evidence to support the occurrence of synergy in within phytomedicines is now accumulating and is reviewed here. Synergistic interactions are documented for constituents within a total extract of a single herb, as well as between different herbs in a formulation. Positive and negative aspects of interactions are discussed together with the methods used to identify and measure synergy. The evidence is divided into experimental, in vitro instances, as well as clinical examples where available. Herbs discussed include Ginkgo biloba, Piper methysticum (Kava-Kava), Glycyrrhiza glabra, Hypericum perforatum, Valeriana officinalis, Cannabis sativa, Salix alba and others.

While potential medication-to-medication interaction alerting engines exist in many clinical applications, few systems exist to automatically alert on potential medication to herbal supplement interactions. We have developed a preliminary knowledge base and rules alerting engine that detects 259 potential interactions between 9 supplements, 62 cardiac medications, and 19 drug classes. The rules engine takes into consideration 12 patient risk factors and 30 interaction warning signs to help determine which of three different alert levels to categorize each potential interaction. A formative evaluation was conducted with two clinicians to set initial thresholds for each alert level. Additional work is planned add more supplement interactions, risk factors, and warning signs as well as to continue to set and adjust the inputs and thresholds for each potential interaction.

Synergy is a process in which some substances cooperate to reach a combined effect that is greater than the sum of their separate effects. It can be considered a natural "straight" strategy which has evolved by nature to obtain more efficacy at low cost. In this regard, synergistic effects may be observed in the interaction between herbal products and conventional drugs or biochemical compounds. It is important to identify and exploit these interactions since any improvement brought by such kind of process can be advantageously used to treat human disorders. Even in a complex disease such as cancer, positive synergistic plant-drug interactions should be investigated to achieve the best outcomes, including providing a greater benefit to patients or avoiding adverse side effects. This review analyzes and summarizes the current knowledge on the synergistic effects of plant-drug interactions with a focus on anticancer strategies.

The first reports of interstitial fibrosis leading to rapidly progressing chronic renal failure (CRF) in young women undergoing slimming treatment appeared at the beginning of the 1990s in Belgium. These slimming pills erroneously contained powdered roots of plants - picked in China - belonging to the Aristolochia instead of Stephania tetranda family. In the following years, after new cases had occurred worldwide, the term aristolochic acid nephropathy (AAN) came into use. Despite numerous warnings from various post-marketing surveillance institutes, products containing aristolochic acid are still widely used by Asiatic

herbal practitioners and easily available on the Internet, where they are marketed without being subject to any regulations. In 2002 the IARC (International Agency for Research on Cancer) conclusively recognized the urothelial carcinogenicity of aristolochic acid. Because of the globalization and the growing use of phytotherapy worldwide, nephrologists should take into account AAN as a possible cause of CRF. In addition to assessing the direct kidney toxicity caused by some products used in phytotherapy, the authors conclude that it is necessary to research more closely possible drug interactions and side effects of commonly used herbs such as Echinacea, Gingko biloba, St. John's wort, ginseng, and garlic, which patients consider to be natural, non-toxic and self-prescribed remedies and whose use they therefore seldom disclose to their doctors.

Various reports suggest a high contemporaneous prevalence of herb-drug use in both developed and developing countries. The World Health Organisation indicates that 80% of the Asian and African populations rely on traditional medicine as the primary method for their health care needs. Since time immemorial and despite the beneficial and traditional roles of herbs in different communities, the toxicity and herb-drug interactions that emanate from this practice have led to severe adverse effects and fatalities. As a result of the perception that herbal medicinal products have low risk, consumers usually disregard any association between their use and any adverse reactions hence leading to underreporting of adverse reactions. This is particularly common in developing countries and has led to a paucity of scientific data regarding the toxicity and interactions of locally used traditional herbal medicine. Other factors like general lack of compositional and toxicological information of herbs and poor quality of adverse reaction case reports present hurdles which are highly underestimated by the population in the developing world. This review paper addresses these toxicological challenges and calls for natural health product regulations as well as for protocols and guidance documents on safety and toxicity testing of herbal medicinal products.

More than 15 million people in the U.S. consume herbal remedies or high-dose vitamins. The number of visits to providers of complementary and alternative medicine exceeds those to primary care physicians, for annual out-of-pocket costs of $30 billion. Use of herbal products forms the bulk of treatments, particularly by elderly people who also consume multiple prescription medications for comorbid conditions, which increases the risk of adverse herb-drug-disease interactions. Despite the paucity of scientific evidence supporting the safety or efficacy of herbal products, their widespread promotion in the popular media and the unsubstantiated health care claims about their efficacy drive consumer demand. In this review, we highlight commonly used herbs and their interactions with cardiovascular drugs. We also discuss health-related issues of herbal products and suggest ways to improve their safety to better protect the public from untoward effects.

Use of alternative medicines may significantly alter laboratory results, and communication among pathologists, clinical laboratory scientists, and physicians providing care to the patient is important in interpreting these results.

Approximately one in 55 hospitalizations in this study may have been caused by adverse events associated with DHS-drug-DHS interactions. To minimize the actual occurrence of adverse events, medical staff education regarding DHS should be improved.

It is suggested that health care professionals and consumers should be aware of the potential for adverse interactions with these herbs, question their patients on their use of them, especially among patients whose disease is not responding to treatments as expected, and urge patients to avoid herbs that could confound their cancer care

Due to the unique cultural factors that have resulted in widespread acceptance of both western and traditional Chinese medicine, Taiwan stands well positioned to report on the prevalence of interactions between western drugs and traditional Chinese medicine and devise ways to reduce their incidence. This study built a multi-herb/western drug interactions database, embedded inside a hospital clinical information system, and then examined the effects that drug interaction alerts had on clinician prescribing behaviour. The results demonstrated that western drug/traditional Chinese medicine interactions are prevalent and that western-trained physicians tend to change their prescribing behaviour more than traditional Chinese medicine physicians in their response to medication interaction alerts.

Echinacea purpurea, Echinacea angustifoli and Echinacea pallida are frequently used as medicinal plants. Besides asking for evidence on their efficacy, there is an increasing interest for safety data. This review systematically presents the available literature on drug interactions, contraindications, adverse events, duration of use, and safety of use in pregnant and nursing women, and assesses the safety profile of corresponding Echinacea preparations. It is noteworthy that all safety data reported are as product specific as the pharmacological or efficacy data are. In pharmacokinetic herb-drug interaction studies performed in vivo, no significant inhibitions of human CYP2D6 and CYP3A4 isoforms have been found after the administration of standardized E. purpurea preparations. However, contradictory results exist in studies using liver microsomes. Adverse events reported during clinical trials following administration of Echinacea spp. mono-preparations were generally mild and mostly without causality. Due to published long term studies with continuous ingestion of different Echinacea preparations up to 6 month with no reported toxicological concerns, Echinacea can be recommended also for long-term use. Moreover, the contraindications in cases of autoimmune diseases and immune-suppression are questionable, since lipophilic Echinacea preparations containing alkamides suppress cellular immune responses, and beneficial effects in autoimmunity were reported. The same applies for the use during pregnancy. Although there has been some impact reported on embryonic angiogenesis in mice, no association with an increased risk for major or minor malformations during organogenesis was found in a literature review. Altogether, the different evaluated Echinacea preparations are well-tolerated herbal medicines in the management in children and adults alike.

The safety and efficacy of herbal medicines remain major issues of concern especially in the developing world where the use is high. The World Health Organisation estimates up to 80% of the population in Africa relies on herbal medicines for treatment of many diseases. Minimum safety evaluations need to be done for both the herbal and conventional drugs, in particular when there is a high likelihood of co-administration. This is particularly important in Africa where there is increased access to antiretrovirals in the treatment of HIV/AIDS, which are being used in a population background characterized by rampant use of herbal medicines. Many techniques used in the discovery and evaluation of conventional drugs can be adapted to herbal medicines. Such evaluations will add value to herbal medicines as doctors and patients will be better informed on which drugs and herbal medicines to take or not take together. This can also lead to the adoption of guidelines by regulatory agents such as the European Medicines Agency (EMA), Food and Drug Administration (FDA) and governmental agencies controlling the use of medicines. Of current interest is the evaluation of drug-herb interactions (DHI) involving the absorption, distribution, metabolism and excretion (ADME) of medicines where there is a promising possibility to adopt the current FDA and EMA guidelines on the evaluation of herbal medicines for drug-drug interactions (DDI). In this review we demonstrate progress made so far in DHI and point to possible future developments that will contribute to the safe use of herbal medicines.

As complementary and alternative medicines become increasingly used alongside and with conventional drug therapy, there needs to be greater awareness and discussion among parents, complementary

practitioners and medical practitioners to ensure the overall health and safety of children being exposed to these products.

A large number of herbal remedies (e.g. garlic, mistletoe, Essiac, Lingzhi, and astragalus) are used by cancer patients for treating the cancer and/or reducing the toxicities of chemotherapeutic drugs. Some herbal medicines have shown potentially beneficial effects on cancer progression and may ameliorate chemotherapy-induced toxicities. However, there is no or weak scientific basis for the clinical use of these herbal medicines in cancer management and almost none of these plant medicines have been tested in rigorous clinical trials. There are increased reports on the interaction of herbal medicines and anticancer drugs that is becoming a safety concern. For example, a clinical study in cancer patients reported that treatment of St John's wort at 900 mg/day orally for 18 days decreased the plasma levels of the active metabolite of irinotecan, SN-38, by 42%. In healthy subjects, 2 weeks of treatment with St John's wort at 900 mg/day significantly decreased the systemic exposure of imatinib by 32%. In women with advanced breast cancer, coadministration of garlic supplement reduced the clearance of docetaxol by 23.1-35.1%, although the difference did not achieve statistical significance. Most anticancer drugs undergo Phase I and/or II metabolism and are substrates of P-glycoprotein, breast cancer resistance protein, multidrug resistance associated proteins, and/or other transporters. Induction and inhibition of these enzymes and transporters is considered an important mechanism for herb-anticancer drug interactions. Further studies are warranted to investigate potentially harmful herbal interactions with anticancer drugs in patients.

Morus alba L. (mulberry) is a well-known deciduous tree, belonging to the genus of Morus of Moraceae famlily. Its leaves, twigs, roots (bark) and fruits are widely used in the traditional Chinese medicine. The active constituents of mulberry contained flavonoids, alkaloids, steroids, coumarins, with the significant hypoglycemic, hypolipidemic, antihypertension, anti-oxidation, anti-inflammatory, anti-bacterial, anti-tumor and immunomodulatory activities. This review summarized the research progress of the major pharmacological activity, pharmacokinetics and drug-drug interaction based on CYPs and transporters of mulberry and its active constituents.

The use of traditional herbal medicines has become increasingly popular globally, but in some countries, it is the main or sometimes even the only healthcare service available in the most rural areas. This is especially true for Africa where herbal medicines form a key component of traditional medicinal practices and there is access to a diversity of medicinal plants. Although many benefits have been derived from the use of traditional herbal medicines, many concerns are associated with their use of which herb-drug interactions have been identified to have a rising impact on patient treatment outcome. One type of pharmacokinetic interaction involves the modulation of drug metabolizing enzymes, which may result in enhanced or reduced bioavailability of co-administered drugs. Areas covered: This review highlights the current information available on drug metabolism-associated information with regards to traditional African medicines related to some of the most prevalent diseases burdening the African continent. Expert opinion: It is clear from previous studies that enzyme modulation by traditional African medicines plays a significant role in the pharmacokinetics of some co-administered drugs, but more research is needed to provide detailed information on these interactions, specifically for treatment of prevalent diseases such as tuberculosis and hypertension.

Many herbal medications are used to treat diseases but while they are often efficacious, their safety is rarely considered by physicians or users. One particular safety concern is the risk of interactions with drugs, which often lead to toxicity or loss of therapeutic efficacy. In order to assess this risk, it is important to consider all potential mechanisms of pharmacokinetic interference. A large number of in vivo and invitro experiments and clinical studies have cast light on the possible effects of botanical products and phytochemicals on the many enzymes and transporters involved in gastrointestinal drug absorption. This

review gives an overview and assessment of the most widely sold herbal medicinal products, including liquorice, garlic, ginger, ginkgo, green tea, St. John's wort, saw palmetto, turmeric, valerian, milk thistle and echinacea, on the basis of the available scientific evidence. Sound knowledge of the mechanisms of herb-drug interactions is essential for clinical risk assessment, in turn vital to healthcare practitioners in their efforts to reduce minimise risk and ensure that taking herbal medicinal products is as safe as possible.

Future research of herbal products for menopausal women should include long-term safety assessments because women may use these products for prolonged periods of time. Growing numbers of women take prescription medications and concurrently use herbal products for alleviation of menopausal symptoms. Because of possible herb-drug interactions, both drug and supplement manufacturers should provide basic pharmacokinetic data to reduce the risk of adverse interactions. In addition, herbal products produced to high quality standards are essential for ensuring consumer safety. Regulatory frameworks must be in place to ensure that herbal ingredients' identities have been verified, that they have been properly quantified per unit dose, that the product is within tolerance limits for contaminants, that the product's safety and effectiveness under the recommended conditions of use have been assessed before sale to the public, and that a system is in place to detect and deal with adverse reactions when they arise. This article explores these and related concerns.

The berries of Lycium barbarum, a perennial plant native to Asia and southeastern Europe, have been used for centuries in traditional Chinese medicine to treat poor vision, anemia, inflammation, and cough. They are also consumed as food and used in soup recipes. Lycium has gained immense popularity in the United States over the past decade because of its antioxidant properties. It is available in health food stores and is marketed via the Internet in juice form, typically blended with the juices of other berries and fruits. A wide range of health benefits, including cancer prevention and treatment, have been claimed for lycium.

St. John's wort (Hypericum perforatum) has been extensively studied and reviewed for its use in depression; however, there is less salient discussion on its clinical application for a range of other psychiatric disorders. This article outlines the current evidence of the efficacy of St John's wort in common psychiatric disorders, including major depression, bipolar depression, attention-deficit hyperactivity disorder, obsessive-compulsive disorder, social phobia, and somatization disorder. Mechanisms of action, including emerging pharmacogenetic data, safety, and clinical considerations are also detailed.

Herbal medicines supported by evidence of safety and efficacy in the treatment of anxiety, insomnia, fatigue, cognitive enhancement, mental focus, and sexual function are useful as monotherapies, multiherb combinations, and as adjuncts to prescription psychotropics. Relevant mechanisms of action and clinical guidelines for herbs in common use can assist clinicians who want to enhance treatment outcomes by integrating phytomedicinals into their treatment regimens. Research is needed to strengthen the evidence base and to expand the range of disorders that can be treated with herbal extracts. Studies of herbal genomic effects may lead to more targeted and effective treatments.

The use of herbal complementary and alternative medicines is growing among Portuguese cancer patients, contributing to a higher risk for unwanted interactions, especially due to the narrow therapeutic index of most oncolytic drugs. A literature review was carried out in order to determine which medicinal plants are most commonly used by cancer patients, in Europe and USA, and their risk of interaction with the multiple medications taken by those patients. The collected information reveals a high degree of herb-drug interaction suggesting that patients under antineoplastic treatments should avoid the concomitant use of herbal medicines. These findings show that it is extremely important to have a clear knowledge of the herbal complementary and alternative medicines used by Portuguese cancer patients and to assess healthcare professionals' familiarity and attitude towards its use by cancer patients.

In 2012, USA Food and Drug Administration (FDA) approved 39 new drugs, however, there are only two botanical drugs (one topical and one oral) approved by FDA since the publication of the FDA's industry guidelines for the botanical drug product in June 2004. The approval shows the Western guideline can be used for herbal medicines, authors investigate current regulation on herbal medicine clinical research, identify challenges conducting clinical trials, and seek to produce some guidance for potential investigators and sponsors considering a clinical trial in this area. Key words were formulated for searching on Medline and FDA website to locate relevant regulations for clinical research in herbal medicines to understand current environment for herbal medicine usage and examine the barriers affecting herbal medicine in clinical trials. Authors critically explore case study of the 1st FDA approved botanical drugs, Veregen (sinecatechins), green tea leaves extract, a topical cream for perianal and genital condyloma. In consideration of current regulation environment in USA, based on the findings and analysis through the literature review and Veregen case study, authors produce and propose a Checklist for New Drug Application of Herbal Medicines for potential investigators and sponsors considering in a herbal medicine clinical trial.

Many important drugs in the Chinese materia medica (CMM) are known to be toxic, and it has long been recognized in classical Chinese medical theory that toxicity can arise directly from the components of a single CMM or may be induced by an interaction between combined CMM. Traditional Chinese Medicine presents a unique set of pharmaceutical theories that include particular methods for processing, combining and decocting, and these techniques contribute to reducing toxicity as well as enhancing efficacy. The current classification of toxic CMM drugs, traditional methods for processing toxic CMM and the prohibited use of certain combinations, is based on traditional experience and ancient texts and monographs, but accumulating evidence increasingly supports their use to eliminate or reduce toxicity. Modern methods are now being used to evaluate the safety of CMM; however, a new system for describing the toxicity of Chinese herbal medicines may need to be established to take into account those herbs whose toxicity is delayed or otherwise hidden, and which have not been incorporated into the traditional classification. This review explains the existing classification and justifies it where appropriate, using experimental results often originally published in Chinese and previously not available outside China.

St. John's wort (Hypericum perforatum, SJW) is one of the most commonly used herbal antidepressants for the treatment of minor to moderate depression. A major safety concern about SJW is its ability to alter the pharmacokinetics and/or clinical response of a variety of clinically important drugs that have distinctive chemical structure, mechanism of action and metabolic pathways. This review highlights and updates the knowledge on clinical interactions of prescribed drugs with SJW and the implication in drug development. A number of clinically significant interactions of SJW have been identified with conventional drugs, including anticancer agents (imatinib and irinotecan), anti-HIV agents (e.g. indinavir, lamivudine and nevirapine), anti-inflammatory agents (e.g. ibuprofen and fexofenadine), antimicrobial agents (e.g. erythromycin and voriconazole), cardiovascular drugs (e.g. digoxin, ivabradine, warfarin, verapamil, nifedipine and talinolol), central nervous system agents (e.g. amitriptyline, buspirone, phenytoin, methadone, midazolam, alprazolam, and sertraline), hypoglycaemic agents (e.g. tolbutamide and gliclazide), immuno-modulating agents (e.g. cyclosporine and tacrolimus), oral contraceptives, proton pump inhibitor (e.g. omeprazole), respiratory system agent (e.g. theophylline), statins (e.g. atorvastatin and pravastatin). Both pharmacokinetic and pharmacodynamic components may play a role in the interactions of drugs with SJW. For pharmacokinetic changes of drugs by SJW, induction of cytochrome P450s (e.g. CYP2C9 and 3A4) and P-glycoprotein (P-gp) are considered the major mechanism. Thus, it is not a surprise that many drugs that interact with SJW are substrates of CYP3A4, CYP2C9 and P-gp. A comprehensive understanding of clinical drugs that interact with SJW has important implications in drug development. New drugs may be designed to minimize interactions with SJW; and new SJW formulations may be

designed to avoid drug interactions. Further clinical and mechanistic studies are warranted to explore the interaction of SJW with other important drugs and the potential clinical impact.

Complementary and alternative medicine (CAM) represent a group of diverse medical and health care systems, practices, and products that are not considered to be part of conventional medicine. Biofeedback, acupuncture, herbal medication, massage, bioelectromagnetic therapy, meditation, and music therapy are examples of CAM treatments. Some dentists in the United States have used some of these treatments and products in their practices. Complementary medicines include herbal remedies, homeopathic medicines, and essential oils. There has been an increase in the use of herbal medicines in the US over the last 15-20 years. There is a public belief that these medicines are safe because they are made from natural sources. However, some of these products have associated adverse effects including toxicity and drug interactions. The health history taken by the dentist should include questions regarding the taking of herbal and over-the-counter medications. The dentist needs to be informed regarding the herbal and over-the-counter products that may impact the delivery of safe and effective dental treatment. In addition, the use of CAM treatments in dentistry should be based on evidence of effectiveness and safety as demonstrated in randomized clinical trials.

The use of herbal products in the UK is increasing, and over-the-counter herbal supplements are perceived by the public as 'safe' and 'harmless'. Although the majority of them are safe, some herbal medicines carry risks. Heavy metal contamination, adulteration with Western pharmaceuticals and inclusion of prohibited animal and plant ingredients are regularly reported in ethnic medicines. Other herbs are hepato- or nephrotoxic and some interact with prescription medicines. Doctors should be made aware of the need to take a herbal as well as a drug history, and the clinical laboratory has a role in helping understanding of how herbal products may affect laboratory tests and in suggesting relevant lines of investigation in patients whose symptoms may be linked to the use of herbal products.

Multiple Sclerosis (MS) is a demyelinating disease affecting the central nervous system, with no curative medicine available. The use of herbal drugs and dietary supplements is increasing among people with MS (PwMS), raising a need for knowledge about potential interactions between conventional MS medicine and herbal drugs/dietary supplements. This systematic review provides information about the safety of simultaneous use of conventional MS-drugs and herbal drugs frequently used by PwMS. The study included 14 selected disease-modifying treatments and drugs frequently used for symptom-alleviation. A total of 129 published papers found via PubMed and Web of Science were reviewed according to defined inclusion- and exclusion criteria. Findings suggested that daily recommended doses of Panax ginseng and Ginkgo biloba should not be exceeded, and herbal preparations differing from standardized products should be avoided, especially when combined with anticoagulants or substrates of certain cytochrome P450 isoforms. Further studies are required regarding ginseng's ability to increase aspirin bioavailability. Combinations between chronic cannabis use and selective serotonin reuptake inhibitors or non-steroidal antiinflammatory drugs should be carefully monitored, whereas no significant evidence for drug-interactions between conventional MS-drugs and ginger, cranberry, vitamin D, fatty acids, turmeric, probiotics or glucosamine was found.

The literature abounds with reports on the utilization of herbal medications for the treatment of diabetes mellitus since time immemorial, but very few of these herbal products have undergone clinical trials. Also, studies on the herb-drug interactions were limited. Due to the complex phytochemical composition of the herbs, concomitant administration with conventional drugs resulted in alterations of pharmacological effects of some drugs. Evidences of beneficial interactions were identified for medical exploitation.

Methylophiopogonanone A (MOA), an abundant homoisoflavonoid bearing a methylenedioxyphenyl moiety, is one of the major constituents in the Chinese herb *Ophiopogon japonicas* This work aims to assess the inhibitory potentials of MOA against cytochrome P450 enzymes and to decipher the molecular mechanisms for P450 inhibition by MOA. The results showed that MOA concentration-dependently inhibited CYP1A, 2C8, 2C9, 2C19, and 3A in human liver microsomes (HLMs) in a reversible way, with IC_{50} values varying from 1.06 to 3.43 μM. By contrast, MOA time-, concentration-, and NADPH-dependently inhibited CYP2D6 and CYP2E1, along with K_I and k_{inact} values of 207 μM and 0.07 $minute^{-1}$ for CYP2D6, as well as 20.9 μM and 0.03 $minutes^{-1}$ for CYP2E1. Further investigations demonstrated that a quinone metabolite of MOA could be trapped by glutathione in an HLM incubation system, and CYP2D6, 1A2, and 2E1 were the major contributors to catalyze the metabolic activation of MOA to the corresponding *O*-quinone intermediate. Additionally, the potential risks of herb-drug interactions triggered by MOA or MOA-related products were also predicted. Collectively, our findings verify that MOA is a reversible inhibitor of CYP1A, 2C8, 2C9, 2C19, and 3A but acts as an inactivator of CYP2D6 and CYP2E1. SIGNIFICANCE STATEMENT: Methylophiopogonanone A (MOA), an abundant homoisoflavonoid isolated from the Chinese herb *Ophiopogon japonicas*, is a reversible inhibitor of CYP1A, 2C8, 2C9, 2C19, and 3A but acts as an inactivator of CYP2D6 and CYP2E1. Further investigations demonstrated that a quinone metabolite of MOA could be trapped by glutathione in a human liver microsome incubation system, and CYP2D6, 1A2, and 2E1 were the major contributors to catalyze the metabolic activation of MOA to the corresponding *O*-quinone intermediate.

Herbal medicines were the "sole" source of medicine for thousands of years, in every culture since the advent of human civilization. Today, patients are increasing the use of these botanicals for numerous conditions, such as mood and cognition. This article will explore commonly used herbal remedies for mood and cognition functioning. It is imperative that nurses and nurse practitioners obtain expertise with these botanicals with regard to efficacy, adverse effects and contraindications, possible drug interactions, and safety considerations.

While the use of health food and over-the-counter drugs for health promotion and adjuvant therapy is becoming increasingly popular, the concern about adverse effects is mounting. The possible adverse effects that may arise from drug interactions between these herbal preparations and standard modem therapy are equally worrying. Herbal toxicity and adverse effects are well documented in classical Chinese medicinal volumes. Interactions between herbal preparations and standard modem therapy are known. Extensive work needs to be done before useful guidelines can be established. However, based on available reports and clinical observations, some commonly used herbs and Chinese medicines have already demonstrated the need for special attention when used together with modern therapy. This paper analyzes the important material already available, and would serve as a preliminary checklist for patients who are taking herbal preparations, while at the same time receiving treatment from modern medicine

The aim of this work is to provide an update from an overview of the literature of the most frequently consumed herbal remedies during pregnancy, both alone and concomitantly with prescribed medications and particularly on their side effects to the mother and fetus. We have also analyzed some of the adverse interactions that may occur due to concomitant use of herbal and pharmaceutical products during pregnancy. Herbal remedies are not evaluated according to the same standards as pharmaceuticals, and in the USA some of it are not licensed but sold as food supplements. There is a lack of basic knowledge on the part of both clinicians and patients as to the indications for use and safety of herbal medicines used in pregnancy and lactation. If 'traditional use' is the only available information, the pregnant woman should be made aware of this to enable her to make an informed decision concerning potential use.

Web site developers should be cautious in presenting drug-CAM interaction information unless it is comprehensive and regularly maintained. Consumers should also know how to evaluate sites before trusting the content where the consequences are potentially severe.

Asparagus racemosus Willd. (Asparagaceae) is an important medicinal plant of tropical and subtropical India. Its medicinal usage has been reported in the Indian and British Pharmacopoeias and in traditional systems of medicine such as Ayurveda, Unani and Siddha. Asparagus racemosus is mainly known for its phytoestrogenic properties. With an increasing realization that hormone replacement therapy with synthetic oestrogens is neither as safe nor as effective as previously envisaged, the interest in plant-derived oestrogens has increased tremendously making Asparagus racemosus particularly important. The plant has been shown to aid in the treatment of neurodegenerative disorders and in alcohol abstinence-induced withdrawal symptoms. In Ayurveda, Asparagus racemosus has been described as a rasayana herb and has been used extensively as an adaptogen to increase the non-specific resistance of organisms against a variety of stresses. Besides use in the treatment of diarrhoea and dysentery, the plant also has potent antioxidant, immunostimulant, anti-dyspepsia and antitussive effects. Due to its multiple uses, the demand for Asparagus racemosus is constantly on the rise; however, the supply is rather erratic and inadequate. Destructive harvesting, combined with habitat destruction in the form of deforestation has aggravated the problem. The plant is now considered 'endangered' in its natural habitat. Therefore, the need for conservation of this plant is crucial. This article aims to evaluate the biological activities, pharmacological applications and clinical studies of Asparagus racemosus in an attempt to provide a direction for further research. Keeping in mind the fact that it is the active principle that imparts medicinal value to a plant; consistency in quality and quantity needs to be maintained to ensure uniform drug efficacy. Also, deliberate or inadvertent adulteration needs to be dealt with at an early stage. To overcome these prevalent problems, the availability of genetically superior and uniform planting material is essential. This can be obtained by a combination of various biotechnological tools involving chemoprofiling, tissue culture and use of molecular markers. Along with the application of these methods, proper agro-techniques and adequate marketing opportunities would encourage cultivation of Asparagus racemosus and thereby contribute to its conservation. There are also several gaps in the existing literature with regard to the pharmacological actions of Asparagus racemosus. These include an incomplete understanding about the interaction/synergy between Asparagus racemosus and other plant constituents in polyherbal formulations; lack of information regarding the mode of action of the various constituents of Asparagus racemosus, etc. Consequently, we have suggested a 'systems biology' approach that includes metabolite profiling, metabolic fingerprinting, metabolite target analysis and metabonomics to enable further research.

Evidence for the safety and effectiveness of dietary supplements is mixed. The extent to which older people use dietary supplements concomitantly with conventional medications is often under-appreciated by physicians. We conducted a literature review on clinical considerations associated with dietary supplement use, focusing on benefits and harms, motivations for use and contribution to polypharmacy among older people. Vitamin D $\geq$ 800 IU has demonstrated benefits in fracture prevention. Vitamins A, E, and β-carotene have been associated with an increase in total mortality in several meta-analyses. A range of non-vitamin dietary supplements have been studied in randomized controlled trials but their efficacy remains largely unclear. Supplement use has been associated with a range of adverse events and drug interactions yet physicians rarely initiate discussions about their use with older patients. Older people may take dietary supplements to exercise control over their health. Given the contribution of supplements to polypharmacy, supplements may be targeted for "deprescribing" if the risk of harm is judged to outweigh benefits. This is best done as part of a comprehensive, patient-centered approach. A respectful and non-judgmental discussion may result in a shared decision to reduce polypharmacy through cessation of dietary supplements. KEY MESSAGES Herbal medications and other dietary supplements are highly prevalent

among older people. Physicians are often unaware that their patients use herbal medications and other dietary supplements concomitantly with conventional medications. Herbal medications and other dietary supplements contribute to high rates of polypharmacy, particularly among older people with multimorbidity. Herbal medications and other dietary supplements can interact with conventional medications and be associated with a range of adverse events. Physicians need to be patient-centered and non-judgmental when initiating discussions about herbal medications and other dietary supplements. This is important to maintain and develop patient empowerment and self-management skills.

Although the use of dietary supplements appears to be very common among patients who also take prescription medications, most potential drug-dietary supplement interactions found were not serious. However, literature support was sparse at best. Health care providers should continue to inquire about dietary supplement use and consider the potential for interactions, regardless of their severity.

In the past century, as medical research has become increasingly precise, it has become clear that the incidence and progression of many diseases involve multiple factors and pathologies; this is particularly true for the degenerative and metabolic diseases facing industrialized societies. At the same time, it becomes increasingly clear that single-target action drugs cannot effectively treat these diseases. Researchers are looking toward the chemical industry as well as traditional herbal medicines to find multi-target interventions. Thus, a new era in drug discovery has begun. Specifically, three approaches have proven effective in seeking multi-target drugs. These are: (1) designing drugs with multiple components; (2) discovering drugs through the study of synergistic compound-compound interactions in medicinal herbs or among chemical drugs and herbal components; and (3) developing drugs to tackle complex multi-component diseases. The authors conclude that there is an increasing need for multi-component remedies to treat the complex chronic diseases afflicting modern populations. Given this situation and the growing body of evidence that these new approaches are effective, multi-target intervention appears to have great potential for discovering, designing, and developing effective new drugs for today's diseases.

A wide variation in prevalence of CAM use by patients with diabetes was identified. Healthcare professionals should be aware of their patients' use of CAM to ensure treatment optimization, avoid herb-drug interactions and promote medication adherence in diabetes. Diabetic reviews and clinical guidelines should incorporate exploration of patient use of CAM as many patients do not proactively disclose the use of CAM to their healthcare professionals.

Patients taking SJW concomitantly with CSA or other medications whose absorption and metabolism are mediated by cytochrome P-450 and/or P-glycoprotein should require close monitoring. Potential herb-prescription drug interactions are not just limited to SJW. Inquiries regarding the usage of herbal supplements should be an integral component of a transplant recipient's medication history.

Jordanians have a positive perception towards herbs and their ability to treat diseases. However, their knowledge about food/beverage-drug interactions was poor. There is therefore a need to enhance the community awareness of food/beverage/herb-drug interactions.

Arctiin is the major pharmacological ingredient of Fructus Arctii, and arctigenin is the metabolite of arctiin formed via the catalysis of human intestinal bacteria. The present study aims to investigate the inhibition profile of arctiin and arctigenin on important phase II drug-metabolizing enzymes UDP-glucuronosyltransferases (UGTs), indicating the possible herb-drug interaction. In vitro screening experiment showed that 100 μM of arctiin and arctigenin inhibited the activity of UGT1A3, 1A9, 2B7, and 2B15. Homology modeling-based in silico docking of arctiin and arctigenin into the activity cavity of UGT2B15 showed that hydrogen bonds and hydrophobic interactions contributed to the strong binding free energy of arctiin (-8.14 kcal/mol) and arctigenin (-8.43 kcal/mol) with UGT2B15. Inhibition kinetics study

showed that arctiin and arctigenin exerted competitive and noncompetitive inhibition toward UGT2B15, respectively. The inhibition kinetic parameters (Ki) were calculated to be 16.0 and 76.7 μM for the inhibition of UGT2B15 by arctiin and arctigenin, respectively. Based on the plasma concentration of arctiin and arctigenin after administration of 100 mg/kg of arctiin, the [I]/Ki values were calculated to be 0.3 and 0.007 for arctiin and arctigenin, respectively. Based on the inhibition evaluation standard ([I]/Ki < 0.1, low possibility; 0.1 < [I]/Ki < 1, medium possibility; [I]/Ki > 1, high possibility), arctiin might induce drug-drug interaction with medium possibility. Based on these results, clinical monitoring the utilization of Fructus Arctii is very important and necessary.

Herba Erigerontis injection (HEI) is an aqueous solution derived from whole plants of Erigeron breviscapus, which may be co-administered with warfarin to treat cardiovascular and cerebrovascular disorders. This research was conducted to make sure whether HEI would affect anticoagulation of warfarin to guarantee reasonable medication. The pharmacodynamic study was designed to measure prothrombin time (PT) and activated partial thromboplastin time (APTT) values, and international normalized ratio (INR) values were calculated. For pharmacokinetic study, ultra performance liquid chromatography-tandem mass spectrometer (UPLC-MS/MS) technology was applied to measure plasma concentrations of warfarin enantiomers. The influence of HEI on plasma protein binding rate of warfarin was assessed by ultrafiltration. Pharmacodynamic study demonstrated that both HEI alone and co-administered with warfarin could increase PT and INR values significantly ($P < .01$), whereas the APTT values were unaffected ($P > .05$). Pharmacokinetic study manifested that C_{max} , AUC and $t_{1/2}$ prolonged significantly ($P < .01$) for R/S-warfarin in presence of HEI. Low (3.6 mL/kg), medium (7.2 mL/kg) and high (10.8 mL/kg) doses of HEI could decrease plasma protein binding rate of warfarin significantly ($P < .01$). The results mean that HEI can potentiate the anticoagulant response of warfarin through both pharmacodynamics and pharmacokinetics.

The extensive use of herbal drugs and their multiple components and modes of action suggests that they may also cause drug interactions by changing the activity of human cytochrome P450 enzymes. The purpose of the present review is to present the available data for the top 14 herbal drug sales in the U. S. Studies describing the effects of herbal drugs on phenotyping substrates for individual CYPs were identified by a comprehensive MEDLINE search. Drugs included Allium sativum (Liliaceae), Echinacea purpurea (Asteraceae), Serenoa repens (Arecaceae), Ginkgo biloba (Ginkgoaceae), Vaccinium macrocarpon (Ericaceae), Glycine max (Fabaceae), Panax ginseng (Araliaceae), Actea racemosa (Ranunculaceae), Hypericum perforatum (Hypericaceae), Silybum marianum (Asteraceae), Camellia sinensis (Theaceae), Valeriana officinalis (Valerianaceae), Piper methysticum (Piperaceae), and Hydrastis canadensis (Ranunculaceae) preparations. We identified 70 clinical studies in 69 publications. The majority of the herbal drugs appeared to have no clear effects on most of the CYPs examined. If there was an effect, there was mild inhibition in almost all cases, as seen with garlic or kava effects on CYP2E1 and with soybean components on CYP1A2. The most pronounced effects were induction of CYP3A and other CYPs by St. John's wort and the inhibitory effect of goldenseal on CYP3A and CYP2D6, both being borderline between mild and moderate in magnitude. With the exceptions of St.John's wort and goldenseal, the information currently available suggests that concomitant intake of the herbal drugs addressed here is not a major risk for drugs that are metabolized by CYPs.

Metformin is one of the most common medicines for the treatment of type 2 diabetes, however, recent studies suggest that concomitant antihyperglycemic agents should be administered for better efficacy. Yukmijihwang-tang (YMJHT) is a nephroprotective polyherb prescribed for renal disorders or diabetic mellitus in traditional Korean medicine. Therefore, the pharmacokinetics between metformin and YMJHT were examined for their coadministration. Rats were orally coadministered with metformin and YMJHT as

a combination group or metformin and distilled water as the corresponding control. Then, the metformin concentration in plasma and its pharmacokinetic parameters including maximum concentration (C_{max}) and area under the plasma concentration time curve (AUC) were analyzed. There were no interactions between metformin and YMJHT in the single coadministration at intervals within 5 min. However, pretreatments with YMJHT for 6 days increased the metformin concentration and its C_{max} and AUC ($p<0.05$). The repeated coadministration for 8 days increased the C_{max} of metformin ($p<0.05$). Conversely, when the combination was coadministered at 2h -intervals, there were no interactions between metformin and YMJHT after a single dosing or repeated dosing of coadministration for 7 days. These results of the present study will help structure proper dosing regimens for the concomitant therapy of metformin and YMJHT.

In recent years there has been a notable increase in the consumption of medicinal plants in Spanish society. This might be due to the fact that in some cases they have shown themselves to be efficient in treating certain pathologies and to the erroneous perception that these products are innocuous. Medicinal plants behave as authentic medicines since the chemical substances of which they are formed can have a biological activity in humans. For this reason, their joint administration with "conventional medicines" can produce variations in the magnitude of the effect. This type of interaction, just like those produced between two or more medicines, can produce pharmacokinetic mechanisms if they affect the processes of absorption, distribution, metabolism and excretion, or pharmacodynamic mechanisms if they affect the result of the pharmacological action. In the medical literature there are few articles and notifications of cases concerning the adverse effects and interactions that affect medicinal plants, which probably reflects an under-notification of these phenomena. If we add to this the lack of experimental data and controlled studies, perception of their prevalence is difficult or nearly impossible. This article sets out, in an order that will be explained later, the findings of an exhaustive review of the medical literature with the aim of making its existence known to the reader, without going into other considerations, such as the degree of evidence for example, which will be the subject of forthcoming articles.

The specialty of allergy and immunology has seen the second largest increase in the popularity of CAM (second only to practitioners who treat lower back pain). Almost all of the CAM interventions have displayed adverse effects, usually in the form of a hypersensitivity reaction. Allergists and clinical immunologists need to become more knowledgeable about CAM so that they can inform patients about the use and possible abuse of these modalities.

Diabetes mellitus is the most common metabolic disorder. The major cause of mortality and morbidity here is due to the complications caused by increased glucose concentrations. All the available commercial antidiabetic drugs are associated with side effects. The combination therapy could be a new and highly effective therapeutic strategy to manage hyperglycemia. Combination of commercial drugs with phytochemicals may reduce the side effects caused by these synthetic drugs. Herbal products have been thought to be inherently safe, because of their natural origin and traditional use rather than based on systemic studies. New formulation and cocrystallisation strategies need to be adopted to match the bioavailability of the drug and the phytochemical. This review describes in detail, the observed synergy and mechanism of action between phytochemicals and synthetic drugs in effectively combating. The mode of action of combination differs significantly than that of the drugs alone; hence isolating a single component may lose its importance thereby simplifying the task of pharma industries.

The use of herbal supplements is common among the elderly, a population that takes a disproportionate share of prescription medications compared to that taken by younger populations. Among the problems uncovered by these studies was a lack of dialog between medical professionals and patients about the use of herbal supplements. Prescribers need to consider the use of herbal supplements and discuss the matter with their elderly patients when making decisions about pharmacological treatments.

Herbal medicine (HM) use is growing worldwide. Single herb preparations, ethnic and modern HM formulations are widely used as adjunct therapies or to improve consumer wellbeing. Areas covered: This final part in the publication series summarizes common tendencies in HM use as adjunct or alternative medicine, education of healthcare professionals and consumers, current and proposed guidelines regulating of production. We discuss potential HM-HM and HM-drug interactions that could lead to severe adverse events in situations where HMs are taken without proper medical professional oversight. Expert commentary: A number of serious problems have arisen with the steady global increase in HM use. HM interaction with conventional drugs (CD) may result in inadequate dosing of CD or adverse reactions; HM-HM interaction within herbal supplements could lead to toxicity of formulations. Inadequate education of clinicians and patients regarding medicinal properties of HMs must be addressed regionally and globally to ensure consumer safety

Certainly, extensive work is needed to make sure that patients should take a regimen of protective and restorative therapy under an experienced healthcare professional. This article updates on the current knowledge of promising natural products used in neurological disorders.

In recent years, kava kava (Piper methysticum, Forst. f., Piperaceae) has been implicated in a number of liver failure cases. Ever since this has kept the scientific world busy. Even though, on closer inspection, the majority of the case reports are probably not connected to kava intake, hepatotoxic effects of kava cannot generally be ruled out. In this article the major theories as to the mechanism of kava hepatotoxicity are summarized. But in spite of all these hypotheses, there is still no satisfactory answer. In any case, further studies, that might hopefully restore the reputation of kava, are required.

Herbal preparations for depression are often preferred over pharmaceutical drugs because they are available without prescription and because they are commonly assumed to be safe. St. John's wort (SJW) is one of the best-known and best-selling herbal therapies for depression. Meta-analyses of randomized controlled trials of SJW for major depression suggest that SJW is superior to placebo, is similarly effective compared with conventional antidepressant drugs, and tends to have fewer side effects compared with antidepressant agents, but there is a large degree of heterogeneity among the placebo-controlled studies, and trials from German-speaking countries tend to report more favorable findings. A small number of studies suggest SJW is safe to use during pregnancy and breastfeeding. Although SJW is relatively well tolerated, it is prone to many important drug-drug interactions.

Herbal products are being increasingly used all over the world for preventive and therapeutic purposes because of the belief of their safety. They have become an important part of health care system in many countries since they can easily be purchased in the health food stores or online. However, the lack of sufficient study on their efficacy and toxicity, inadequate controls of their availability, reduce their safety. Unlike conventional drugs, herbal products are not regulated for purity and potency. Herbal products contain substances which can induce or inhibit enzymes that take part in drug metabolism. Therefore the concurrent use of drugs with some medicinal plants can cause serious adverse effects and can also decrease the efficacy of the therapy. Particularly, drugs with narrow therapeutic index and plants which can affect drug metabolizing enzymes when used together, may lead to unpredictable adverse reactions. Impurities, contaminants and adulterants found in the herbal products, are the most common malpractises in herbal raw-material trade. In this review the unpredictable adverse effects of herbal products due to their possible interactions with drugs and also due to the adulteration and contamination with prohibited chemicals will be discussed in detail.

Complementary and alternative medicines (CAMs), in particular herbal medicines, are commonly used by cancer patients in conjunction with chemotherapy treatment for their anticancer properties and supportive

care. However, the effects of many of these herbs are not well-documented due to limited studies done on them. Severe herb-drug interactions (HDIs) have been recorded in some cases, and failure to recognize these harmful HDIs can lead to dire consequences in cancer patients. This study discusses clinically-relevant interactions between anticancer drugs (ACDs) and herbs classified into 7 categories: cancer treatment and prevention, immune-system-related, alopecia, nausea and vomiting, peripheral neuropathy and pain, inflammation, and fatigue. Some promising patents which contain these herbs and thus may manifest these interactions are also presented in this article. Pharmacokinetic interactions involved mainly induction or inhibition of the cytochrome P450 isozymes and p-glycoprotein, while pharmacodynamic interactions were related to increased risks of central nervous system-related effects, hepatotoxicity and bleeding, among others. Clinicians should be vigilant when treating cancer patients who take CAMs with concurrent chemotherapy since they face a high risk of HDIs. These HDIs can be minimized or avoided by selecting herb-drug pairs which are less likely to interact. Furthermore, close monitoring of pharmacological effects and plasma drug levels should be carried out to avoid toxicity and ensure adequate chemotherapeutic coverage in patients with cancer.

Students agreed this course prepared them to identify essential oil therapeutic uses and potential essential oil-drug interactions, and interpret literature. The introduction of aromatherapy principles to pharmacy students will prepare a new generation of healthcare professionals on the role of alternative medicines.

Drugs derived from natural resources represent a significant segment of the pharmaceutical market as compared to randomly synthesized compounds. It is a goal of drug development programs to design selective ligands that act on single disease targets to obtain highly effective and safe drugs with low side effects. Although this strategy was successful for many new therapies, there is a marked decline in the number of new drugs introduced into clinical practice over the past decades. One reason for this failure may be due to the fact that the pathogenesis of many diseases is rather multi-factorial in nature and not due to a single cause. Phytotherapy, whose therapeutic efficacy is based on the combined action of a mixture of constituents, offers new treatment opportunities. Because of their biological defence function, plant secondary metabolites act by targeting and disrupting the cell membrane, by binding and inhibiting specific proteins or they adhere to or intercalate into RNA or DNA. Phytotherapeutics may exhibit pharmacological effects by the synergistic or antagonistic interaction of many phytochemicals. Mechanistic reasons for interactions are bioavailability, interference with cellular transport processes, activation of pro-drugs or deactivation of active compounds to inactive metabolites, action of synergistic partners at different points of the same signalling cascade (multi-target effects) or inhibition of binding to target proteins. "-Omics" technologies and systems biology may facilitate unravelling synergistic effects of herbal mixtures.

Concomitant herbal and antipsychotic treatment could produce either beneficial or adverse clinical effects in schizophrenic population. Potential herb-drug pharmacokinetic interactions need to be further evaluated

With the increasing use of herbal supplements by cancer patients, surgical staff need to screen patients pre-surgically for use of these supplements. Clinical practice guidelines are needed for screening and prevention of herbal supplement usage to prevent potential adverse events that may arise from herbal medications taken alone or combined with conventional therapies during the perioperative period.

The present interest and widespread use of herbal remedies has created the possibility of interaction between them and pharmaceutical drugs if they are used simultaneously. Before the recent reports of apparent hepatotoxicity associated with its use, kava (Piper methysticum Forst. F.), was one of the top 10 selling herbal remedies in Europe and North America. This adverse effect was not previously encountered with the traditional beverage which was prepared as a water infusion in contrast to the commercial products which are extracted with organic solvents. Kavalactones, the active principles in kava, are potent inhibitors of

several of the CYP 450 enzymes, suggesting a high potential for causing pharmacokinetic interactions with drugs and other herbs which are metabolized by the same CYP 450 enzymes. Furthermore, some kavalactones have been shown to possess pharmacological effects, such as blockade of GABA receptors and sodium and calcium ion channels, which may lead to pharmacodynamic interactions with other substances which possess similar pharmacological proprieties. St. John's wort (Hypericum perforatum L.), used extensively for the treatment of mild to moderate clinical depression, has long been considered safer than the conventional pharmaceutical agents. However, its ability, through its active constituents hypericin, pseudohypericin and hyperforin, to induce intestinal P-glycoprotein/MRD1 and both intestinal and hepatic CYP3A4 enzyme, could markedly reduce the distribution and disposition of their co-substrates. In addition, St. John's wort is a potent uptake inhibitor of the neurotransmitters serotonin, norepinephrine and dopamine all of which have a role in mood control. Consequently, the very real potential for a pharmacodynamic interaction between the herb and pharmaceutical drugs which share this mechanism of action and, like St. John's wort, are used for mood elevation. However, presently there is very little evidence to substantiate actual pharmacokinetic and/or pharmacodynamic interaction between drugs and kava or St. John's wort. This review provides a brief overview of the existing data on interactions of kava and St. John's wort with pharmaceutical agents and as a result reveals the urgent need for detailed investigations to identify clinically significant interactions for these herbal remedies that have the potential to cause adverse effects.

Recently, the demand for supplements has steadily been increasing with the diffusion of alternative and supplemental medicines throughout the world. Therefore, the supplements have frequently been taken with many drugs. Here, we have introduced the pharmacokinetic and pharmacological interactions between them.

Quercetin (QCN) is commonly used in high doses as a dietary supplement for weight loss. Psychotic patients are at greater risk of developing obesity than the general population. The present study was designed to understand the impact of QCN on the exposure of quetiapine (QTE), an anti-psychotic drug with narrow therapeutic index and brain penetrating capability. The content of QTE in rat plasma was analyzed through liquid chromatography-tandem mass spectrometry. The results showed a significant ($p < 0.05$) increase in exposure of QTE (peroral dosed) in the animals pre-treated with QCN as compared to the control group. All the animals pre-treated with QCN, succumbed to death within 3-5 min of intravenous dosing of QTE (1 mg/kg). The studies in rat liver S9 fraction indicated that QCN could increase the metabolic stability of QTE by inhibiting the activity of CYP enzymes. The brain to plasma ratio of QTE increased upon QCN pre-treatment (2.6 vs 7.7), which could be attributed to P-glycoprotein inhibition at the blood-brain barrier by QCN. The current set of studies indicated that serious herb-drug interaction between QCN and QTE might occur when they are co-administered. Caution is advised for concomitant use of QCN rich dietary supplements with QTE.

Herbal medicinal use has increased dramatically in recent years. The increasing use of these products is of concern, and their use may not be recognized by the treating physicians. Many of these remedies have potential for adverse interactions with medications commonly prescribed for various cardiovascular disorders. Despite their widespread use, limited data exists regarding the efficacy of herbs such as echinacea, garlic, ginseng, gingko, ephedra, and St. John's wort. Of special concern is the ability of herbal remedies to potentiate effects of prescription drugs with a narrow margin of safety. An increasing awareness of the potential for harmful effects of herbal remedies has given the impetus for aggressive interventions to inquire about the use of these agents and systematic reporting of adverse events emanating from their use. This review briefly summarizes important adverse interactions of commonly used herbal remedies with prescription cardiovascular medications.

Approximately 49% of Americans take dietary supplements and spend approximately $15 billion annually. Most patients believe that supplements are innocuous substances, and they use them for added health benefits or for certain diseases. However, problems may be associated with dietary supplement use, including potential side effects and drug interactions. It is important that clinicians are aware of the legislative issues related to supplements, are informed about their risks, and are able to work with their patients to ensure safe use. Evidence-based resources and guides to provide optimal medical care for patients who wish to use supplements are available for clinicians.

Herbal medicines, an important group of multicomponent therapeutics, are widely and increasignly used worldwide. Despite the popularitiy of herbal medicines, the clinical evidence that support the use of most herbal medicines is weak. Pharmacokinetic and absorption, distribution, metabolism and excretion (ADME) studies have been integrated into modern drug development, but ADME studies are generally not needed for herbal remedy discovery and development. For the majority of herbal medicines, data on their ADME and pharmacokinetic properties in humans are lacking or scant. An extensive literature search indicates that there are limited data on ADME properties of herbal medicines in humans. Many herbal compounds undergo Phase I and/or Phase II metabolism in vivo, with cytochrome P450s (CYPs) and uridine diphosphate glucuronosyltransferases (UGTs) playing a major role. Some herbal ingredients are substrates of P-glycoprotein (P-gp/MDR1/ABCB1) which is highly expressed in the intestine, liver, brain and kidney. As such, the activities of these drug metabolizing enzymes and drug transporters are critical determining factors for the in vivo ADME processes of herbal remedies. There are increasing ADME studies of herbal remedies, but these studies are mainly focused on a small number of herbal medicines including St John's wort, milk thistle, curcumin, echinacea, ginseng, ginkgo, and ginger. For an herbal medicine, the pharmacological activity is gained when the active agents or the active metabolites reach and sustain proper levels at their sites of action. Both the dose levels and ADME processes of active herbal components in the body govern their target-site concentrations and thus the therapeutic responses. In this regard, a safe and optimal use of herbal medicines requires a full understanding of their ADME profiles. To optimize the use of herbal remedies, further studies to explore their ADME properties in humans are certainly warranted.

It is estimated that three quarters of the world population rely on herbal and traditional medicine as a basis for primary health care. Therefore, it is one of the most important and challenging tasks for scientists working in drug research to investigate the efficacy of herbal medicine, to dissect favorable from adverse effects, to identify active principles in medicinal plants and to ban poisonous plants or contaminations from herbal mixtures. In the present review, some problems are critically discussed. Botanical misidentification or mislabeling of plant material can play a role for toxic reactions in humans. Some plant descriptions in traditional herbal medicine (e.g. traditional Chinese medicine) have changed over time, which may lead to unintended intoxication by using wrong plants. A problem is also the contamination of herbals with microorganisms, fungal toxins such as aflatoxin, with pesticides and heavy metals. Unprofessional processing, which differs from safe traditional preparation represents another potential source for herbal poisoning. Unwanted effects of herbal products may also develop by the interaction of herbs with conventional drugs upon concomitant intake. The art of herbal medicine is to dissect pharmacologically and therapeutically valuable herbal drugs from harmful and toxic ones and to develop combinations of medicinal plants as safe and efficient herbal remedies. Standardization and strict control measures are necessary to monitor sustainable high quality of herbal products and to exclude contaminations that badly affect patients consuming herbal medicine.

The objective of this study was to evaluate the scientific evidence on the safety and efficacy of Essiac. This review serves as a clinical support tool. Electronic searches were conducted in 10 databases, 20 additional

journals (not indexed in common databases), and bibliographies from 50 selected secondary references. No restrictions were placed on the language or quality of the publications. Standardized inclusion and exclusion criteria were used for selection. A review of the literature on Essiac and essiac formulations showed a lack of high-quality clinical trials to substantiate any of Essiac's traditional uses. Weak evidence from preclinical, animal, and laboratory data warranted a discussion regarding Essiac's use for cancer, but the results are inconclusive. Several other essiac preparations are noted in the literature, adding confusion to the exact formula and its proposed benefits. In general, there is a lack of both safety and efficacy data for Essiac and essiac formulations. Well-designed trials testing Essiac or individual herbal components are necessary to make firm recommendations.

Concurrent use of dietary supplements with over-the-counter and prescription pharmaceuticals has become increasingly common, and with this trend, so has the incidence of adverse drug-supplement interactions. In the current market, consumers have no way to distinguish between safe and potentially harmful supplements. Thus, the primary objective of this study was to test the hypothesis that messages designed to increase consumers' awareness of potential health risks of concurrent use of dietary supplements with over-the-counter and prescription pharmaceuticals would promote further consideration and action, as evidenced by (a) seeking additional information from an authoritative source or qualified health care professional and (b) changing dietary supplement usage patterns. To test this hypothesis, an innovative consumer information delivery system, referred to as the Buyer Information Network (BuyIN), was utilized. BuyIN uses currently available, Web-enabled point-of-sale (POS) technology to provide up-to-date, evidence-based, health- and safety-related messages to consumers at the retail checkout counter. Results showed that more than one-fourth (27.1%) of consumers (n = 199) who purchased targeted items reported they were aware of the messages. Of this subgroup of aware consumers, 11.2% reported that they sought additional information from a physician or pharmacist, 11.5% reported that they visited the website listed on the coupon, and 10.5% indicated that they changed their dietary supplement usage patterns as a result of the messages. Future research should include a large-scale study of a fully implemented and capable system at multiple test sites around the country, including investigating the utility of BuyIN in different retail settings.

To date, there have been few systematic studies of the antiplatelet and/or anticoagulant effects of natural products. According to the Natural Medicines Comprehensive Database, approximately 180 dietary supplements have the potential to interact with warfarin, and more than 120 may interact with aspirin, clopidogrel, and dipyridamole. These include anise and dong quai (anticoagulant effects); omega 3-fatty acids in fish oil, ajoene in garlic, ginger, ginko, and vitamin E (antiplatelet properties); fucus (heparin-like activity); danshen (antithrombin III-like activity and anticoagulant bioavailability); and St. John's Wort and American Ginseng (interference with drug metabolism). Other supplements, such as high doses of vitamin E (vitamin K antagonist activity), alfalfa (high-vitamin K content), and coenzyme Q10 (vitamin K-like activity), may affect blood clotting, which is dependent on vitamin K. Studies are needed to understand the role of various dietary supplements in thrombosis and their interactions with standard anticoagulants and antiplatelet drugs.

The elucidation of the toxicological mechanisms of herbal medicines is becoming more and more important with the increasing application of herbal medicines, for treatment of various diseases and the promotion of health. Furthermore, it is widely recognized that as herbal components undergo bioactivation, there is a critical need for a greater understanding of herbal toxicity induction.

The participants in this study had a strong trust in CAM and used a wide variety of sources to gather information on CAM safety, though their knowledge base was poor. As the use of CAM grows, further

research on how to disseminate reliable information on safety and efficacy to this potentially vulnerable population is required.

A number of herbal medicines are increasingly used by cancer patients worldwide, despite the fact that the clinical evidence that supports their use to fight cancer is weak or lacking. Pharmacokinetic studies have been integrated into modern drug development, but they are generally not needed for herbal remedies. To update our knowledge in this field, this paper highlights the pharmacokinetic properties of anticancer herbal medicines and the clinical relevance. To retrieve relevant data, the authors have searched through computer-based literatures by full text search in Medline (via Pubmed), ScienceDirect, Current Contents Connect (ISI), Cochrance Library, CINAHL (EBSCO), CrossRef Search and Embase ((all from inception to May 2011). An extensive literature search indicatesthat there are limited data on the pharmacokinetic properties of anticancer herbal medicines in humans. There are increasing pharmacokinetic studies of anticancer herbal remedies, but these studies are mainly focused on a small number of herbal medicines including curcumin, ginseng, ginkgo, ginger and milk thistle. For an anticancer herbal medicine, the pharmacological activity is gained when the active agents or the active metabolites reach and sustain proper levels at their sites of action. Both the dose levels and pharmacokinetic processes of active herbal components in the body determine their target-site concentrations and thus the anticancer effect. In this regard, a safe and optimal use of anticancer herbal medicines requires a full understanding of their pharmacokinetic profiles. To optimize the use of anticancer herbal remedies, further studies to explore their pharmacokinetic properties and the relevance to pharmacodynamics and toxicity in humans are certainly warranted.

Given the unparalleled popularity of botanicals in the United States, it is safe to say that almost every psychopharmacological prescriber will see some patients using Chinese herbs. Data show that between 36% and 42% of Americans use complementary and alternative medicine (CAM) each year and that persons suffering from depression and anxiety (67%) use CAM services significantly more than do their nonanxious and nondepressed counterparts (39%). This article gives an overview of several classical Chinese medical single herbs and herbal formulas commonly used for persons with psychiatric disorders and discusses some of the herbs that have the potential to interact with various pharmaceutical drugs. In addition, the article reviews scientific evidence and, at times, the lack thereof to validate the use of Chinese herbs and formulas in treating psychiatric conditions. Overall, the article seeks to prepare the pharmacological prescriber for working with patients concomitantly taking psychiatric medications and Chinese herbs.

Deoxyschizandrin and schisantherin A are major bioactive lignans isolated from Fructusschisandrae which has been widely used as a tonic in traditional Chinese medicine for manyyears. Inhibition of UDP-glucuronosyltransferases (UGTs) by herbal components might be animportant reason for clinical herb–drug interaction. The aim of the present study is toinvestigate the inhibitory effect of deoxyschizandrin and schisantherin A on major UGTisoforms. Recombinant UGT isoforms were used as enzyme source, and a nonspecific substrate4-methylumbelliferone (4-MU) was utilized as substrate. The results showed that 100 μM ofdeoxyschizandrin and schisantherin A exhibited strong inhibition on UGT1A3, and negligibleinhibition on other tested UGT isoforms. Furthermore, deoxyschizandrin and schisantherin Awere demonstrated to inhibit UGT1A3 in a concentration-dependent manner, with IC50 valueof 10.8±0.4 μM and 12.5±0.5 μM, respectively. Dixon and Lineweaver–Burk plots showedthat inhibition of UGT1A3 by deoxyschizandrin was best fit to competitive inhibition type, andinhibition kinetic parameter (Ki) was calculated to be 0.48 μM. Inhibition of UGT1A3 byschisantherin A gave the best fit for types of noncompetitive inhibition, and the results showedKi to be 11.3 μM. All these experimental data suggested that herb–drug interaction might occurwhen deoxyschizandrin or schisantherin A containing herbs were co-administered with drugswhich mainly undergo UGT1A3-mediated metabolism. However, given that many in vivofactors could influence the in vitro–in vivo extrapolation (IVIVE), these in vitro inhibitoryparameters should be considered with caution.

Cranberry juice is a popular beverage with many health benefits. It has anthocyanins to supplement dietary needs. Based on in vitro evidence cranberry juice is an inhibitor of CYP enzymes and at higher amounts as potent as ketoconazole (CYP3A) and fluconazole (CYP2C9). There is, however, a discrepancy between in vitro and in vivo observations with respect to a number of substrates (cyclosporine, warfarin, flurbiprofen, tizanidine, diclofenac, amoxicillin, ceflacor); with the exception of a single report on midazolam, where there was a moderate increase in the AUC of midazolam in subjects pre-treated with cranberry juice. However, another study questions the clinical relevancy of in vivo pharmacokinetic interaction between cranberry juice and midazolam. The controversy may be due to a) under in vitro conditions all anthocyanin principles may be available to have a concerted effort in CYP inhibition; however, limited anthocyanin principles may be bioavailable with varying low levels in the in vivo studies; b) a faster clearance of the active anthocyanin principles under in vivo conditions may occur, leading to low threshold levels for CYP inhibition; c) efficient protein binding and/or rapid tissue uptake of the substrate may have precluded the drug availability to the enzymes in the in vivo studies. With respect to pharmacodynamic aspects, while the debate continues on the issue of an interaction between warfarin and cranberry juice, the summation of the pharmacodynamics data obtained in patients and healthy subjects from different prospectively designed and controlled clinical trials does not provide overwhelming support for the existence of a pharmacodynamic drug interaction for normal cranberry juice ingestion. However, it is apparent that consumption of large quantities of cranberry juice (about 1-2 L per day) or cranberry juice concentrates in supplements for an extended time period (>3-4 weeks) may temporally alter the effect of warfarin. Therefore, the total avoidance of cranberry juice by warfarin users may not be warranted by the published studies. However, in certain situations of higher intake of cranberry juice or concentrate there may be a need to monitor both warfarin doses and its effect.

Although most drug interactions are clinically insignificant, some pose a significant risk. A basic knowledge of the mechanisms of drug interactions can help pharmacists to identify and avert potentially risky combinations. Review all medications, including dietary supplements and nonprescription drugs, when taking a medication history. Pay special attention to patients who take several medications, use herbal products, or use prescription medications associated with serious adverse events or toxicities.

Nowadays, complementary and alternative medicine (CAM) is popular all over the world. Billions of dollars are spent in this booming business. For several reasons, young, female, educated, and higher socioeconomic class cancer patients, in particular, have shown interest in these agents. Unfortunately, besides direct (and sometimes serious) side effects, several CAM ingredients are capable of interfering with the metabolism of concurrently used drugs, which may render the therapeutic outcome of the subscribed drug unpredictable. In the case of anticancer drugs, with their usually narrow therapeutic window, this may have dramatic consequences and can lead to unacceptable toxicities in some cases or decreased therapeutic activity in others. Therefore, cancer patients should be warned for these possible interactions and be advised to discuss CAM use openly with their treating physician. The general concept that natural products are harmless should thus be changed into a more realistic and responsible attitude. A tightened legislation and regulation (including Internet advertising and sales) could play a crucial role in this awareness process. This should finally enable safe exploration of the potential advantageous aspects of CAM, while living with cancer.

Digeda-4 decoction is a traditional Mongolian medicine; its effects on cytochrome (CYP) enzymes are still unclear. CYP450 isoenzymes are the main drug metabolic enzymes, and their activities may be induced or inhibited by certain drugs, which lead to drug interactions in clinical use. Effects of Digeda-4 decoction on the activities of CYP450 subtype enzymes CYP1A2, CYP2C9, CYP2E1, CYP2C19, and CYP3A4 in rats were studied by cocktail method, and the pharmacokinetic parameters of five specific probe drugs

(theophylline, tolbutamide, chlorzoxazone, omeprazole, and midazolam) were calculated by DAS software; changes of parameters can be used to evaluate the effects of Digeda-4 decoction on enzyme activities. The experimental rats were divided into three groups: control group, Digeda group, and positive group. Rats in Digeda group were given Digeda-4 decoction through continuous gavage for 14 days. After fasting for 12 hours, the mixed probes drug solution was injected into the tail vein; the blood samples were collected through the orbital vein at different time points. The concentrations of probe drugs in rat plasma were measured by HPLC. Compared with the control group, the half-life time ($t_{1/2}$) of the pharmacokinetic parameters of theophylline, tolbutamide, omeprazole, and midazolam was prolonged, the area under the curve (AUC) increased, and the plasma clearance (CL) decreased in the Digeda group. Continuous gavage administration for 14 days may inhibit the activities of CYP450 subtype enzymes CYP1A2, CYP2C9, CYP2C19, and CYP3A4 of rats. Herb-drug interaction should be noted between Digeda-4 decoction and the drugs metabolized by CYP1A2, CYP2C9, CYP2C19, and CYP3A4.

Corydalis decumbens, a Traditional Chinese Medicine, has been widely used for the alternative and/or complementary therapy of hypertension, arrhythmias rheumatoid arthritis, sciatica, stroke, hemiplegia, paraplegia, and vascular embolism. The aim of this study was to determinate the potential effects of *Corydalis decumbens* on the five cytochrome P450 (CYP) enzyme activities (CYP1A2, CYP3A4, CYP2C9, CYP2C19, and CYP2D6) by cocktail approach. To evaluate whether concurrent use of *Corydalis decumbens* interferes with the effect of several prescription drugs, saline (control group) or *Corydalis decumbens* (XTW group) were administrated via gavage for 7 successive days. A probe cocktail solution (phenacetin, omeprazole, metoprolol, tolbutamide, and midazolam) was given 24 h after the last dose of saline or *Corydalis decumbens*. A specific and sensitive UHPLC-MS/MS method was validated for the determination of five substrates and their metabolites in control group and XTW group. Our results indicated that *Corydalis decumbens* could have inductive effects of CYP2C19 and inhibit the activities of CYP1A2 and CYP3A4. However, *Corydalis decumbens* had no significant influence on CYP2C9 and CYP2D6. The herb-drug interaction should require more attention by careful monitoring and appropriate drug dosing adjustments to the concurrent use of western medications which were metabolized by CYP1A2, CYP2C19, and CYP3A4 in human-*Corydalis decumbens*, Cytochrome P450, Cocktail, Pharmacokinetics, herb-drug interactions.

Current evidence confirms the therapeutic effects of traditional medicine. Further clinical investigation is required to confirm these findings. The current understanding of the molecular mechanisms involved in psychiatric disorders, as well as the new advances in brain imaging permit a rapid and serious evaluation of anxiolytic compounds.

Herbal medication use as a dietary supplement is common. Many Americans use these products, federal legislation has implemented the USDSHEA, and there is now a National Center for Complementary and Alternative Medicine at NIH. Ethical herbal medication use of those single substances shown to be effective is growing. When patients are taking dietary supplements or herbal medications, the ingredients, origin, and potential toxicity or herb-drug interactions need to be determined. Education concerning these products and their potential toxicity, adverse effects, and interactions should become an essential component of medical toxicology. Clinicians caring for patients who may self-administer these products should attempt to obtain this history and familiarize themselves with the potential problems. The American College of Medical Toxicology strongly recommends consultation with or care by a medical toxicologist in cases of suspected or confirmed toxicity, adverse effects, or interactions from dietary supplements. We further encourage patients to report their use of these supplements to their physicians. FDA supervised labeling now requires a “Supplement Facts” label on each dietary supplement bottle marketed in the U.S. that describes and quantitates ingredients; supplements that do not have such a label should be used cautiously,

if at all. The ACMT strongly supports the FDA’s plan to further review and regulate dietary supplements where clinical experience or scientific information suggests the possibility of harm.

Biological-based (BbCAM) methods from complementary and alternative medicine (CAM) may interact with cancer treatments, reduce efficacy, or enhance adverse effects. Although CAM usage has been evaluated well in other cancer entities, data on melanoma patients are still missing. The aim of this study was to determine CAM usage of melanoma patients using a standardized questionnaire to identify potential interactions with established and new systemic melanoma therapies. This multicenter study was carried out in seven German skin cancer centers. During routine care contact, CAM usage of former and current melanoma treatment was assessed in melanoma patients. The probability of interaction was classified into four categories ranging from 'interaction unlikely' (I), 'possible' (II), 'likely' (III), or 'no data' (IV). The questionnaire was filled out by 1157 patients, of whom 1089 were eligible for evaluation. CAM usage was reported by 41% of melanoma patients, of whom 63.1% took BbCAM such as vitamins, trace elements, supplements, or phytotherapeuticals. Of 335 patients with former or current therapy, 28.1% used BbCAM. The melanoma treatment included interferon, radiotherapy, chemotherapy, BRAF-inhibitor, or other tyrosine kinase inhibitors and ipilimumab. On the basis of our model of likelihood of interaction, we found that 23.9% of those on cancer therapy and 85.1% of those also using BbCAM were at some risk of interactions. The main limitation of our study is that no reliable and comprehensive database on clinical relevant interactions with CAM in oncology exists. Most patients receiving a melanoma-specific treatment and using BbCAM methods are at risk for interactions, which raises concerns on the safety and treatment efficacy of these patients. To protect melanoma patients from potential harm by the combination of their cancer treatment and CAM usage, patients should systematically be encouraged to report their CAM use, while oncologists should be trained on evidence of CAM, and patient guidance for saver CAM use.

Panax ginseng should be consumed with caution during pregnancy, especially during the first trimester, and during lactation. Key words: Panax ginseng, asian ginseng, ginseng, pregnancy, lactation, breastfeeding, systematic review

Inhibition of cytochrome P450 (CYP) is a major cause of herb-drug interactions. The CYP1A2 enzyme plays a major role in the metabolism of drugs in humans. Its broad substrate specificity, as well as its inhibition by a vast array of structurally diverse herbal active ingredients, has indicated the possibility of metabolic herb-drug interactions. Therefore nowadays searching inhibitors for CYP1A2 from herbal medicines are drawing much more attention by biological, chemical and pharmological scientists. In our work, a pharmacophore model as well as the docking technology is proposed to screen inhibitors from herbal ingredients data. Firstly different pharmaphore models were constructed and then validated and modified by 202 herbal ingredients. Secondly the best pharmaphore model was chosen to virtually screen the herbal data (a curated database of 989 herbal compounds). Then the hits (147 herbal compounds) were continued to be filtered by a docking process, and were tested in vitro successively. Finally, five of eighteen candidate compounds (272, 284, 300, 616 and 817) were found to have inhibition of CYP1A2 activity. The model developed in our study is efficient for in silico screening of large herbal databases in the identification of CYP1A2 inhibitors. It will play an important role to prevent the risk of herb-drug interactions at an early stage of the drug development process.

Purified active plant constituents were isolated and assessed for their pharmacological activities that constitute a basis of modern drug development. The situation with herbal supplements is different because the extract or dried herb or mixture of herbs contains several substances beside the beneficial one(s) that might produce drug interaction with the conventional medicine(s). Most patients are misinformed and believe that anything "natural" must be safe. This article is focusing on plant-based substances referred as dietary supplements (DS). Examples of reported drug interactions and contraindications associated with DS

with two case studies are presented. As supplements are typically not prescribed, many doctors seem to have no interest in drug-DS interactions since a typical medical history of the patients does not include any questions about self-prescribed remedies of this nature. Rather, patients are left alone when they are tempted to try this or that DS and tend to rely on advice from friends, or on material they read on internet. A better quality control, compliance, public awareness and healthcare professionals vigilance for potential interactions are needed. It is of utmost importance to appreciate the impact of supplements on different stages of pharmacokinetics, especially on drug absorption and metabolism.

Complementary and alternative medical therapies (CAM) are treatments that generally fall outside of the mainstream of conventional medicine. CAM therapies are used by 31-84% of children with cancer, including many children enrolled on clinical trials. CAM therapies are often used for the treatment of side-effects of cancer or cancer therapy, and only rarely as an alternative to conventional therapy. Regulation of CAM therapies varies worldwide, and many therapies have not been subject to scientifically conducted analyses. Adverse events have been described, especially from the contamination of herbs. Only rare reports of interactions of CAM therapies with conventional anticancer treatments have been reported. Several research studies of CAM in children with cancer are underway. In the interim, non-pharmacological therapies such as mind-body medicine, manipulative and body-based therapies and energy therapies may be used for supportive therapy. Research is needed before biologically based CAM therapies may be recommended in conjunction with conventional therapy.

Drug and supplement interactions (DSIs) have drawn widespread attention due to their potential to affect therapeutic response and adverse event risk. Electronic health records provide a valuable source where the signals of DSIs can be identified and characterized. We detected signals of interactions between warfarin and seven dietary supplements, viz., alfalfa, garlic, ginger, ginkgo, ginseng, St. John's Wort, and Vitamin E by analyzing structured clinical data and unstructured clinical notes from the University of Minnesota Clinical Data Repository. A machine learning-based natural language processing module was further developed to classify supplement use status and applied to filter out irrelevant clinical notes. Cox proportional hazards models were fitted, controlling for a set of confounding factors: age, gender, and Charlson Index of Comorbidity. There was a statistically significant association of warfarin concurrently used with supplements which can potentially increase the risk of adverse events, such as gastrointestinal bleeding.

There is convincing evidence for the improvement of pharmacological activity at reduced side effects by hybrid combinations. Future efforts should focus on clinical trials with hybrid combinations to treat a broad range of diverse diseases such as cardiometabolic and neurotropic syndromes, drug resistance phenotypes, and so-called neglected infectious diseases.

Overall, there was a lack of perceived confidence among pharmacists in counseling patients and identifying DHIs as well as with identifying ADEs with the 11 OAAs chosen for this survey. One of the main barriers identified was the lack of knowledge or training. These data provide preliminary information needed to launch educational programs in the student pharmacist curriculum (e.g., elective courses) and continuing education programs to improve overall confidence among pharmacists.

The growing use of herbal dietary supplements (HDS) in the United States provides compelling evidence for risk of herbal-induced liver injury (HILI). Information on HDS products was retrieved from MedlinePlus of the U.S. National Library of Medicine and the herbal monograph of the European Medicines Agency. The hepatotoxic potential of HDS was ascertained by considering published case reports. Other relevant data were collected from governmental documents, public databases, web sources, and the literature. We collected information for 296 unique HDS products. Evidence of hepatotoxicity was reported

for 67, that is 1 in 5, of these HDS products. The database revealed an apparent gender preponderance with women representing 61% of HILI cases. Culprit hepatotoxic HDS were mostly used for weight control, followed by pain and inflammation, mental stress, and mood disorders. Commonly discussed mechanistic events associated with HILI are reactive metabolites and oxidative stress, mitochondrial injury, as well as inhibition of transporters. HDS⁻drug interactions, causing both synergistic and antagonizing effects of drugs, were also reported for certain HDS. The database contains information for nearly 300 commonly used HDS products to provide a single-entry point for better comprehension of their impact on public health.

Medicinal plants are currently being used in our culture. In spite of appropriate warnings from such scientific bodies as the American Society of Anesthesiologists on timing the withdrawal of medicinal plants before surgery, our results indicate that the advice is not followed. We also found that physicians lacked knowledge of the indications for using these plants and their interactions, a situation which is alarming