19 ADME of Herbal Dietary Supplements

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19.1 SUMMARY

Herbal dietary supplements have been used and studied over 5000 years ago by ancient civilizations such as the Chinese, Indian, Greek, Roman, and Egyptian, among others, for the prevention and treatment of various ailments. Today, the most popular traditional healing systems that utilize plant extracts are Chinese herbal medicine (zhōngyào and pinyin), Indian (ayurveda and siddha), traditional African medicine, Graeco-Arabic medicine (unani tibb), Native American medicine, classical Greek and Roman herbal medicine, Japanese (kampo), and so on. In spite of modern medical advances, herbal dietary supplements continue to be widely used for health maintenance, disease prevention, and even disease treatment. Sales of herbal dietary supplements in the United States have increased from ~$4 billion in 1999 to ~$5 billion in 2009.

New herbal products get to the market much faster than pharmaceuticals, as in the United States, these are considered "dietary supplements" and are subject to the regulation specified in the Dietary Supplement Health and Education (DSHE) Act of 1994, which provides a very different framework for the regulation of herbal products

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when compared with pharmaceutical drugs in terms of establishing efficacy, safety, and postmarketing surveillance. Herbal products may contain a single herb or combinations of several different herbs and are defined as such by both FDA (United States Food and Drug Administration) and EMEA (European Medicines Agency) regulatory agencies. Herbal dietary supplement manufacturers, while responsible for ensuring the safety of the herbal product, are not required to submit evidence of safety or efficacy to the FDA before commercialization. In addition, these regulations do not require that manufacturers report adverse events to the FDA and nor is there a guideline on how safety should be established. Hence, there is no impetus for manufacturers of herbal products to characterize the ADME properties of an herbal formulation or assess the potential for herb–drug interactions.

Approximately 15 million adults in the United States use herbal dietary supplements for the treatment of health conditions or for health maintenance; however, only one third inform their physician of this use. One misconception among the general population is that these agents lack adverse effects since they are obtained from a natural source. As a result, these herbal dietary supplements are often coadministered with prescription drugs (e.g., anticancer, anticoagulants, cardiovascular, and antidepressants), which increases the potential of pharmacokinetic and/or pharmacodynamic herb–drug interactions that are not apparent until there is a clinical manifestation. St. John's wort (SJW), a popular herb used in the treatment of depression, has been implicated in a number of clinically significant interactions with pharmaceuticals. Coadministration of SJW with cyclosporine, an immunosuppressant that has a narrow therapeutic index has been fatal; patients who had undergone heart and kidney transplants and stabilized with cyclosporine experienced organ rejection following administration of SJW.

Herb–drug interactions, like drug–drug interactions, can occur via a number of mechanisms. A classical approach to the study of herb–drug interactions involves the assessment of the effect of the herbal dietary supplement on the absorption, metabolism, distribution, and excretion (ADME) of the drug versus the effect of drug on the biodisposition of the herb. The ADME mechanisms for the known herb–drug interactions involve, in most cases, inhibition or induction of hepatic and intestinal drug-metabolizing enzymes of the cytochrome P450 (CYP) family and/or drug transporters such as P-glycoprotein (P-gp). With the increased use of herbal supplements, the incidences of herb–drug interactions are increasing due to several reasons. These include easy availability of the herbs with no requirements for a prescription, lack of awareness of safety issues combined with the general perception that the natural origin of these herbs makes them safe for use, and sometimes the limitations of modern medicine in improving the quality of life which drives the patient to self-medicate themselves with herbal dietary supplements. Therefore, assessment of the safety, efficacy, and potential for herb–drug interactions is warranted during the development of pharmaceuticals. However, unlike evaluation of drug–drug interactions, determining the potential for herb–drug interactions can be quite challenging for various reasons, which has been covered later in this chapter.

This chapter will provide a review of the potential for herb–drug interactions based on the literature reports for those herbs that are most popularly used in the United States. The herbs covered are aloe vera, American and Asian ginseng, bitter orange, black cohosh, cranberry, curcumin, danshen, dong quai, echinacea, evening primrose oil, garlic, ginger, ginkgo, green tea, kava, licorice, milk thistle, saw palmetto, Siberian ginseng, SJW, and valerian. Clinical studies and relevant human *in vitro* studies that

have evaluated metabolism- or absorption-based mechanisms to understand the interactions between these herbs and commonly used drugs are reviewed.

19.2 INTRODUCTION

The study and the use of herbal dietary supplements dates back over 5000 years. Herbal products have been used by ancient civilizations such as the Chinese, Indian, Greek, Roman, and Egyptian, among others, for the prevention and treatment of various ailments. At present, the most popular traditional healing systems that utilize plant extracts include traditional Chinese medicine (TCM), traditional Indian medicine (TIM) (consisting of ayurveda and siddha), traditional African medicine, Unnani Tibb, Native American medicine, and classical herbal medicine (Greek and Roman), and so on. Among the traditional healing systems, TCM and ayurveda herbs are being evaluated for efficacy and safety profiles with acceptable science-based approaches [1,2]. Recently, danshen dripping pill, a TCM, passed US FDA phase II clinical trials for a cardiovascular indication and is currently posed to undergo phase III clinical trials [3]. Benefits of curcumin, an ingredient of turmeric, an ayurvedic herb, and a common ingredient in Indian cuisine are being assessed systematically and data from a few phase I trials support the subsequent phase II trials for a few different indications such as Alzheimer's disease [4] and colorectal cancer [5]. The principles of TCM are based on the harmony of two opposite forces, namely Yin and Yang. When Yin and Yang are in disharmony, it results in disease. Harmony is maintained through acupuncture, massages (e.g., Shiatsu), diet, and herbal medicines [6]. Ayurveda recognizes the connection between the body, mind, and soul and believes that a balance of these three aspects is required for optimal health [1], which is achieved through diet, herbs, exercise (yogasana for the body and the mind), massage, and meditation.

In the United States, dietary supplements are defined by the 1994 Dietary Supplement Health and Education Act (DSHEA) [7,8], as products that are not used exclusively as food but are intended to be consumed in addition to an individual's diet. The law states that dietary supplements are taken by mouth and contain one or more dietary ingredients. Examples of dietary ingredients include vitamins, minerals, herbs, or other biological material, amino acids, and enzymes. Dietary supplements are required to be clearly labeled and may be sold in the form of tablets, capsules, powders, liquids, extracts, or teas. These products are often labeled as not having been approved by the FDA or that the product is not to be used to treat or diagnose a disease; yet, they are commonly used for a wide range of purposes including treatment of a disease state. Some of the common reasons for consumption of dietary supplements in the United States include supplementing a necessary substance not found in large enough quantities in the diet (e.g., vitamins), as a prophylactic for a disease or condition, for boosting the immune system, or as a tonic for improving general health (physical state such as stimulating weight loss etc., or mental state such as sharpening memory, etc.), and sometimes also for the treatment of a disease state. Herbs are defined as a part of the plant such as roots, stems, tree bark, leaves, flowers, fruits, or seeds or a product prepared from these plant parts. Herbal products may contain a single herb or a combination of multiple herbs.

The 20 top-selling herbal dietary supplements in the United States in 2009 include cranberry, soy, saw palmetto, garlic, echinacea, ginkgo, milk thistle, SJW, ginseng,

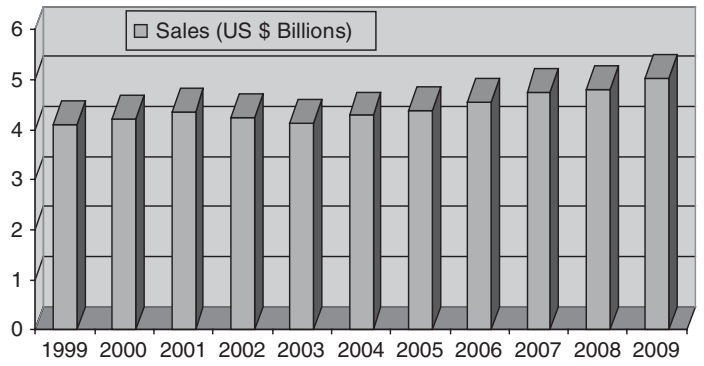

Figure 19.1 Herbal sales in United States from 1999 to 2009. *Source:* Adapted from *Herbal Gram.* 2010;86:62–65.

black cohosh, green tea, evening primrose, valerian, horny goat weed, bilberry, elderberry, grape seed, ginger, aloe vera, and horse chestnut [9]. Sales of herbal products has been on an upward trend from 2003 onward and increased from ~$4.1 billion in 1999 to $5.03 billion in 2009 as shown in Fig. 19.1.

Information presented in this chapter is limited to the commonly used herbal medicinal products that are commercially available in the United States. These will be referred to as *herbal dietary supplements* and do not include nutraceuticals such as vitamins and other dietary constituents. A list of the herbs covered herein for which absorption and/or metabolism-related interactions are reported with other commonly used drugs in humans, either *in vitro* or based on clinical data, are presented in Table 19.1.

19.3 REGULATORY PERSPECTIVES

Herbs are perceived as dietary supplements in the United States. A general outlook regarding herbs is that they are safe because they originate from a natural source. Hence, congressional action directed that herbs in the United States will be considered to be "dietary supplements" and will be regulated by the DSHEA of 1994, which was an amendment of the Federal Food, Drug, and Cosmetic (FDC) Act to establish standards with respect to dietary supplements and for other purposes [10]. Frankos *et al*. [11] have presented a concise review on FDA regulations pertaining to dietary supplements. It is interesting and important to understand the evolution of the federal regulations as it pertains to drugs, food, food additives, and dietary supplements and its role in ensuring public safety. Milestones in the history of the development of the current-day regulations are summarized below:

1. The history of the US federal regulation of foods and drugs began with the signing of the Pure Food and Drugs Act in 1906. This act sought to explicitly prohibit adulteration in foods, drinks, and drugs. In addition, this act provided regulations to ensure accurate labeling of products [12].
2. In 1938, "The Food, Drug, and Cosmetic Act" (FD&C Act) replaced the Pure Food and Drugs Act of 1906. The FD&C Act was the first law worldwide by

TABLE 19.1 List of Herbs with Absorption-Mediated or Metabolism-Mediated Effect of Herb on Commonly Used Drugs

Herb	Test System	Probe Drug	CYP/P-gp	Outcome	Mechanism	References
Asian ginseng (*Panax ginseng*)	*In vivo*	Debrisoquine	CYP2D6	Change in metabolite/parent ratio	Inhibition	Gurley *et al*. (2005) [67,79]
Black cohosh (*Actaea racemosa*)	*In vivo*	Debrisoquine	CYP2D6	Change in metabolite/parent ratio	Weak inhibition	Gurley *et al*. (2005) [67,79]
Curcumin (*Curcuma longa*)	*In vivo*	Caffeine	CYP1A2	Decreased metabolite formation	Inhibition	Chen *et al*. (2010) [97]
		Caffeine	CYP2A6	Increased urinary metabolite formation	Induction	
	In vitro (recombinant human CYP)	Benzyloxyresorufin	CYP2B6	Decreased metabolite formation	Inhibition	Appiah-Opong *et al*. (2007) [95]
		Diclofenc	CYP2C9		Inhibition	
		Benzyloxyresorufin, dibenzylfluorecein	CYP3A4		Inhibition	
	In vitro (human liver microsomes, human liver cytosol for SULT and LS180 cells for SULT and UGT)	Phenacetin	CYP1A2	Decreased metabolite formation in the presence of curcumin, curcuminoid mixture, and curcuminoid extract	Weak inhibition	Volak *et al*. (2008) [96]

(*continued overleaf*)

TABLE 19.1 (*Continued*)

Herb	Test System	Probe Drug	CYP/P-gp	Outcome	Mechanism	References
		Bupropion	CYP2B6		Strong inhibition	
		Flurbiprofen	CYP2C9		Moderate inhibition	
		S-mephenytoin	CYP2C19		Strong inhibition	
		Dextromethorphan	CYP2D6		Weak inhibition	
		Triazolam	CYP3A4		Moderate inhibition	
		Acetaminophen	SULT		Strong inhibition	
		Acetaminophen	UGT		Strong inhibition	
Danshen (*Salvia miltiorrhiza*)	*In vivo*	Warfarin	CYP2C9	Enhanced anticoagulation	Inhibition	Izzat *et al*. (1998) [99]
		Midazolam	CYP3A4	Increased oral clearance	Induction	Qui *et al*. (2010) [100]
	In vitro (human liver microsomes)	Phenacetin	CYP1A2	Decreased metabolite formation	Inhibition	Yang *et al*. (2010) [39]
Dong quai (*Radix angelica*)	*In vitro* (human liver microsomes)	Bupropion	CYP2B6	Decreased metabolite formation	Inhibition	Sevior *et al*. (2010) [101]
		Omeprazole	CYP2C19			Sevior *et al*. (2010) [101]
Echinacea (*Echinacea purpurea*)	*In vivo*	Caffeine	CYP1A2	Change in metabolite/parent ratio	Inhibition	Gorski *et al*. (2004) [104]
		Midazolam	CYP3A4		Induction	
Garlic (*Allium sativum*)	*In vivo*	Chlorzoxazone	CYP2E1	Change in metabolite/parent ratio	Inhibition	Gurley *et al*. (2005) [67,79]

	In vitro (recombinant human CYP)	7-Benzyloxyresorufin	CYP3A4P-gp	Decrease in metabolite formation (CYP3A) and stimulation of ATPase assay (P-gp)	Inhibition	Foster *et al*. (2001) [123]
Ginkgo (*Ginkgo biloba*)	*In vivo*	Nifedipine	CYP3A4	Increase parent plasma concentration	Inhibition	Smith *et al*. (2001) [66]
		Midazolam	CYP3A4	Decreased AUC and C_{max} for parent	Induction	Robertson *et al*. (2008) [168]
		Fexofenadine	P-gp	Reduction in T_{max}	Induction	
		Talinolol	CYP3A4	Increased AUC, C_{max}, and $t_{1/2}$ for parent	Inhibition	Fan *et al*. (2009) [171]
		Valproic acid and phenytoin	CYP2C19	Increased parent plasma concentrations	Inhibition	Kupiee *et al*. (2005) [162]
		Omeprazole	CYP2C19	Decreased parent/metabolite ratio	Induction	Yin *et al*. (2004) [163]
		Midazolam	CYP3A	Increased AUC for parent	Inhibition	Uchida *et al*. (2006) [169]
		Tolbutamide	CYP2C9	Decreased AUC for parent	Induction	
		Nifedipine	CYP3A4	Increased C_{max}	Inhibition	Smith *et al*. (2001) [66]

(*continued overleaf*)

TABLE 19.1 (*Continued*)

Herb	Test System	Probe Drug	CYP/P-gp	Outcome	Mechanism	References
	In vitro (recombinant human CYP)	7-Ethoxy-3-cyanocoumarin	CYP1A2	Decreased metabolite formation	Strong inhibition	Zou *et al*. (2002) [154]
		7-Methoxy-4-trifluoro methylcoumarin	CYP2C9		Strong inhibition	
		7-Hydroxy-3-cyanocoumarin	CYP2C19		Strong inhibition	
	In vitro (human liver microsomes)	Paclitaxel	CYP2C8	Decreased metabolite formation	Moderate inhibition	Etheridge *et al*. (2007) [155]
		S-warfarin	CYP2C9		Moderate inhibition	Mohutsky *et al*. (2006) [156]
		Testosterone	CYP3A4		Moderate inhibition	He and Edeki (2004) [157]
Green tea	*In vitro* (human liver microsomes)	Irinotecan	CYP3A4	Decreased metabolite formation	Inhibition	Mirkov *et al*. (2007) [195]
			UGT1A1			
		Tolbutamide	CYP2C9	Decreased metabolite formation	Inhibition	Nishikawa *et al*. (2004) [196]
		Bufuralol	CYP2D6			
		Testosterone	CYP3A4			
Kava	*In vivo*	Chlorzoxazone	CYP2E1	Decreased serum ratio of metabolite/parent	Inhibition	Gurley *et al*. (2005) [67,79]

Licorice (*Glycyrrhiza glabra*)	*In vitro* (recombinant human CYP)	7-Ethoxy-4-trifluoromethyl coumarin	CYP2B6	Time- and concentration-dependent inactivation	Inhibition and inactivation	Kent *et al*. (2002) [209]
		7-Benzyloxy-trifluromethyl coumarin	CYP3A4			
		7-Ethoxy-4-trifluoromethyl coumarin	CYP2C9	Decreased metabolite formation	Competitive inhibition	
	In vitro (human liver microsomes)	Benzyloxyresorufin	CYP3A	Decreased metabolite formation	Inhibition	Budzinski *et al*. (2000) [210]
Milk thistle (*Silybum marianum*)	*In vivo*	Metronidazole	P-gp	Decreased serum concentration and AUC of metronidazole	Induction	Rajnarayana *et al*. (2004) [226]
	In vitro (recombinant human CYP)	7-Benzyloxy-trifluromethyl coumarin	CYP3A4	Mechanism-based inhibition	Inhibition	Sridar *et al*. (2004) [234]
		7-Ethoxy-4-trifluoromethyl coumarin	CYP2C9			
	In vitro (human hepatocytes)	Testosterone	CYP3A4	Decreased metabolite formation	Inhibition	Venkataramanan *et al*. (2000) [233]
		4-Methyl umbelliferone	UGT1A6/9			

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TABLE 19.1 (*Continued*)

Herb	Test System	Probe Drug	CYP/P-gp	Outcome	Mechanism	References
Saw palmetto (*Serenoa repens*)	*In vitro* (recombinant human CYP)	7-Methoxy-4-trifluoromethyl coumarin	CYP2C9	Decreased metabolite formation	Inhibition	Yale *et al*. (2005) [241]
		3-[2-(*N*, *N*-diethyl-*N*-methyl amino)ethyl]-7-methoxy-4-methyl coumarin	CYP2D6			
		7-Benzyloxy trifluromethyl coumarin	CYP3A4			
St. John's wort (SJW)	*In vivo*	Chlorzoxazone	CYP2E1	Decrease in ratio of metabolite/parent	Induction	Gurley *et al*. (2002) [118,180]
		Midazolam	CYP3A4			
		Voriconazole	CYP2C19	Decrease in ratio of metabolite/parent	Induction	Rengelshausen *et al*. (2005) [252]
		Digoxin	P-gp	Change in apparent permeability	Induction	Gurley *et al*. (2008) [80,106,200,230]; Johne *et al*. (1999) [47]; Mueller *et al*. (2004) [264]
		Fexofenadine	P-gp	Change in apparent permeability	Induction	Dresser *et al*. (2003) [265]; Wang *et al*. (2002) [48,266]

Talinolol	P-gp	Change in apparent permeability	Induction	Schwarz *et al*. (2007) [267]
Tacrolimus	CYP3A4 and P-gp	Increased clearance of parent drug	Induction	Mai *et al*. (2003) [269]
Imatinib	CYP3A4 and P-gp	Increased clearance of parent drug	Induction	Frye *et al*. (2004) [270]; Smith *et al*. (2004) [271]
Irinotecan	CYP3A4	Increased clearance of the active metabolite	Induction	Mathijssen *et al*. (2002) [272]
Indinavir	CYP3A4	Decreased plasma concentration of parent	Induction	Piscitelli *et al*. (2000) [273]
Nevirapine	CYP3A4	Increased oral clearance	Induction	Erickson *et al*. (1999) [274]
Nifedipine	CYP3A4	Increased oral clearance	Induction	Wang *et al*. (2009) [276]
Verapamil	CYP3A4	Increased oral clearance	Induction	Tannergren *et al*. (2004) [277]
Atorvastatin	CYP3A4	Increased oral clearance	Induction	Andre'n *et al*. (2007) [278]
Simvastatin	CYP3A4	Increased oral clearance	Induction	Sugimoto *et al*. (2001) [279]
Norethindrone and ethinylestradiol	CYP3A4	Increased oral clearance	Induction	Hall *et al*. (2003) [281]
Norethindrone and ethinylestradiol	CYP3A4	Increased oral clearance	Induction	Murphy *et al*. (2005) [283]

(*continued overleaf*)

TABLE 19.1 (*Continued*)

Herb	Test System	Probe Drug	CYP/P-gp	Outcome	Mechanism	References
		Ketodesogestrel and ethinylestradiol	CYP3A4	Increased oral clearance	Induction	Pfrunder *et al*. (2003) [282]
		Fexofenadine	P-gp	Decreased plasma concentrations	Induction	Dresser *et al*. (2003) [265]; Wang *et al*. (2002) [48,266]
		Omeprazole	CYP3A4	Increased formation of CYP3A4-mediated sulfoxidation and decreased concentration of parent	Induction	Wang *et al*. (2004) [286]
			CYP2C19	Increased formation of CYP2C19-mediated hydroxylation and decreased concentration of parent	Induction	

	In vitro (recombinant human CYP)	7-Benzyloxy trifluromethyl-coumarin	CYP3A4	Decreased metabolite formation	Inhibition	Zou *et al*. (2002) [154]
		3-[2-(*N*, *N*-di-ethyl-*N*-methyl amino) ethyl]-7-methoxy-4-methylcoumarin	CYP2D6			
		7-Ethoxy-3-cyanocourmarin	CYP1A2			
		7-Methoxy-4-trifluoromethyl coumarin	CYP2C9			
		7-Ethoxy-3-cyanocourmarin	CYP2C19			
Valerian	*In vitro*	Dibenzylfluorescein	CYP3A4	Decreased metabolite formation	Inhibition	Lefebvre *et al*. (2004) [290]

the FDA to require scientific safety testing before a drug could be approved for marketing and it placed the burden of proof on the manufacturer to do so [13]. This act was instituted in response to a 1937 tragedy when a Tennessee drug company marketed a new pediatric formulation of sulfanilamide in which diethylene glycol (DEG) was added as a solubilizer, which also served to make its taste appealing to the pediatric patients [14]. DEG had never been tested for safety before its use in this product and was responsible for over 100 deaths. In addition, the FD&C act established a category of foods for special dietary use and required that the labeling include information on the vitamin, mineral, or other dietary content.

3. Following the enactment of the FD&C Act of 1938, FDA attempted to regulate dietary supplements [15]. One approach undertaken was to classify these products as drugs based on health claims made on the label, while another was to publish regulations which required that the dietary supplement products be declared as drugs if containing potencies exceeding 150% of the US recommended daily allowance. This was followed by the vitamin and mineral legislation (the Rogers/Proxmire amendment) in 1976, prohibiting the FDA from limiting the potency or nutrient combination of vitamin and mineral supplements and from classifying them as drugs based solely on their potency or combination.
4. Another landmark in the legislative history of dietary supplements is the1990 "Nutrition Labeling and Education Act" (NLEA) [16]. It required that the labels of all packaged foods contain nutrient information and allowed the FDA to establish the appropriate scientific evaluation and approval standards needed. The FDA chose to ensure that standards set for dietary supplements would be similar to that needed for drug approvals (Dietary Supplement Act of 1992). As required by this act, the FDA put forth "A Notice of Proposed Rule" (ANPR) in 1993. The guidelines within this act regulated certain dietary supplements as drugs. The ANPR elicited considerable protest from the public and the dietary supplement industry because FDA appeared to be reproposing regulatory provisions withdrawn or struck down by court actions in previous years. The ANPR was a significant motivating factor in industry and congressional effort to develop and pass the DSHEA of 1994.
5. The purpose of DSHEA was to allow the public increased access to these products that would otherwise have been curtailed if they had been subject to the same regulations as the pharmaceuticals, while still allowing the FDA to intervene if there are safety issues, false claims, or adulteration. These regulations provide a very different platform compared to the pharmaceuticals for establishing efficacy and safety and for conducting postmarketing surveillance. Under this Act, manufacturers of herbal products are responsible for ensuring the safety of the herbal product; however, they are not required to provide proof of safety and efficacy to make certain limited claims regarding the use of the herb. Also, these regulations do not require that manufacturers report adverse events to the FDA, and they do not specify how safety should be established. Hence, there is no impetus for manufacturers of herbal products to characterize the potential for herb–drug interactions.

   Key features of this act include the specific categorization of dietary supplements as food; clarification that dietary supplements are not food additives and

hence not subject to premarket safety testing and FDA approval, ensures the current good manufacturing practice (cGMP) regulations for dietary supplements and allows certain statements of well-being claims without obtaining premarket authorization from the FDA. The dietary supplement and nonprescription drug consumer protection act of 2006 required dietary supplement companies to report adverse events to the FDA and since 2008 to list an address or phone number on dietary supplement product labels that customers can use to report serious adverse events and report to the FDA.

The DSHEA defines a dietary supplement as "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)." A dietary supplement is further defined as "a product that is intended for ingestion in the form of capsule, powder, soft gel, gel cap or other form, if not represented for use as a conventional food item or as a sole item of a meal or a diet, and contains one or more dietary ingredients and is labeled as a "dietary supplement"."

6. To address the deficiencies within the DSHEA, Gershwin *et al*. [14] have put forth a proposal to have dietary supplement manufacturers submit human safety data for premarket approval by the FDA. Their proposal has a number of benefits which include allowing the FDA to fulfill its mission of consumer protection for dietary supplements, to address concerns of the mainstream medical community, to minimize toxicities, to resolve consumer confusion, and to restore consumer confidence. In addition, Collins *et al*. [17] reported differences between dietary supplement containing ω-3 fatty acid and those ω-3-fatty acid formulations that are available by prescription, thereby further emphasizing the need for dietary supplements to be regulated in a manner similar to pharmaceutical drugs.

19.4 GENERAL ISSUES WITH ASSESSMENT OF HERB–DRUG INTERACTIONS

It has been a regulatory requirement to conduct different *in vitro* and, if necessary, clinical studies to assess a drug's potential for causing interactions with other drugs that are typically coadministered. This information is presented in the label of the drug product. However, a quick review of the drug product labels for products entering market in the past five years demonstrates that information regarding the potential for adverse effects or lack of efficacy due to interaction of the drug with an herbal dietary supplement arising from their concomitant use is lacking. Bent and Ko [18] have reviewed the contributing factors for the challenges associated with obtaining improved confidence with herbal products.

When approaching the study of herb–drug interaction, there are two main questions. The first is what does the drug do to the biological fate of the herb? Given the extent of information currently available, this question is rather difficult to answer, as the biodisposition of the herb including the pharmacokinetic (PK) characteristics is often not very well characterized. The second question is what does the herb do to the

biodisposition of the drug? Theoretically, this question can be addressed, albeit not without significant challenges (presented below) to interpreting the data in a clinically relevant manner and these are listed below.

Most herbal dietary supplements are isolated from a natural source such as roots, tree bark, stem, leaves, flowers, fruits, or seeds by one or more processes of extraction. As a result, they contain multiple chemical constituents that may include alkaloids, glycosides, flavonoids, sterols, saponins, tannins, and terpenes [19]. In most cases, more than one compound contributes to the therapeutic activity. Some herbal products also contain multiple herbs as it is believed that they exert complementary effects. In most cases, the active ingredient(s) is not known. Hence, assessment of herb–drug interaction is not quite relevant to the clinical scenario if performed with just a single compound that is known to be the lead compound for eliciting pharmacological effect. Therefore, a mixture of all the chemical constituents that is present in the final herbal dietary supplement needs to be utilized in the assessment of interaction potential to be representative of the clinical scenario. However, it is not an easy task to maintain consistency with respect to the type of chemical constituents and their concentrations between batches.

1. *Interbatch Consistency for Potency:* Several environmental factors, such as the location of the plant, altitude, the quality of the soil, variation in temperature, extent of rainfall, shade, dew, humidity, frost, as well as chemical treatment (fertilizers, pesticides, antimicrobials, etc.) can influence the chemical composition that is found in the plant extract. Hence, it is very common to have batch-to-batch variation with respect to both the types of compounds present in the extract as well as their concentrations. For example, analysis of 25 ginseng products that were commercially available demonstrated a 15- to 200-fold variation in the concentration of the two ingredients that are believed to be active [20].
   Some manufacturers utilize the process of standardization, whereby several batches of the herb containing differing amounts of the active ingredient are combined in an effort to obtain the desired concentration of the active ingredient in the product. While such an approach provides for minimal interbatch variation in the dose of the active ingredient, the rest of the presumed nonactive components remain highly variable and the risk for alteration in the biodisposition and safety of the coadministered drug still exists, if the rest of the compounds in the herbal product contribute to an herb–drug interaction.
2. *Contaminants:* Contamination and adulteration of herbal products have been reported to be an issue after chemical analysis of some TCMs and ayurvedic herbal products [21–26]. In particular, these preparations were found to contain lead, mercury, and arsenic at levels that would result in serious health problems if taken at recommended doses. The contamination of herbals with pesticides, bacteria, molds, fungi, and mycotoxins can also result in health issues [27]. These contaminants present the potential for alteration of the true potential of the herbal product to interact with the drug-metabolizing enzyme being assessed and should be considered in the interpretation of data.
3. Most clinical trials that have been conducted with herbal products offer limited utility due to small sample size, less rigorous study design, and most importantly use of products where the composition is not very well defined [28].

4. The percentage of patients who self-medicate with herbal products and volunteer the information to physicians is alarmingly low presumably due to the perception that they are taking something perceived to be "safe" [29,30]. Hence, it is very likely that a clinically reported adverse event that may have been caused due to alteration of the drug PK by the herb would not be investigated as an herb–drug interaction due to lack of accurate patient history.
5. The regulatory status that herbs are assigned in the United States, that is, as dietary supplements, does not require manufacturers of herbal products to evaluate the potential for herb–drug interactions.
6. Assessing the PK of herbal drugs is fairly complex due to multiple bioactive compounds in the product as well as due to the dose of a single compound being in the lower milligram range due to which the plasma concentrations are often very low (picogram to nanogram per liter). Hence, the bioanalytical methods need to be very sensitive to assess the PK of the major constituents of the herb.

These facts make evaluation of herb–drug interaction relatively challenging when compared to the typical assessment of drug–drug interaction(s) during the development process of a pharmaceutical drug product.

19.5 UNDERLYING MECHANISMS FOR HERB–DRUG INTERACTIONS

For most herb–drug interactions, the potential for such an interaction is not known until it manifests clinically in the form of adverse effects or lack of pharmacology of either the drug or the herb. Theoretically, both PK and pharmacodynamic (PD) mechanisms may be implicated; however, this chapter focuses on the PK-based mechanisms only. Alteration in the PK of the drug due to interaction with the herb can occur at the level of ADME. This chapter focuses on the herb–drug interactions that arise out of interaction of the herb with a transporter for which the drug is also a substrate or those which are metabolism mediated. The PK profile of many drugs is known to be altered by coadministration of herbal products which is mediated by the herb by either altering the absorption of the drug or by inhibiting or inducing the drug-metabolizing enzymes, most commonly the CYP enzyme(s), which contribute to the metabolism of the drug. Butterweck and Derendorf [31] have presented a review article on this subject.

19.5.1 Absorption-Based: Herb–Drug Interactions due to Association with Transporters

Clinically reported interactions of herbal dietary supplements with concomitant administration with drugs have been reported for several drugs. Examples include cyclosporine, tacrolimus, imatinib, irinotecan, digoxine, fexofenadine, simvastatin, saquinavir, and indinavir, which are known to be substrates for P-gp, also known as *multidrug resistance protein* (MDR1) or ABCB1, a well-researched drug transporter protein [32] that is described in the chapter titled ***ABC Drug Transporters and their Impact on Drug Disposition/Drug Sensitivity and Resistance***. P-gp mediates the ATP-dependent efflux of drugs from cells, is expressed in a number of tissues, and is responsible for the transport of an extremely large number of substrates [33]. P-gp presents a high transport capacity and broad substrate specificity: a number of

clinically relevant drugs with structurally different features and belonging to different classes (examples include digoxin, loperamide, berberine, irinotecan, doxorubicin, vinblastine, paclitaxel, and fexofenadine) can be effluxed by P-gp [34]. Substrates of P-gp are generally hydrophobic molecules either cationic or neutral [33–35].

Some P-gp drug substrates are able to inhibit P-gp-mediated transport of other substrates leading to potential drug–drug interactions [35–38]. A number of herbal supplements used by cancer patients in combination with cancer drugs have been reported to modulate P-gp expression and/or activity [39]. Piperine from black pepper and silymarin from milk thistle were reported to inhibit P-gp activity *in vitro* [39]. Curcumin from turmeric and several catechins from green tea were shown to reduce P-gp expression and activity *in vitro* [40]. Using the *in vitro* caco-2 cell model, Hou *et al*. reported that 30 μM concentration of curcumin increased the accumulation of rhodamine 123 (a P-gp substrate) by approximately twofold in the receiver cell similar to verapamil, a known P-gp inhibitor [41]. In this study, curcumin inhibited P-gp expression and rhodamine efflux by about 30% and the authors proposed that curcumin inhibits the AP-1 (activator protein-1) transcriptional factor and NF-κβ (nuclear factor -κβ), which regulates MDR1 expression. Terhaag and colleagues conducted a clinical study with a randomized, open-labeled design using 12 healthy volunteers and a wash out period of one week between the administration of a single oral dose of 50 mg talinolol and the concomitant administration of curcumin (300 mg/day for six days) and a single oral dose of 50 mg on day 7 [42]. The effect of curcumin administration on talinol PK was a 53% increase in oral clearance and decreases in both area under the concentration curve (AUC) and C_{max} (by 33 and 28%) compared to administration of talinolol alone. The authors attributed the observed decrease in talinolol AUC and C_{max} to low intraluminal concentration of curcumin or to upregulation of ATP-binding cassette transporters such as MRP2. One of the challenges with predicting absorption-related interactions is sometimes the lack of *in vitro* to *in vivo* correlation as demonstrated by the talinolol—curcumin example. Han and colleagues [43] conducted a clinical study to investigate the effect of concomitantly administered silymarin on the PK of talinolol in healthy Chinese volunteers and its association with a *MDR1* C3435T genetic polymorphism. Eighteen healthy adult men (six *MDR1* 3435CC homozygotes, six *MDR1* 3435CT heterozygotes, and six *MDR1* 3435TT homozygotes) were recruited in a two-phase, randomized, single-blind, crossover design. The PK of talinolol was measured after coadministration of placebo or 140-mg silymarin capsules three times daily for 14 days. The peak plasma concentration (C_{max}) of talinolol was significantly higher after silymarin administration as compared with placebo ($p = 0.007$). The area under the plasma concentration-time curve of talinolol from 0 to 36 h (AUC_{0-36h}) and when extrapolated to infinity ($AUC_{0-\infty}$) was increased by $36.2 \pm 33.2\%$ and $36.5 \pm 37.9\%$, respectively, by silymarin coadministration. The oral clearance (CL/F) of talinolol was decreased by $23.1 \pm 16.6\%$ ($p < 0.001$) during the silymarin-treated phase. No change in the time to peak concentration (t_{max}) and the blood elimination half-life ($t_{1/2}$) of talinolol was observed between the placebo and silymarin-treated phases.

Studies indicate that P-gp expression, similar to CYP3A, is inducible. CYP enzymes and P-gp are regulated via the pregnane X-receptor (PXR), which controls the transcription of their genes (P-gp encoded by *MDR1*). Herbal dietary supplements can modify the first-pass effect for drugs through changes in the PXR activity or by direct competitive or allosteric interference at the active substrate-binding regions of CYP enzymes and transport proteins [44].

SJW induces the activity of intestinal CYP3A4 and P-gp via the common regulator PXR [45]. In addition, some SJW constituents inhibit CYP isoenzymes (1A2, 2C9, 2C19, 2D6, and 3A4) [46]. Therefore, an initial inhibition of human CYP3A4 by SJW leads at first to an increased bioavailability of CYP3A4/P-gp substrates, such as digoxin or fexofenadine [47,48], but is then followed by a decrease in bioavailability due to enzyme induction. Hyperforin has been identified as the constituent in SJW responsible for PXR-mediated stimulation of CYP and P-gp. Guggul (*Commiphora mukul*), a resin, from the mukul tree is approved as a cholesterol-lowering drug in India and is known to induce the expression CYP3A4 and P-gp to a similar extent to SJW [49].

Cell lines such as caco-2 that express P-gp and inside-out membrane vesicles prepared from these cell lines can be used to determine whether a drug is a P-gp substrate or inhibitor. Mice deficient in Mdr1a or Mdr1a/b are also used for assessing the role of P-gp *in vivo*. Knockout mice may be used as a reference for complete inhibition of P-gp [50]. The clinical significance of a P-gp inhibitor can be investigated in humans by assessing P-gp-mediated clearance or exposure using digoxin as a model probe substrate [51].

Mardin–Darby canine kidney (MDCK) cell lines stably expressing organic anion transporters (OATs) such as OAT1, OAT3, and OAT4 have been used to assess *in vitro* the potential for renal transport of anionic drugs [52]. Mouse knockout models (OATP1b) for *in vivo* experiments have also been developed and reflect more closely activity associated with OATP1B1 and OATP1B3, respectively [53]. Aristolochic acids present in some TCM preparations have been shown to inhibit human OAT1, OAT3, and OAT4 [54].

In vitro cell-based and *in vivo* mouse-based knockout mice are used to assess substrates and inhibitors of the breast cancer resistance protein (BCRP) transporter [53]. Tamaki *et al*. [55] evaluated the inhibitory effects of nine herbal extracts on BCRP-mediated transport using *in vitro* membrane vesicles isolated from mammalian cells expressing wild-type BCRP (SB-BCRP-M-VT) and methotrexate as a BCRP-specific probe substrate. Extracts of soybean, black cohosh, rutin, and passion flower almost completely inhibited BCRP-mediated transport of methotrexate at $100\,\mu M$ and chlorella, milk thistle, and Siberian ginseng inhibited BCRP-mediated transport of methotrexate by 22, 45, and 36%, respectively [55].

19.5.2 Metabolism-Based: Herb–Drug Interactions due to CYP Inhibition

There have been several clinical reports of herb–drug interactions arising due to inhibition of one or more of the CYPs commonly responsible for drug metabolism. Typically, an increase in side effect(s) will be expected if an herb has the potential to inhibit metabolism of a drug, thereby decreasing metabolic clearance of the drug and increasing plasma drug concentration. The commonly used *in vitro* and *in vivo* methods of assessing the potential for drug–drug interaction [56] can also be employed to evaluate the potential for herb–drug interaction with the exception of *in silico* methods. Since the utility of *in silico* methods to predict the binding properties of ligands to mammalian CYPs lies in having knowledge of the chemical structure of the bioactive molecule (drug/herb), the identity of the pharmacologically active molecule in the herb needs to be known. Since most herbs contain multiple bioactive compounds,

application of *in silico* methods and data interpretation to predict clinical herb–drug potential is not as straightforward.

19.5.3 Metabolism-Based: Herb–Drug Interactions due to CYP Induction

If an herb causes induction of a CYP that is responsible for the metabolism of the drug, it will result in increased metabolic clearance of the drug. Typically, this results in reduced pharmacological effect or lack of therapeutic effect of the drug, since, with a few exceptions, most metabolites are usually less pharmacologically active than the parent drug. Although the commonly employed experimental methods can be used to assess herb–drug interactions, the limitations posed due to the inherent nature of the herbal products applies here as well, as discussed above in Section 19.3. Examples of drug interactions that occur due to induction of CYP enzymes after administration of herbal products, such as SJW, are reported on the FDA website. The warning reported on the FDA web site for SJW is "This herb is considered an inducer of liver enzymes, which means it can reduce the concentration of medications in the blood. SJW can reduce the blood level of medications such as Lanoxin, the cholesterol-lowering drugs Mevacor and Altocor (lovastatin), and the erectile dysfunction drug Viagra (sildenafil)" [57].

19.6 COMMONLY USED HERBS IN THE UNITED STATES OF AMERICA

The 20 top-selling dietary supplements in the United States according to information resources incorporated in 2009 include cranberry, soy, saw palmetto, garlic, Echinacea, ginkgo, milk thistle, SJW, ginseng, black cohosh, green tea, evening primrose, valerian, horny goat weed, bilberry, elderberry, grape seed, ginger, aloe vera, and horse chestnut [9]. The market information firm SPINS of Schaumburg, Illinois, has a slightly different list of top 20 selling dietary supplements for 2009 and include aloe vera, flaxseed, wheatgrass, acai, turmeric, milk thistle, stevia, elderberry, saw palmetto, Echinacea, garlic, Echinacea with goldenseal combination, oregano oil, valerian, ginkgo, chlorophyll/chlorella, black cohosh, cranberry, evening primrose, and green tea [9]. In this chapter, we have covered a number of the top 20 selling herbal dietary supplements from both sources and in addition covered popular traditional Chinese herbals, danshen and dong quai. A more recent comprehensive review of clinical evidence for drug–herb interactions has been presented in a review article by Kennedy and Seely [58], while Izzo and Ernst [59] have reviewed preclinical data to determine the potential for herb–drug interaction in addition to the clinical data. Relevant herb–drug interactions reported in the literature in humans, *in vitro* and clinically, are summarized in Table 19.1.

19.6.1 Aloe (*Aloe vera*, Family Asphodelaceae)

The succulent leaf of *Aloe vera* contains clear gel which has skin healing and soothing properties in addition to moisturizing when used topically for minor cuts and burns including sunburns [60,61]. *A. vera* juice or capsules are also being used orally in the treatment of diabetes, asthma, epilepsy, and osteoarthritis because of its anti-inflammatory effect [62,63]. This herb is very widely used orally as an adjunct treatment

of diabetes II; there are no published clinical reports of ADME-based interactions with other drugs.

19.6.2 American and Asian Ginseng (*Ginseng* sp., Family Araliaceae)

The root of ginseng is believed to have a number of different therapeutic uses and is most often used in dried form, either whole or sliced. Ginseng leaf is sometimes used, also in the dried form. The Asian ginseng (*Panax ginseng*) and the American ginseng (*Panax quinquefolius*) are taken orally and used as nourishing stimulants (such as in energy drinks), anti-inflammatory, for prevention of cancer, and in the treatment of erectile dysfunction in men due to their vasodilating effect [64]. The active ingredients are ginsenosides.

In vitro assessment of some of the active ingredients of ginseng in cDNA-expressed CYP system showed that ginsenoside Rd caused weak inhibitory activity against CYP3A4 (with IC_{50} values of 58 and 74 μM for two different substrates) and CYP2D6 (IC_{50} of 76 μM) and even weaker inhibition of CYP2C19 and CYP2C9 activities with IC_{50} values over 100 μM, while ginsenoside Rc increased the activity of CYP3A4 (∼1.5-fold) and CYP2C9 (∼1.7-fold), although assay artifact was not completely ruled out [65]. Clinical studies have shown that ginseng does not have the potential to cause CYP- or P-gp-based drug interactions [66–71] except for some slight changes observed in metabolite-to-parent ratio when using debrisoquine as a CYP2D6 probe after pretreatment with *P. ginseng* in a study reported by Gurley *et al*. [67]. It has been reported clinically that concomitant use of *P. ginseng* and phenelzine resulted in mania for which the mechanistic basis is not known, however, thought to be pharmacological [72,73]. A few clinical cases have been reported of ginseng affecting platelet aggregation when coadministered with warfarin, which are considered to have a pharmacological basis [74].

19.6.3 Bitter Orange (*Citrus aurantium*, Family Rutaceae)

Bitter orange is included in several herbal weight loss products and is believed to possess antioxidant properties, although a literature review reported by Bent *et al*. [75] determined that the weight loss produced by treatment with bitter orange was not statistically significant. The effect of bitter orange on the CYP isozymes was evaluated by Gurley *et al*. [76] after daily dosing for 28 days, and it was observed that there was no change in the CYP activity.

19.6.4 Black Cohosh (*Actaea racemosa*, Family Ranunculaceae)

The dried roots of Black cohosh (formerly known as *Cimicifuga racemosa*) contain glycosides, isoferulic acids with anti-inflammatory effects, and phytoestrogens, among several other active substances [77]. Hence, it is often used as an antirheumatic and antispasmodic as well as to treat dysmenorrhea and to ease menopausal symptoms [78].

At a dose of 2180 mg/day taken for 28 days, which is significantly higher than the recommended daily dose of 40–200 mg, a clinical study reported by Gurley *et al*. [79] using CYP-selective probe substrates for CYP1A2, CYP2D6, CYP2E1, and CYP3A4 showed that there was no effect of black cohosh on CYP1A2, CYP2E1, and CYP3A4. However, a weak inhibition of CYP2D6 was clinically observed based on altered PK of

debrisoquin as the probe substrate in the same study. A later study, also conducted by Gurley *et al*. [80], using the same probe, showed that black cohosh after a daily dose of 80 mg for 14 days did not inhibit CYP2D6. Another clinical study, also reported by Gurley *et al*. [81], confirmed the absence of any CYP3A4-mediated interaction based on midazolam PK, although the dose of black cohosh was relatively lower (80 mg/day for 14 days). Clinical evaluation of digoxin PK after 40 mg/day dose for 14 days with black cohosh showed no potential for black cohosh to elicit drug interaction due to P-gp inhibition [82].

19.6.5 Cranberry (*Vaccinium macrocarpon*, Family Ericaceae)

The ripe fruits of Cranberry are known for anticoagulant, anti-inflammatory, and antimicrobial properties including antiparasitic activity. It is often used as a prophylaxis and/or treatment of urinary tract infections [83].

Six clinical studies have been reported for herb–drug interactions with cranberry administered either in the form of juice (5 of 6 studies) or in the form of a capsule (one of six studies) containing concentrated extract of cranberry. Cranberry juice did not alter the PK of flurbiprofen [84], cyclosporine [85], midazolam [86], tizanidine [86], and warfarin [86–88]. However, the area under the international normalized ratio (INR)–time curve (AUC_{INR}) for warfarin was slightly increased (30% increase) when capsules of concentrated cranberry extract (daily dose of 3 g for 14 days) were used as reported by Abdul *et al*. [89]. In this study, there was no impact on baseline INR, warfarin PK, or platelet aggregation suggesting that cranberry pretreatment did not have a significant effect on the clotting of blood.

19.6.6 Curcumin (*Curcuma longa*, Family Zingiberaceae)

Curcumin, a hydrophobic polyphenolic compound belonging to the curcuminoid class [90], is one of the principal active ingredients of turmeric which is a commonly used spice in Indian cuisine as well as a coloring pigment. Turmeric is obtained from the dried rhizomes of *Curcuma longa* and has been used for its medicinal properties in ayurvedic medicine for centuries. More recently, systematic study of the pharmacology of curcumin has gained interest due to evidence that it has anti-inflammatory, antioxidant, antiviral, antifungal, and anticancer properties [91,92]. Curcumin has potential against various malignant diseases such as diabetes mellitus, arthritis, and Alzheimer's and has been described as the "ideal spice for life" by Aggarwal *et al*. [93]. Baum *et al*. [94] showed that oral doses of up to 4 g/day for six months were found to be safe. Cheng *et al*. [4] demonstrated that curcumin is not toxic to humans up to 8000 mg/day when taken by mouth for three months. This study as well as another clinical study conducted by Sharma *et al*. [5] provided preliminary evidence that curcumin has the potential to serve as a chemopreventive agent for cancer.

Appiah-Opong *et al*. [95] studied the interactions of curcumin, a mixture of its decomposition products, and four of its individually identified decomposition products (vanillin, vanillic acid, ferulic aldehyde, and ferulic acid) on five major human drug-metabolizing CYPs using human recombinant CYPs *in vitro*. It was observed that curcumin strongly inhibited CYP2C9 (IC_{50} 4.3 μM) and showed moderate inhibition of CYP3A4 and CYP2B6 with IC_{50} values of 16.3 and 24.5 μM, respectively. Curcumin was observed to be a noncompetitive inhibitor of CYP2C9 (K_i 11.5 $\pm$ 0.8 μM),

whereas inhibition of CYP3A4 (K_i $7.4 \pm 3.5\,\mu M$) and CYP2B6 (K_i $33.2 \pm 14.0\,\mu M$) was of a competitive type. In a separate study reported by Volak *et al*. [96], curcumin as well as curcuminoid extract and curcuminoid mixture were evaluated *in vitro* for its potential effects on drug-metabolizing enzymes *in vitro*. In their study, they determined that curcumin was a potent inhibitor of sulfotransferase (SULT) > CYP2C19 > CYP2B6 > UDP-glucuronosyltransferase (UGT) > CYP2C9 > CYP3A with IC_{50} values ranging from 0.99 ± 0.04 to $25.3 \pm 1.3\,\mu M$. SULT inhibition study with curcumin was conducted in LS 180 cells, CYP studies in human liver microsomes and UGT separately in both LS 180 cells and human liver microsomes. The inhibition of CYP3A activity by curcuminoid extract was determined to be competitive inhibition (K_i of $11.0 \pm 1.3\,\mu M$) which was consistent with the results reported by Appiah-Opong *et al*. [95], whereas mixed competitive–noncompetitive inhibition was attributed to the inhibition of CYP2C9 and CYP2C19 activities with corresponding K_i values of 10.6 ± 1.1 and $7.8 \pm 0.9\,\mu M$, respectively.

Chen *et al*. [97] conducted a clinical study in healthy male volunteers by administering 1 gm of curcumin orally (once daily) for 14 consecutive days and on the 15th day coadministering with 100-mg caffeine. Curcumin was shown to inhibit CYP1A2 activity by 28.6% as measured by decreased formation of caffeine metabolite, 1,7-dimethylxanthine. An increase (48.9%) in CYP2A6 activity was also observed in this study. Additional clinical studies are needed to fully validate curcumin's ability to interact with pharmaceutical medications by inhibition of CYP1A2 and other drug-metabolizing enzymes.

19.6.7 Danshen (*Salvia miltiorrhiza*, Family Lamiaceae)

Danshen is the dried root or rhizome of *Salvia militiorrhiza*. It is primarily used for the treatment of cardiovascular diseases, including angina pectoris, stroke, and myocardial infarction [98]. The major active components of danshen are tanshinones.

Tanshinones are substrates for P-gp and are potent competitive inhibitors of CYP1A2 with K_i of less than $1\,\mu M$ [39]. Izzat *et al*. [99] reported that patients on chronic warfarin therapy with coadministration of danshen had enhanced anticoagulation and bleeding. Additional clinical studies are needed to demonstrate that inhibition of warfarin metabolism (i.e., through inhibition of CYP2C9) may result in the enhanced anticoagulation observed in combination therapy with danshen. Qui *et al*. [100] reported that danshen induces CYP3A4 in healthy volunteers. Midazolam oral clearance in this study increased by 35% and C_{max} and AUC decreased by 31 and 27%, respectively.

19.6.8 Dong Quai (*Radix angelica sinensis*, Family Apiaceae)

Dong quai, a root preparation, is used to treat menstrual cramps, regulate menstrual periods, and lessen menopausal symptoms. Dong quai is thought to promote natural progesterone synthesis, a hormone that declines during menopause. It has also been reported to have medicinal use in certain cardiovascular conditions. The root of this herb is used to treat fatigue, anemia, and high blood pressure [6].

Sevior *et al*. [101] reported that dong quai inhibited CYP2B6 and CYP2C19 *in vitro* in human liver microsomes with IC_{50} values ranging between 3 and $5\,\mu M$. Clinical herb–drug interaction studies involving dong quai and substrates of CYP2C19 and CYP2B6 need to be conducted to determine if the interactions are clinically relevant.

In a clinical study conducted by Page and Lawrence [102], coadministration of dong quai and warfarin increased the anticoagulant effect of warfarin resulting in higher INR ratios. It has been hypothesized that this effect is PD rather than PK. Additional studies are needed to understand the risks associated with coadministration of dong quai and other blood thinning agents.

19.6.9 Echinacea (*Echinacea* sp., Family Asteraceae)

Roots and sometimes other plant parts from multiple species of the *Echinacea* genus are used, namely, *E. pupurea, E. angustifolia*, and *E. pallida* in the treatment of upper respiratory tract infections [103]. Echinacea products contain alkylamides that are known to modulate CYP activity, in particular, CYP1A2 and CYP3A4 [104]. However, the type and concentration of the alkylamide present can vary depending on the *Echinacea* species [105]. This is perhaps the cause for the conflicting reports in the literature regarding the effect of Echinacea products on CYP activity *in vivo* [76,80].

Coadministration of Echinacea has been reported to either decrease the clearance of caffeine as reported by Gorski *et al*. [104] or have no effect on the PK of caffeine as reported by Gurley *et al*. [76]. A potential mechanism suggested for the lower clearance of caffeine is the inhibition of CYP1A2 by Echinacea. In this study, slight inhibition of CYP2C19 was also observed; however, the extent of inhibition was considered to be clinically insignificant [104]. Similarly, these two clinical studies also reported different outcome on the effect of Echinacea on CYP3A4. Gorski *et al*. reported increased systemic clearance of midazolam associated with increased oral bioavailability of midazolam suggesting inhibition of intestinal CYP3A4 and induction of hepatic CYP3A4 [104], whereas Gurley *et al*. reported no effect on CYP3A4 activity [76]. Also, the PK of digoxin, a P-gp substrate, was unaffected after administration of Echinacea [106]. Thus, currently, there are no clinical case reports that point to serious safety-impacting interactions of this herb with other drugs.

19.6.10 Evening Primrose Oil (*Oenothera biennis*, Family Onagraceae)

Evening primrose oil (EPO) is an oil that is extracted from the flowers of *Oenothera biennis* and is rich in linoleic acid and γ-linolenic acid (GLA), a polyunsaturated fatty acid [107]. EPO is generally used for the treatment of allergy-induced eczema, premenstrual syndrome, breast pain and tenderness, diabetic neuropathy, rheumatoid arthritis, and osteoporosis [108,109]. There are no published literature reports on interactions of EPO with other drugs.

19.6.11 Garlic (*Allium sativum*, Family Liliaceae)

Garlic, which is a common herb used in various cuisines, is also used in the reduction of hypertension and hyperlipidemia including prevention of arteriosclerosis [110]. It is also thought to possess some immune system strengthening and antimicrobial effect [111,112], which makes it the herb of choice in HIV-infected patients [113]. There are many known active ingredients in garlic cloves; however, the organosulfur compounds, such as allicin, alliin, *S*-allylcysteine, *S*-allylmercaptocysteine, diallyl sulfide, dipropyl sulfide, and dipropyl disulfide, are believed to be the therapeutic ingredients [114–117].

Case studies have been reported in the literature implicating interactions with garlic and other drugs such as anticoagulants, antiretrovirals, hypoglycemic, and analgesics.

Administration of garlic capsules twice daily for 14 days to normal healthy volunteers did not alter the PK of probe substrates that are metabolized by CYP3A4 such as midazolam [118] and alprazolam [119] or of dextromethorphan [119] which is metabolized by CYP2D6. However, garlic inhibited CYP2E1, as determined by the assessment of PK of the CYP2E1-selective probe substrate, chlorzoxazone [67].

After administration of garlic orally for three weeks to healthy volunteers, a twofold decrease in the plasma exposure of the coadministered HIV protease inhibitor, saquinavir, was observed [120]. This was hypothesized to be due to decreased bioavailability of saquinavir, which could be a result of P-gp inhibition, as saquinavir is a known substrate of CYP3A4 [121] and P-gp [122], and it has been shown that garlic does not modulate the *in vivo* activity of CYP3A4 using midazolam [118] and alprazolam [119] as probes, as discussed earlier. In fact, it was later shown that raw garlic and garlic products cause slight to moderate inhibition of P-gp *in vitro* [123], although the inhibition was not as strong compared to verapamil, a potent P-gp inhibitor. However, in a separate study reported by Gallicano *et al*. [124], single-dose PK of ritonavir, another HIV protease inhibitor, was unaltered after consecutive daily dosing of garlic for four days. It is postulated that a longer duration of dosing for garlic might contribute to alteration of ritonavir PK. In contrast, Laroche *et al*. [125] reported severe gastrointestinal toxicity for two HIV-infected patients who were taking garlic capsules for a little over two weeks before beginning ritonavir (400 or 600 mg, bid) treatment. This toxicity was attributed to the coadministration of garlic and ritonavir as it was found to be reversible when either drug was discontinued and recurred when a lower dose of ritonavir (100 mg) was coadministered with garlic. Although the underlying mechanism for the interaction between garlic and ritonavir needs to be further investigated, it has been postulated that either ritonavir modulates the metabolism of garlic leading to production of toxic metabolites or the garlic constituents might inhibit the CYP3A4-based metabolism [126] or P-gp-mediated transport of ritonavir [125], thereby leading to increased ritonavir concentrations. It is also possible, given that ritonavir autoinduces its metabolism during the first two weeks of therapy [127], that the effect of concomitantly administered garlic may be more pronounced after a single dose of ritonavir as compared to after multiple doses. Studies conducted with garlic products or the known active ingredients have shown some potential for interaction with P-gp as well as inhibition of cDNA-expressed CYP enzymes *in vitro* [123].

Interaction with docetaxel, a CYP3A4 substrate, was assessed clinically in women with metastatic breast cancer receiving docetaxel weekly for three weeks [128]. Three days after the initial dose of docetaxel, patients received 600 mg of garlic twice daily for 12 consecutive days. Docetaxel PK was assessed after each dose, and it was found that garlic did not significantly affect the disposition of docetaxel. However, there was some potential that garlic decreased the clearance of docetaxel in patients carrying a CYP3A5*1A allele.

Following a three-month dosing of garlic extract, assessment of acetaminophen PK showed a slight increase in sulfation of acetaminophen, however, did not alter the extent of oxidative and glucuronidation metabolites [129]. Overall, the authors concluded that garlic did not affect the PK of acetaminophen. In addition, diallyl sulfone has

been shown to inhibit the oxidation of acetaminophen to its hepatotoxic metabolite, *N*-acetyl-*p*-benzoquinone imine, in human liver microsomes [130].

PD-based herb–drug interactions have also been reported for garlic with anticoagulants and antihyperglycemic agents. *In vitro* and *in vivo* studies conducted with certain organosulfur compounds present in garlic have demonstrated that garlic inhibits platelet aggregation in humans [131–134]. There are case reports of postoperative bleeding [135,136] and spontaneous spinal epidural hematoma that are considered to be linked to ingestion of garlic products [137,138]. Thus, the anticoagulant effect of garlic is responsible for increased clotting time and INR after concomitant dosing of garlic and warfarin [139–142]. Similarly, garlic extracts have been shown to produce antihyperglycemic effects in animals [143–145] and humans [146,147]. A literature report [148] described that the concomitant administration of chlorpropamide (which is used to treat diabetes), garlic, and bitter melon led to enhanced hypoglycemic response. This is another example of a PD herb–drug interaction, as each by itself exhibits antihyperglycemic properties.

19.6.12 Ginger (*Zingiber officinale*, Family Zingiberaceae)

Ginger is a commonly used botanical in many culinary preparations and is most commonly used as a household remedy for nausea, especially during the first trimester of pregnancy [149]. It is also reported to have antiemetic property including treatment of gastrointestinal infectious diseases, anti-inflammatory, and antiplatelet activity [150].

There are no reported clinical studies that have assessed the potential for its interaction with other drugs via CYP- or P-gp-related mechanism. On the basis of its pharmacological properties, Jiang *et al*. [151] assessed its potential to cause bleeding when coadministered with warfarin and reported no alteration in warfarin PK or in the coagulation parameters after administration of ginger.

19.6.13 Ginkgo (*Ginkgo biloba*, Family Ginkgoaceae)

The leaves of *Ginkgo biloba* contain powerful antioxidants and are mainly used for improving memory and for cerebral insufficiency and peripheral vascular disease [103,152]. The known active constituents, ginkgolide and bilobalide, have been shown to function as antagonists of the platelet-activating factor (PAF) receptor and therefore have antiplatelet aggregation activity [153].

In vitro study with cDNA-expressed CYPs has shown that the ginkgolic acids present in ginkgo biloba were potent inhibitors of CYP1A2, CYP2C9, and CYP2C19 with IC_{50} values ranging from 2.41 to 4.88 μM [154]. Ginkgo also moderately inhibited CYP2C8 [155], CYP2C9 [156], and CYP3A4 [157] *in vitro* in human liver microsomes; however, the studies reported in the literature to determine the potential of *Ginkgo* to inhibit CYP2C19 and CYP2D6 present conflicting results [154,158–160].

In contrast to the moderate (apparent K_i of 14.8 μM) inhibition of CYP2C9 observed *in vitro* in human liver microsomes [156], ginkgo did not show any potential for interaction with CYP2C9 probe substrates, as evidenced by unaltered steady-state PK of diclofenac or on the urinary metabolic ratio of tolbutamide [156]. Consistent with this *in vivo* finding, the PK of another CYP2C9 substrate, flurbiprofen, was also unaffected by ginkgo [161].

There was a case report of elevated levels of antiepileptic drugs, valproic acid and phenytoin, in a 55-year-old man taking ginkgo in addition to herbs, and since the common CYP that metabolized both is CYP2C19, inhibition of CYP2C19 by ginkgo is suggested as the underlying reason [162]. Yin *et al*. [163] conducted a clinical study to look at effects of ginkgo treatment on the PK of omeprazole and hydroxylation of omeprazole. They reported a significant decrease in the ratio of AUC of the parent to AUC of its hydroxylated metabolite, with the decrease being higher in a poor metabolizer than an extensive metabolizer with regard to CYP2C19 genotype, thus indicating that ginkgo induced CYP2C19.

Smith *et al*. [66] reported a clinical study in healthy volunteers to assess the effect of ginkgo on the PK of nifedipine, a CYP3A4 substrate. A 53% increase in the peak plasma concentration of nifedipine at 30 min postdose was reported in this study, suggesting inhibition of CYP3A4. In contrast, another clinical study reported later by Yoshioka *et al*. [164] showed that ginkgo did not alter nifedipine PK. In addition, Markowitz *et al*. [165] reported a clinical study to assess the effect of ginkgo on CYP3A4 using alprazolam as a CYP3A4 substrate and CYP2D6 using dextromethorphan as a substrate. The data indicated that administration of ginkgo had no effect on both these CYP isozymes. A similar outcome for CYP3A4 was observed in a separate study reported by Yasui-Furukori *et al*. [166]. In this study, ginkgo extract was administered once daily for 30 days to 14 patients undergoing treatment with donepezil, a cholinesterase inhibitor, for Alzheimer's disease. Neither the plasma concentration of donepezil, which is metabolized by CYP3A4 and CYP2D6 [167], nor the cholinesterase activity in the red blood cell or the cognitive function of the patients over the duration of the study was significantly altered by ginkgo. In addition, a few other studies to clinically evaluate the effect of ginkgo on CYP3A4 are reported below. Robertson *et al*. [168] reported that ginkgo did not significantly alter the PK of antiretrovirals (lopinavir and ritonavir); however, it was observed that the AUC of midazolam decreased, suggesting induction of CYP3A metabolism. Uchida *et al*. [169] reported that ginkgo inhibited CYP3A metabolism resulting in increased AUC of midazolam and induction of CYP2C9 as evidenced by the decrease in AUC of tolbutamide. Additional studies are needed to elucidate the induction or inhibition effects of ginkgo on CYP3A metabolism since the existing reports in the literature are conflicting.

Similarly, assessment of the potential of ginkgo to cause P-gp-related interaction with drugs that are P-gp substrates gave mixed results when studied using digoxin and talinolol as P-gp probes. Ginkgo did not cause any significant alteration of digoxin PK [170], while it significantly increased the bioavailability of talinolol [171]. Therefore, similar to CYP3A4, the clinical potential for ginkgo to cause herb–drug interactions due to P-gp-related mechanism needs to be investigated further.

Several clinical reports of hemorrhage have implicated gingko either postoperatively [172–175] or when taken concomitantly with drugs that have anticoagulant activity such as warfarin [176,177] or clopidogrel [178] and nonsteroidal anti-inflammatory agents such as ibuprofen, aspirin, and rofecoxib [179]. Since, ginkgo does not seem to modulate any of the CYP activities to produce metabolism-based interactions with other drugs based on PK of known probe drugs for various CYP enzymes [156,180–182], the underlying mechanism for these case reports appears to be PD-based rather than metabolism related. However, the outcome of a prospectively designed repeat-dose (14 days) clinical study that was randomized, double-blind, and placebo-controlled in

young healthy male volunteers was that the administration of an extract of ginkgo does not cause significant changes in blood coagulation parameters [183]. Similarly, another study evaluated the effect of coadministration of ginkgo and acetylsalicylic acid on blood coagulation parameters and demonstrated that ginkgo did not produce any additional effect on bleeding time or other coagulation parameters [184].

Other sporadic reports of clinical interactions of ginkgo with other drugs, such as antihyperglycemic metformin [185] or antipsychotic risperidone [186] and antidepressant trazodone [187,188], are available and these are thought to be PDs based and hence are not discussed here.

19.6.14 Green Tea (*Camellia sinensis*, Family Theaceae)

Green tea is a popular beverage and is also available in the form of capsules containing concentrated extract. It is commonly recognized as an antioxidant and has been shown to have anti-inflammatory [189] and antineoplastic properties [190] and is often used as a prophylactic for cancer [191] as well as to aid weight loss [192,193]. There are several catechins in green tea extract which are active ingredients, of which the most abundant is epigallocatechin gallate and its recommended daily dose for therapeutic effect is 100–750 mg [194,195].

Green tea was shown to strongly inhibit CYP2C9, CYP2D6, and CYP3A4 activities in human liver microsomes using tolbutamide, bufuralol, and testosterone as probe substrates [196]. Also, Mirkov *et al*. [195] demonstrated that the catechins from green tea inhibited the CYP3A4-catalyzed oxidation of irinotecan and UGT1A1-catalyzed conjugation of its metabolite, SN-38, in human liver microsomes; however, they did not induce CYP3A4 in human hepatocytes.

In contrast to the *in vitro* studies, a clinical study conducted by Donovan *et al*. [197] to assess the effect of decaffeinated green tea on CYP2D6 and CYP3A4 showed no potential for herb–drug interaction via these two isozymes. In a later study conducted by Chow *et al*. [198] using a similar dose but with a longer duration (4 weeks vs 14 days in the prior study), it was observed that there was no effect on the activities of CYP1A2, CYP2C9, CYP2D6, or CYP3A4, although there was a slight inhibition of CYP3A4 activity as evident from an increase in buspirone AUC, however, it was considered to be clinically insignificant.

19.6.15 Kava (*Piper methysticum*, Family Piperaceae)

Kava (roots and rhizome) is used as an anxiolytic [103]. There have been numerous clinical cases of hepatotoxicity with coadministration of kava with other drugs [199].

Clinical studies with specific probe substrates have shown that kava inhibits CYP2E1 [79]; however, no effect was found on other CYPs such as CYP1A2, CYP2D6, and CYP3A4 [79,200]. A separate clinical study conducted by Gurley *et al*. [201] showed no significant alteration in digoxin PK due to coadministration of kava, due to which there does not appear to be any potential for clinical interaction of kava with other drugs that are P-gp substrates.

Clinical lack of efficacy has been reported for levodopa used to treat Parkinson's disease [202]. Serious adverse effect of being in a semi-comatose state has been reported for concurrent use of benzodiazepine alprazolam [203], while concomitant use of paroxetine to treat depression led to a lethargic state with diffuse muscular weakness and

some cognitive difficulty [204]. However, these interactions are thought to be PD in nature due to the direct effect of kava at dopamine and GABA receptors [205] rather than metabolism dependent.

19.6.16 Licorice (*Glycyrrhiza glabra*, Family Leguminosae)

The root of licorice has traditionally been used to treat sore throat and has recently been clinically shown to be effective [206]. It is a commonly used herb used in Chinese and Japanese traditional medicine. Licorice is also recognized as a natural sweetener, since the active ingredient, glycyrrhizin or glycyrrhizic acid, is 50 times sweeter than sugar [207,208].

In vitro studies conducted with expressed human P4503A4, 2B6, and 2C9 and glabridin, an isoflavone present in licorice, demonstrated time- and concentration-dependent inactivation of CYP2B6 and CYP3A4, while CYP2C9 was competitively inhibited [209]. Another *in vitro* study conducted by Budzinski *et al*. [210] in human liver microsomes with an extract of licorice showed that CYP3A4-mediated metabolism of benzyloxyresorufin was inhibited. However, Shon *et al*. [211] observed no significant change in the PK of midazolam in healthy volunteers who were given licorice extract for seven days, indicating that licorice does not show the potential for interaction with drugs that are substrates for CYP3A4. Thus, the nonconcordance of *in vitro* data to clinical studies could presumably be due to the different sources of the herb in these studies that could presumably have led to varying chemical composition.

There have been clinical reports of life-threatening hypokalemic paralysis reported in association with long-term licorice consumption [212,213]. It is unclear whether the hypokalemic paralysis is related to the inhibition of 5α-, 5β-reductase and 11β-dehydrogenase which *in vitro* studies have shown glycyrrhizin and glycyrrhetic acid to be potent inhibitors of [214,215]. These enzymes play a role in steroid metabolism; hence, the *in vitro* inhibition studies suggest that the decreased steroid metabolism could potentiate the effect of endogenous and administered steroids [216]. Homma *et al*. [217] evaluated the effect of three Chinese herbal products, containing equal amounts of glycyrrhizin, on prednisolone PK and also measured the ratio of AUC of prednisone to AUC of prednisolone which is an indicator of 11β-hydroxysteroid dehydrogenase activity. In this study, a significant increase (15.2%) in plasma prednisolone AUC was observed with one of the herbal preparation with a corresponding decrease in the ratio, while a significant decrease (17.2%) in prednisolone AUC was observed on coadministration of another herbal product with a corresponding increase in the ratio. Coadministration with the third product did not significantly alter the prednisolone plasma AUC or the ratio. This difference could be due to the presence of other components in the herbal product that could have different effects on steroid metabolism. These studies, taken as a whole, emphasize the challenges faced in assessing herb–drug interactions.

19.6.17 Milk Thistle (*Silybum marianum*, Family Asteraceae)

The extract of the seeds of *Silybum marianum* has been reported to have a hepatoprotective effect and is often used to reverse drug-mediated hepatotoxicity [218]. It is often used by patients diagnosed with viral hepatitis [219]. A typical extract of milk

thistle contains ~4–6% silymarin, which is considered to be the primary active ingredient, about 65–80% silymarin (a flavonolignan complex), and 20–35% fatty acids, including linoleic acid [220].

Several studies have been reported with drugs such as aminopyrine [221], irinotecan [222], indinavir [223–225], metronidazole [226], nifedipine [227], phenylbutazone [221], ranitidine [228], and rosuvastatin [229] as well as with standard probe substrates [118] such as caffeine (CYP1A2), debrisoquin (CYP2D6) [230], chlorzoxazone (CYP2E1), and midazolam (CYP3A4) [231], which assessed the effect on the activity of various CYP isozymes after daily dosing with milk thistle for 7, 14, 17, 21, or 28 days and observed no significant impact. There was a minor reduction in the AUC of indinavir in the two clinical studies reported by Piscitelli *et al*. [223] and by DiCenzo *et al*. [224]; however, it was considered to be clinically insignificant for indinavir. Consistent with these results, another active ingredient, silibinin, was reported to have no effect on the isozyme activity *in vitro* in human liver microsomes when evaluated by Beckmann-Knopp *et al*. [232] using erythromycin (CYP3A4), chlorzoxazone (CYP2E1), S(+)-mephenytoin (CYP2C19), caffeine (CYP1A2), or coumarin (CYP2A6) as probe substrates. However, Venkataramanan *et al*. [233] reported that silymarin at a high concentration of 0.1–0.25 mmol/L, significantly decreased CYP3A4-mediated 6β-hydroxylation of testosterone as well as glucuronyltransferase activity in human hepatocytes. Sridar *et al*. [234] have reported that silibinin is a mechanism-based inhibitor of CYP3A4 and CYP2C9. These studies indicate that a systematic assessment is important to be able to predict interaction of milk thistle with drugs metabolized by CYP2C9, CYP2D6, CYP2E1, or CYP3A4.

Milk thistle did not alter digoxin PK *in vivo* indicating that it did not inhibit P-gp [82]. However, in contrast, a decrease in serum metronidazole concentrations was observed and it was attributed to an upregulation of P-gp [226]. In addition, *in vitro* studies with silymarin demonstrated increased accumulation of daunorubicin in cells expressing P-gp phenotype compared to cells that did not express P-gp, and photoaffinity labeling showed a direct interaction with P-gp binding [235]. Similarly, the cytotoxic effects of doxorubicin were potentiated *in vitro* by silibinin [236] and high affinity labeling to P-gp was inferred to be the cause [237]. Thus, the literature reports of significant modulation of P-gp by the active constituents silymarin and silybinin show the potential for clinical interaction of milk thistle with other P-gp substrates. Therefore, additional studies are required to understand the impact of milk thistle treatment on P-gp.

19.6.18 Saw Palmetto (*Serenoa repens*, Family Arecacea/Palmae)

Dried ripe fruits of Saw Palmetto are widely used for the treatment of stages I and II of benign prostatic hyperplasia [238]. Fatty acids, flavanoids, and plant sterols are the active ingredients in saw palmetto [239]. No serious clinical side-effects have been reported in patients taking saw palmetto [240].

Yale and Glurich reported potent inhibition of cDNA-expressed human P4502C9, 2D6, and 3A4 by saw palmetto [241]. In contrast to these data, two independent clinical studies conducted in healthy volunteers by Gurley *et al*. [118] and Markowitz *et al*. [242], with selective CYP substrates for CYP1A2, CYP2D6, CYP2E1, or CYP3A4, showed no significant potential for herb–drug interactions mediated through these CYPs.

19.6.19 Siberian Ginseng (*Eleuthrococcus senticosus*, Family Araliaceae)

The roots of Siberian ginseng have immunomodulatory properties and are used as an adaptogen to confer resistance to the effects of stress [243]. The major pharmacological constituents of Siberian ginseng are the eleutherosides.

The effect of Siberian ginseng on CYP2D6 and CYP3A4 activities was assessed after daily dosing for 14 days using dextromethorphan and alprazolam as probe substrates, respectively [244]. No significant change in the PK of both these probes was observed in this study. This was consistent with the results of the *in vitro* study using cDNA-expressed human CYP3A4 where the extract of Siberian ginseng did not inhibit CYP3A4 [210]. A case report of increased serum digoxin concentrations without any signs of toxicity in a patient taking Siberian ginseng was investigated further [245]. It appeared that Siberian ginseng contained some digoxinlike entities that posed interference in the serum digoxin assay and ruled out involvement of P-gp interaction [246].

19.6.20 St. John's Wort (*Hypericum perforatum*, Family Hypericaceae)

SJW is a very popular herb used in the treatment of mild, moderate, and major depression [247,248], which is typically used in a chronic setting. Two major classes of biologically active compounds include the hypericins which are anthraquinones with antiviral and anticancer activity and the hyperforins which are prenylated acylphloroglucinols which display potent antimicrobial activity and are thought to be the primary bioactive ingredient for antidepressive effects of the herb [249].

When used as a monotherapy, treatment with SJW is quite safe. However, there are several clinical reports of adverse effects on concomitant administration of SJW with different drugs as a result of PK-based interaction due to either or both induction of CYP and intestinal P-gp which have been reviewed by Zhou and Lai [250]. This review cites studies reporting interactions with anticancer agents, anti-inflammatory drugs, antimicrobials, antiretrovirals, cardiovascular drugs, CNS drugs, contraceptives, hypoglycemic, immunosuppresants, and drugs acting on the respiratory system. The interaction of SJW with other drugs was observed ~14 days after daily administration of SJW; studies conducted after acute administration of SJW showed no potential for interaction, thereby suggesting that induction of CYP enzymes and/or P-gp could be the underlying mechanism [251–253].

Several clinical reports and clinical studies with SJW have confirmed the ability of SJW to induce CYP3A4, CYP2C19, and CYP2E1, and/or P-gp with no effect on activities of CYP1A2, CYP2C9, or the noninducible CYP2D6 [254–260]. Typically, the observed enzyme induction is reversible one week after cessation of SJW treatment [261]. It has been demonstrated that SJW extract and hyperforin treatment of primary human hepatocytes causes induction of CYP3A4 via the activation of PXR [262,263].

The interaction of SJW with P-gp substrates was evident from the lowered plasma concentrations of well-known P-gp substrates including digoxin [47,106,264] and fexofenadine [265,266]. Decreased plasma concentrations have also been observed for talinolol, another clinical probe for P-gp, when administered after pretreatment with SJW [267]. These talinolol PK data combined with a corresponding increase in MDR1 mRNA as well as protein levels of P-gp in the intestinal mucosa in humans, reported in the same study, indicate that SJW induces P-gp [267]. It is also believed that the hypericin in SJW is responsible for the induction of P-gp [264].

The use of SJW is very common in patients who have undergone organ transplant procedure and are undergoing treatment with an immunosuppressant such as cyclosporine or tacrolimus, since these patients also tend to experience depression. The interaction of SJW and cyclosporine has been the most well documented with reports of patients transplanted with heart, liver, or kidney and stabilized on cyclosporine showing acute rejection of the transplanted tissue which was associated with decrease in plasma cyclosporine level, after taking SJW at therapeutic doses [268]. Improvement was observed in most patients after discontinuation of SJW. Mai *et al*. [269] reported that after dosing stable renal transplant patients with SJW, a decrease in tacrolimus concentration but not of mycophenolic acid was observed, thereby confirming that induction of CYP3A4 and P-gp is responsible for the increased drug clearance, since tacrolimus is a substrate for both P-gp and CYP3A4, while mycophenolic acid is primarily metabolized by glucuronidation.

Patients on antineoplastic therapy also tend to self-medicate with SJW. Two independent clinical trials in healthy volunteers have been reported with SJW and two anticancer agents, imatinib [270,271] and irinotecan [272]. Imatinib is a potent inhibitor of Bcr-abl and c-kit tyrosine kinase and is mainly metabolized by CYP3A4 and is a P-gp substrate, while SN-38 is the active metabolite of irinotecan which is a CYP3A4 substrate. In both these studies, decreased plasma concentration of the anticancer agent, imatinib, or the active metabolite of irinotecan, SN-38, was reported after pretreatment with SJW.

Failure of anti-HIV therapy has been observed with antiretrovirals such as indinavir [273] and nevirapine [274], which are both CYP3A4 substrates. Decrease in the plasma concentration of the protease inhibitor, indinavir, was observed in healthy volunteers dosed with SJW for 14 days in an open-label trial that is attributed to the induction of CYP3A4. The nonnucleoside analog, nevirapine, which is metabolized by CYP3A4 and CYP2D6, showed increased oral clearance in five HIV-infected patients, when SJW was coadministered suggesting induction of CYP3A4. HIV viral load, as determined from the measurement of HIV mRNA, was also significantly increased in a patient after he took SJW concomitantly with indinavir and lamivudine [275]. It is postulated that the reported interaction between SJW and the antiretrovirals was due to the induction of CYP3A4 by SJW.

Induction of CYP3A4 has also caused failure of therapy for several cardiovascular drugs which are metabolized by CYP3A4 to a significant extent such that the autoinduction leads to a decrease in the serum concentration of these drugs making them less effective. These include the calcium channel blockers nifedipine [276] and verapamil [277], and the antihyperlipidemic drugs, atorvastatin [278], and simvastatin [279] but not pravastatin [279] which is not a substrate for CYP3A4 or for P-gp. In addition, clinical cases of increase in coagulation parameters when taking anticoagulants such as warfarin (racemic mixture of *R*- and *S*-enantiomers) have been reported, and it is documented that while *S*-warfarin is metabolized by CYP2C9, the *R*-enantiomer is metabolized by CYP1A1 and CYP3A4 [280].

SJW has been shown to increase the clearance of contraceptives such as ethinylestradiol, norethindrone, and ketodesogestrel, which was attributed to the induction of CYP3A4 as these drugs are substrates for CYP3A4 [281–283].

Hypoglycemic drugs such as tolbutamide is metabolized predominantly by CYP2C9 and its coadministration with SJW did not alter its PK [284], suggesting that SJW does not modulate CYP2C9 activity. In contrast, the PK of gliclazide, another CYP2C9

substrate used in the treatment of diabetes, was significantly altered by SJW in the absence of any significant change in CYP2C9 genotype [285], thus suggesting that the mechanism was independent of CYP2C9.

SJW has been shown to reduce plasma concentrations of fexofenadine, a long-acting antihistaminic drug, which is used as a P-gp substrate [265,266].

Plasma levels of voriconazole, an antifungal agent and CYP2C19 substrate, decreased after long-term coadministration of SJW in a clinical study [252]. This observation supports the enzymatic induction of CYP2C19.

Clinical study that involved coadministration of omeprazole with SJW over a period of 2 weeks resulted in decreased plasma concentrations of omeprazole and increased concentration of metabolites, CYP3A4-mediated sulfoxidation, and 2 C19-catalyzed hydroxylation, indicating induction of both these CYP enzymes by SJW [286].

19.6.21 Valerian (*Valeriana officinalis*, Family Valerianaceae)

The extract of dried roots of valerian has been historically used to treat insomnia as an alternative to benzodiazepine and sometimes as an anxiolytic, hypnotic, and anticonvulsant [287,288]. It is sometimes also used in the treatment of migraine due to claims of its muscle relaxant property as well as in the treatment of gastrointestinal cramps and irritable bowel syndrome. The primary chemical components of valerian are valerenic acid and its derivatives, valepotriates, alkaloids, furanofuran lignans, and free amino acids [289]

Organic extracts of the valerian root have shown inhibition of CYP3A4 *in vitro* up to 88% [290], whereas valerenic acid, an active component in valerian, has demonstrated a much lower inhibitory potential toward CYP3A4 and minor inhibition of CYP2C9 and CYP2C19 [291]. Donovan *et al*. [292] evaluated the effect of valerian extract dosed at 1000 mg/day for 16 days and observed minimal alteration of CYP3A4 activity that was not clinically significant and no effect on CYP2D6. Gurley *et al*. [79] reported that dosing valerian at a total daily dose of 375 mg for 28 days had no impact on CYP1A2, CYP2D6, CYP2E1, and CYP3A4. While there are no literature reports of the potential for valerian to interact with P-gp substrates, no clinical reports of adverse events linked to valerian are currently available.

19.7 CONCLUSIONS AND FUTURE PERSPECTIVES

It is estimated that ~30% of patients in the United States currently use herbal dietary supplements [293]. Similarly, in other developed countries such as Australia, New Zealand, and some of the European countries, an estimated one third of adults use herbal supplements for promoting health and managing diseases [294]. The proportion of adults using herbal remedies increases sharply in many developing countries such as China and India, where more than 80% of the population is known to use herbal products [294]. Reasons for the increased use of herbal products include the popular belief that remedies of natural origin are safe, affordable, and easily available (i.e., local health foods, neighborhood grocery stores, and discount supermarkets) [295]. Many patients while taking herbal dietary supplements do not inform their physicians and a reason cited for this lack of communication may be fear of disapproval by their physicians or a desire to control personal therapy [296]. An important and real

safety concern associated with the use of herbal dietary supplements is that the ADME properties are rarely known, leading to an increased risk of unexpected interactions when concomitantly administered with prescription medications. The PK interactions of prescription medications by herbs that have been reported are primarily associated with inhibition or induction of CYP and P-gp enzymes; however, in many cases, the *in vitro* data do not accurately predict the clinical outcome. Thus, further studies are necessary to be able to develop a predictive assessment for clinical herb–drug interactions.

Currently, a knowledge gap exists with the interaction of prescription medication on the PK and PD of herbs and herbal formulations. With the cost of prescription medications skyrocketing and an increased health-awareness in the general population, it is inevitable that the use of herbal dietary supplements will increase. It is the need of the hour, therefore, that studies are conducted with scientific rigor and acceptable norms to characterize herbal medicines with regulatory oversight, much like is done today with pharmaceutical drugs.

ABBREVIATIONS

AUC	Area Under the Concentration Curve
C_{max}	Maximum Concentration
CYP	Cytochrome P450
EMEA	European Medicines Agency
FDA	Food and Drug Administration
P-gp	P-glycoprotein
T_{max}	Time Required to Reach C_{max}
$t_{1/2}$	Half-Life
UGT	Uridine Glucuronosyltransferase

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