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REVIEW ARTICLE

Herbal Remedies in the United States: Potential Adverse Interactions With Anticancer Agents

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ABSTRACT

Purpose
Interest in the use of herbal products has grown dramatically in the Western world. Recent estimates suggest an overall prevalence for herbal preparation use of 13% to 63% among cancer patients. With the narrow therapeutic range associated with most anticancer drugs, there is an increasing need for understanding possible adverse drug interactions in medical oncology.

Methods
In this article, a literature overview is provided of known or suspected interactions of the 15 best-selling herbs in the United States with conventional allopathic therapies for cancer.

Results
Herbs with the potential to significantly modulate the activity of drug-metabolizing enzymes (notably cytochrome P450 isozymes) and/or the drug transporter P-glycoprotein include garlic (*Allium sativum*), ginkgo (*Ginkgo biloba*), echinacea (*Echinacea purpurea*), ginseng (*Panax ginseng*), St John's wort (*Hypericum perforatum*), and kava (*Piper methysticum*). All of these products participate in potential pharmacokinetic interactions with anticancer drugs.

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

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INTRODUCTION

In recent years, interest in complementary and alternative medicine (CAM) has grown rapidly in the industrialized world. The National Center for Complementary and Alternative Medicine defines CAM as a group of diverse medical and health care systems, practices, and products not considered part of conventional medicine. Biologically based therapies in CAM use substances found in nature, such as herbs, foods, and vitamins. Herbal remedies include dietary supplements (any product other than tobacco intended for ingestion as a supplement to the diet, including vitamins, minerals, antioxidants, herbal products, metabolites, and other products), phytomedicine (the use of plants or plant parts to achieve a therapeutic effect), and botanical medicine or phytomedicine (botanic supplements used as medicine). Factors contributing to this increase are dissatisfaction with conventional allopathic therapies, patients' desire to be more active in their own health care, and patients' philosophical orientations.[1,2] It is estimated that up to one third of the entire population in the United States used CAM in the last 12 months; the majority of those individuals use herbal products on a routine basis.[3-5] An estimated 15 million adults combined herbal remedies with prescription medications, with more recent estimates putting this figure at approximately 16%.[6-8] With a larger number of the population using herbal treatments, combined with allopathic therapies, the risk for herb-drug interactions is a growing concern.

Table 1. Top-Selling Herbal Supplements in the United States

2002 Rank	Herb	Plant Name	Primary Clinical Indications	Retail Sales in 2002* ($US)	2001 Rank
1	Garlic	*Allium sativum*	Hypercholesterolemia	34,509,288	3
2	Ginkgo	*Ginkgo biloba*	Dementia, intermittent claudication	32,998,528	1
3	Echinacea	*Echinacea purpurea*†	Prevention of common cold	32,448,966	2
4	Soy	*Glycine max*	Menopausal symptoms	28,252,518	5
5	Saw palmetto	*Serenoa repens*	Benign prostate hyperplasia	23,053,036	6
6	Ginseng	*Panax ginseng*	Physical and mental fatigue	21,686,192	4
7	St. John's wort	*Hypericum perforatum*	Mild depression	14,969,575	7
8	Black cohosh	*Actaea racemosa*‡	Menopausal symptoms	12,333,188	10
9	Cranberry	*Vaccinium macrocarpon*	Urinary tract infection	11,857,782	9
10	Valerian	*Valeriana officinalis*	Insomnia, stress	8,120,329	8
11	Milk thistle	*Silybum marianum*	Alcoholic cirrhosis and hepatitis	7,762,350	12
12	Evening primrose	*Oenothera biennis*	Premenstrual syndrome	6,024,896	13
13	Kava	*Piper methysticum*	Anxiety	4,423,427	11
14	Bilberry	*Vaccinium myrtillus*	Diabetic retinopathy	3,381,351	15
15	Grape seed	*Vitis vinifera*	Allergic rhinitis	3,054,816	14

*Data obtained from Blumenthal[12].
†Other species include *E. angustifolia,* and *E. pallida.*
‡Formerly *Cimicifuga racemosa.*

The major cause of the concern is the potential for herbs to interact with prescription drugs, altering their pharmacokinetic characteristics and leading to clinically significant interactions. More than 100,000 deaths per year in the United States can be attributed to drug interactions, placing drug interactions between the fourth and sixth leading cause of death,[9] and it has been suggested that the greater part of these might be linked to the use of herbs.[10] Given the narrow therapeutic range associated with most anticancer agents, there is an increasing need to understand possible adverse drug interactions in medical oncology.[11] This report reviews the existing data on known or suspected interactions between the best-selling, over-the-counter herbal medicines in the United States (Table 1) and conventional prescribed drugs, with further discussion of their clinical implications for the chemotherapeutic treatment of cancer.

USE OF CAM BY CANCER PATIENTS

CAM use is more common among patients with cancer than in the general population.[13] By the late 1990s, surveys showed that CAMs were widely used by cancer patients, with a prevalence ranging from 7% to 64% of patients sampled in 26 studies conducted worldwide (average prevalence, 31.4%).[14,15] Follow-up evaluations indicate that this use has steadily increased, with a current overall prevalence for CAM use of 37% to 83%, and for herbal preparations of 13% to 63% (Table 2). Between 54% and 77% of patients receiving conventional therapy use CAMs,[8,17] and up to 72% do not inform their treating physician.[5,28] Interestingly, patients with breast cancer tend to use more CAMs than individuals with other types of malignancy,[23] presumably because more women than men use CAMs.[6,29,30]

POTENTIAL MECHANISMS FOR INTERACTIONS

Combined use of herbs with anticancer drugs may increase or reduce the effects of either component, possibly resulting in clinically important interactions. Obviously, synergistic therapeutic effects may complicate the dosing regimen of long-term medications or lead to unfavorable toxicities. Herbal preparations may interact with conventional anticancer drugs at various anatomic or physiological sites, changing the rate of elimination or the amount of drug absorbed. Although interactions are most likely to arise secondary to altered pharmacokinetics of the involved drugs,[10,31,32] pharmacodynamic interactions[33,34] and intrinsic toxicity of several herbs have also been documented.[35]

When an herb is given in combination with anticancer drugs, all aspects of pharmacokinetics might be affected, including absorption (resulting in altered absorption rate or oral bioavailability), distribution (mostly caused by protein-binding displacement), metabolism, and excretion. Most known drug interactions are due to changes in metabolic routes related to altered expression or functionality of cytochrome P450 (CYP) isozymes. This class of enzymes, particularly the CYP3A4 isoform, is responsible for the oxidation of the majority of currently prescribed anticancer drugs, resulting in more polar and usually inactive metabolites (Fig 1).[36,37] Elevated CYP activity (induction), translated into a more rapid metabolic rate, may result in a decrease in plasma concentrations and in total loss of ther-

Table 2. Prevalence of Complementary and Alternative Medicine Use Among Cancer Patients

Main Treatment	Disease	No. of Patients	Method	Prevalence (%)	Comments	Reference
Herbs, vitamins, diet	Various	151	Interview	CAM: males, 56; females, 30	38% users had confidence in CAM	16
Herbs, vitamins, diet	Various	304	Interview	CAM: Patients on conventional therapy, 54	40% of patients abandoned conventional therapy for CAM	17
Herbs, vitamins, diet	Ovarian cancer	295	Questionnaire	CAM since diagnosis	CAM mostly used in conjunction with conventional medicine	18
Herbs, homeopathy, diet	Various	300	Questionnaire	52% used CAM	Younger patients more likely to use CAM	19
Chinese medications	Various	100	Questionnaire	64% used CAM	Prevalence in females (76%) compared with males (58%)	20
Herbal medicine, vitamins	Breast cancer	112	Interview	14% used herbal therapy	23% used megavitamins	21
Herbal medicine, vitamins	Breast cancer	411	Questionnaire	25% used herbal therapy	50% used vitamins; overall CAM use was 67%	2
Herbal medicine	Breast cancer	379	Interview	14% used herbal therapy	Overall CAM use was 48%	22
Herbal medicine	Various	617	Questionnaire	44% used herbal therapy	Overall CAM use was 75%	23
Herbal medicine, vitamins	Breast cancer	453	Questionnaire	63% used herbal therapy	Overall CAM use was 83%; 77% combined herbals with conventional medicines; 36% did not inform physicians	8
Herbal medicine, vitamins	Breast cancer	763	Questionnaire	49% used herbal therapy	87% used vitamins	24
Herbs, vitamins, diet	Breast cancer	236	Questionnaire	20% used herbal therapy	Overall CAM use was 65%	25
Herbs, vitamins, diet	Prostate cancer	268	Questionnaire	Up to 80% used CAM	24% did not inform physicians	26
Herbal medicine, vitamins	Prostate cancer	50	Interview	22% used herbal therapy	Overall CAM use was 37%	27
Herbal medicine, vitamins	Prostate cancer	190	Questionnaire	13% used herbal therapy	Overall CAM use was 43%; 72% did not inform physician	28

Abbreviation: CAM, complementary and alternative medicine.

apeutic effect. Conversely, suppression (inhibition) of CYP activity may trigger a rise in plasma concentrations and lead to exaggerated toxicity commensurate with overdose.

One of the principal mechanisms that can explain interactions with anticancer agents given orally is the affinity for ATP binding-cassette transporters expressed in the intestinal epithelium and directed towards the gut lumen (Fig 1). The three major classes of drug transporters, referred to as P-glycoprotein (ABCB1),[38] multidrug resistance-associated protein-1 (MRP1; ABCC1) and its homologue MRP2 (cMOAT; ABCC2),[39] and breast cancer-resistance protein (BCRP; ABCG2),[40] may play a significant role in mediating transmembrane transport of anticancer drugs. Extraction of anticancer drugs by extensive metabolism in the gut wall and/or the liver during first-pass (ie, before reaching the systemic circulation) is another potential mechanism involved in suspected interactions for various agents.[41]

KNOWN HERB-DRUG INTERACTIONS

Garlic

In 2002, garlic (*Allium sativum*) was the best-selling herbal medicine in the United States, with total retail sales of more than $34 million.[12] Garlic has long been used as a culinary spice and medicinal herb. For more than 5,000 years, garlic has been cultivated in the Middle East and was first mentioned in Chinese medicine in 510 A.D. Early trials suggested the potential of garlic to lower cholesterol and triglyceride levels in serum,[42,43] but a recent trial has shown almost no benefit.[44] Garlic has also been shown to alter blood coagulation by increasing platelet aggregation and increasing fibrinolysis.[45] Garlic has been used in a variety of conditions, including atherosclerosis, chronic candidiasis, hypertension, hyperlipidemia, hypertriglyceridemia, peptic-ulcer disease, peripheral vascular disease, and sickle-cell anemia, and as a chemopreventative agent for gastrointestinal tumors.[46]

Effects of garlic on drug-metabolizing enzymes. Allicin, a sulfur compound and the active ingredient in garlic, is produced from alliin in the presence of the enzyme alliinase when fresh garlic is crushed or chewed. This also produces other sulfur compounds, including aloene, allyl sulfides, and vinyldithiins.[47] In vitro studies have shown that garlic constituents modulate the activity of various CYP isozymes. Extracts of fresh garlic, garlic oil, and freeze-dried garlic exhibit an inhibitory effect on CYP2C9*1, CYP2C19, CYP3A4, CYP3A5, and CYP3A7 metabolism, whereas no effect on CYP2D6 was observed.[48,49] Rats treated with diallyl sulfide, diallyl disulfide, allylmethyl sulfide and allyl mercaptan had a suppression of CYP2E1 activity as a result of competitive inhibition.[50-57] In addition, diallyl sulfone is known to be a suicide inhibitor of CYP2E1, forming a

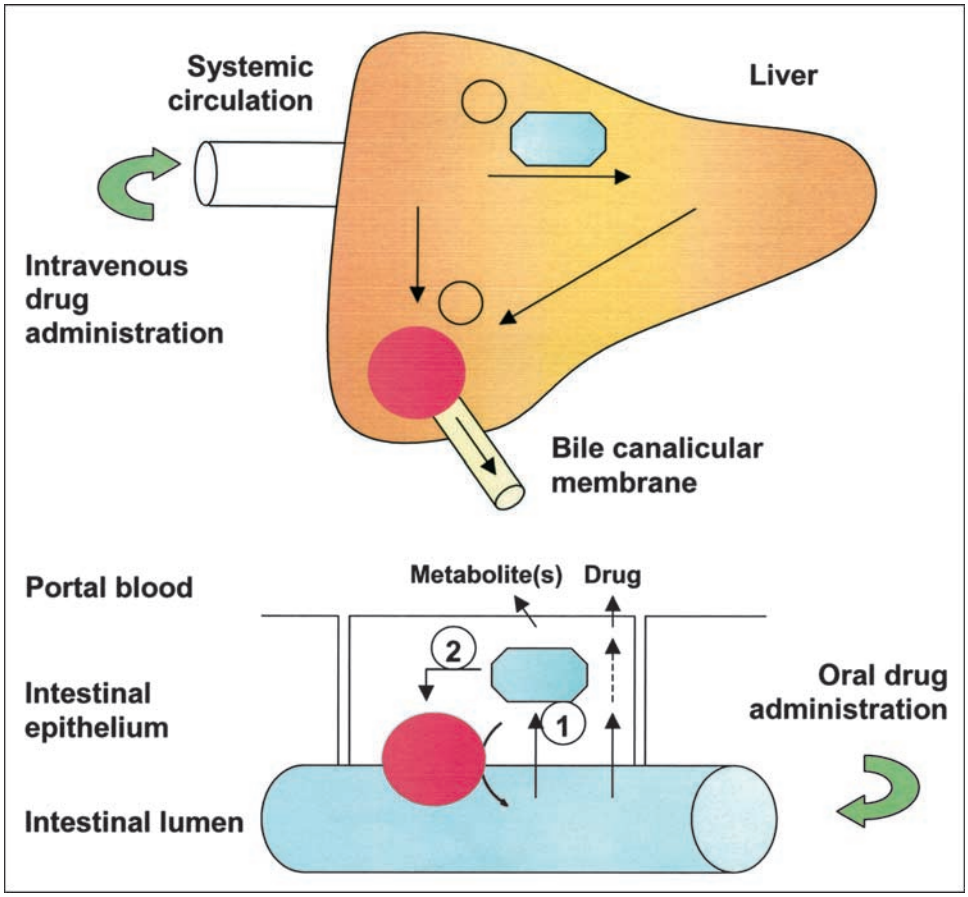

Fig 1. Common mechanisms for possible interactions between herbs and anticancer drugs. Herbs can either induce or inhibit activity of cytochrome P450 (CYP) isozymes (1) or active transport by ATP binding cassette transporter proteins (ABC TP;2) in the liver (top) or in the intestinal epithelium (bottom).

complex leading to autocatalytic destruction.[58] However, long-term administration (eg, > 6 weeks) led to enhanced activity and increased expression of CYP1A, CYP2B,[52,59,60] and CYP3A.[61] Studies using in vitro and in vivo animal models have also indicated that various garlic constituents used at very high concentrations can induce the activity of CYP3A4[62] and conjugating enzymes such as glutathione *S*-transferases and quinone reductases.[56,63-65]

Pharmacokinetic interactions with garlic. An almost 40% decrease in 6-hydroxychlorzoxazone/chlorzoxazone ratio reported in one study suggests that CYP2E1 activity is also inhibited in humans receiving garlic for 4 weeks (Table 3).[66] Clinical studies using probe-drug cocktails have shown that garlic has no significant effect on the activity of CYP1A2 (caffeine), CYP2D6 (debrisoquine, dextromethorphan), and CYP3A4 (alprazolam, midazolam).[66,68] Two previous trials indicated that garlic significantly decreases the systemic exposure to the HIV protease inhibitors saquinavir[70] and ritonavir.[69] These protease inhibitors are not only metabolized by CYP3A4,[71] but are also substrates for P-glycoprotein.[72] The data obtained using alprazolam and midazolam as probe substrates for CYP3A4 suggest that the pharmacokinetic alterations of saquinavir and ritonavir after garlic treatment are not due to induction of CYP3A4 but, more likely, to modulation of the activity of another (unknown) enzyme or a drug transporter, although an interaction at the level of P-glycoprotein is unlikely.[48] Although product composition and designs of the clinical studies vary widely,[47] there appears to be little likelihood of significant interactions between garlic and anticancer drugs that are predominantly metabolized by CYP2D6 or CYP3A4.

Ginkgo

A staple in Chinese medicine, ginkgo (*Ginkgo biloba*) is used for a variety of ailments[73] and has multiple actions, including antiedemic, antihypoxic, antioxidant, antiplatelet, free-radical scavenging, and microcirculatory properties.[73] It has been used in patients for asthma, brain trauma, cochlea deafness, depression, free-radical damage to the retina, impotence, myocardial reperfusion, and vertigo.[74,75] In some European countries, ginkgo has been approved for dementia, intermittent claudication, memory improvement, and tinnitus.[73] A recent clinical trial on normal, healthy adults in which a leading ginkgo extract did not produce any significant improvement in cognitive effects,[76] likely contributed to the recent decline of ginkgo from the top-selling position it held at least since 1995.[12]

Table 3. Pharmacokinetic Interactions with Garlic (Allium sativum)

Drug	Herbal Regimen	No. of Participants	Parameters	Effects	Reference
Acetaminophen	300 mg/3 months	16	AUC, urinary recovery	No significant differences	67
Alprazolam	1,800 mg bid/14 days	14	AUC, C_{max}, $T_{1/2}$	No significant differences	68
Caffeine	500 mg tid/28 days	12	Paraxanthine/caffeine ratio	No significant difference	66
Chlorzoxazone	500 mg tid/28 days	12	6-hydroxylation ratio	39% decrease*	66
Debrisoquine	500 mg tid/28 days	12	Urinary recovery	No significant difference	66
Dextromethorphan	1,800 mg bid/14 days	14	Dextrophan urine ratio	No significant differences	68
Midazolam	500 mg tid/28 days	12	1-hydroxyl serum ratio	No significant change	66
Ritonavir	10 mg bid/4 days	10	AUC	17% decrease†	69
Saquinavir	GalliPure bid/20 days	10	AUC, C_{max}	51% and 54% decreased‡	70

NOTE. All participants in these studies were volunteers.
Abbreviations: $T_{1/2}$, half-life of the terminal phase; AUC, area under the time-concentration curve; C_{max}, maximum concentration; CL, clearance; CL/F, apparent oral clearance; F, oral bioavailability.
*Postulated mechanism, induction of CYP2E1.
†$P > .05$.
‡Postulated mechanism, inhibition of ABCB1 P-glycoprotein.

An important consideration for clinicians is the notion that one of the principal components of ginkgo, ginkgolide B, is a potent antagonist of the platelet-activating factor, thereby increasing the fluididity of blood.[77,78] Although this can be beneficial in patients with intermittent claudication, it may have a detrimental effect on patients undergoing anticoagulation therapy—for example, patients with a prior history of deep vein thrombosis, patients who have an indwelling catheter and are receiving warfarin, and patients who have an inherent inability to produce platelets. Case reports of patients who were taking ginkgo and had spontaneous bleeding events, including fatal intracerebral mass bleedings, have been summarized recently.[79-82] Although it has been reported that antioxidants and free-radical scavengers can actually prevent cancer,[83] there is the possibility that these agents could also interfere with chemotherapy (eg, alkylating agents, anthracyclines, epipodophyllotoxins, and platinum analogues) and radiation therapy by acting as free-radical scavengers.[84]

Effects of ginkgo on drug-metabolizing enzymes. In rats, repeat exposure to high-doses of an extract of ginkgo markedly increased the mRNA expression and functional activity of several hepatic drug-metabolizing enzymes of the CYP family, including pentoxyresorufin *O*-dealkylase (CYP2B) and testosterone 6β-hydroxylase (CYP3A).[85,86] In these studies, the levels of CYP1A, CYP2E1, and CYP2C9 were affected to a lesser extent, consistent with phenotyping data obtained in healthy volunteers receiving ginkgo for 12 days[87] or 28 days.[66] In the former study, however, it was noted that ginkgo was a moderate inducer of CYP2C19.[87] In addition to inducing effects, studies using human models in vitro and in vivo have indicated that various components of ginkgo can also be potent inhibitors of CYP2C9, CYP2C19,[88] and CYP3A4.[89]

Pharmacokinetic interactions with ginkgo. Long-term administration of ginkgo to volunteers (for up to 28 days) had no effect on the pharmacokinetics of antipyrine, a nonspecific probe of hepatic oxidation,[90] or the 1-hydoxymidazolam/midazolam concentration ratio, a marker of CYP3A activity.[66] In another study, however, ginkgo increased the plasma concentrations of the CYP3A4 substrate nifedipine by 53% (Table 4),[93] confirming the potential for enzyme inhibition observed in vitro.[95] The discrepant findings for effects of ginkgo on CYP3A4 observed in this trial and in the phenotyping studies is possibly related to the highly variable phytochemical composition of commercially available ginkgo extracts,[96] as well as applied dose regimens and the duration of exposure to ginkgo. The potential importance of the change in CYP2C19 activity noted previously in a cocktail screening approach,[87] was verified by the observation that ginkgo significantly reduced the metabolism of omeprazole, a CYP2C19 substrate, in Chinese patients.[94]

Ginkgo was recently shown to have no effect on the pharmacokinetics of oral digoxin, a substrate for P-glycoprotein,[97] that does not undergo significant oxidative metabolism.[91] In this context, it is noteworthy that digoxin has near complete bioavailability after oral administration,[98] suggesting that transport is not an important limiting step in digoxin absorption. Hence, it cannot be excluded that some constituents of ginkgo extracts interfere with the pharmacokinetics of other agents for which P-glycoprotein-mediated drug transport is the crucial process in oral absorption. Collectively, these clinical data indicate that gingko may interfere with the pharmacokinetics of anticancer drugs metabolized by CYP2C19 or CYP3A4.

Echinacea

Echinacea is one of the most commonly used alternative medicines in the world, representing 10% of the herbal market.[99] There are nine species of the genus *Echinacea*, a member of the sunflower family, found in North America.

Table 4. Pharmacokinetic Interactions With Ginkgo (*Ginkgo biloba*)

Drug	Herbal Regimen	No. of Participants	Parameters	Effects	Reference
Antipyrine	400 mg/13 days	24	$T_{1/2}$	No significant difference	90
Caffeine	280 mg bid/12 days	12	Paraxanthine/caffeine ratio	No significant difference	87
Caffeine	60 mg tid/28 days	12	Paraxanthine/caffeine ratio	No significant difference	66
Chlorzoxazone	280 mg bid/12 days	12	6-hydroxylation ratio	15% increase*	87
Chlorzoxazone	60 mg tid/28 days	12	6-hydroxylation ratio	23% increase*†	66
Dapsone	280 mg bid/12 days	12	4′-hydroxyl urine excretion	43% increase‡	87
Debrisoquine	280 mg bid/12 days	12	Urinary recovery	No significant difference	87
Debrisoquine	60 mg tid/28 days	12	Urinary recovery	No significant difference	66
Digoxin	80 mg tid/21 days	8	AUC, C_{max}, CL/F	No significant differences	91
LHRH	80 mg tid/8 weeks	7	FSH, LH, prolactin, TSH	No significant differences	92
Mephenytoin	280 mg bid/12 days	12	4′-hydroxyl urine ratio	8.6% increase§	87
Midazolam	60 mg tid/28 days	12	1-hydroxyl serum ratio	No significant change	66
Nifedipine	120 mg/18 days	22	C_{max}	53% increased¶	93
Omeprazole	280 mg bid/12 days	18	5-hydroxyl AUC ratio	68% decrease§‖	94

NOTE. All participants in these studies were volunteers.
Abbreviations: $T_{1/2}$, half-life of the terminal phase; AUC, area under the time-concentration curve; C_{max}, maximum concentration; CL, clearance; CL/F, apparent oral clearance; F, oral bioavailability.
*Postulated mechanism, induction of CYP2E1.
†P = .201.
‡Postulated mechanism, induction of N-acetyltransferase II.
§Postulated mechanism, induction of CYP2C19.
‖Omeprazole to 5-hydroxyomeprazole ratio.
¶Postulated mechanism, inhibition of CYP3A4.

The most common and widespread of these are *Echinacea angustifolia*, E. *purpurea*, and E. *pallida*, each of which has a long history of medicinal use. The majority of pharmacologic studies since 1939 have been conducted on E. *purpurea* preparations made from the fresh pressed juice of the flowering plant.[100,101]

Hundreds of studies have been published during the preceding 50 years on the chemistry, pharmacology, and clinical applications of echinacea. Many of these have reported using echinacea for immune system stimulation.[102-106] The major proposed mechanisms of action include increased numbers of granulocytes, enhanced phagocytic performance, inhibition of virus proliferation, cytokine activation, increased T-lymphocyte production, and an increase in the T4/T8 cell ratio.[106,107] Echinacea is currently used to assist in the prevention of cold and influenza symptoms,[108] *Candida* infections, chronic respiratory infections, prostatitis, and rheumatoid arthritis,[102,104,109,110] although well-controlled studies have shown little, if any, benefit.[102,111]

Effects of echinacea on drug-metabolizing enzymes. Many chemical compounds have been identified from echinacea species, and it is currently not possible to attribute the pharmacologic effects to any specific substance.[112] Constituents that have been identified include volatile oil, caffeic acid derivatives, polysaccharides, polyines, polyenes, isobutylamides, and flavonoids of the quercetin and kaempferol type. Both an extract of echinacea[113] as well as quercetin[114] have been shown to significantly inhibit the activity of CYP3A4 and CYP2C9.[95] Some flavonoids present in echinacea extracts can either inhibit or activate human CYPs and drug transporters, depending on their structures, concentrations, and assay conditions.[10] In particular, quercetin and kaempferol are known to inhibit MRP1[115] and increase the expression of CYP1A1,[116,117] whereas quercetin induces CYP3A4 in human hepatocytes.[62] This latter effect is consistent with a recent study indicating that oral intake of echinacea induces the activity of CYP3A in healthy volunteers.[118]

Pharmacokinetic interactions with echinacea. Midazolam, a substrate for CYP3A4 and CYP3A5, was cleared 42% faster during an 8-day echinacea treatment in 12 volunteers, and there was a 23% reduction in midazolam AUC.[118] The oral bioavailability of midazolam in this study was significantly increased from 24% to 36% in the presence of echinacea, indicating that the hepatic and intestinal availabilities were altered in opposite directions. These data suggest that echinacea is likely to interact with anticancer drugs that are a substrate for CYP3A4 and that the interaction will depend on the relative extraction of drugs at the hepatic and intestinal sites and the route of administration. Like several other herbal preparations, echinacea from retail stores often does not contain the labeled species.[99] Obviously, the high variability observed in concentration of constituents of the herb may have implications for echinacea's ability to modulate drug absorption and disposition.

Soy

The use of soy (*Glycine max*) and soy-derived products for the treatment of menopause in women is growing with

the fear of possible side effects of traditional hormone replacement therapy.[119] The principal constituents of soy, the isoflavones genistein and daidzein, are structurally similar to 17β-estradiol and produce weak estrogenic effects (ie, phytoestrogens).[120] At present it seems prudent to discourage soy-derived products in patients with estrogen-dependent tumors (eg, breast cancer or endometrial cancer), because experimental data indicate that soy can stimulate the growth of these tumors in mice.[121-123] Furthermore, as genistein can negate the inhibitory effect of tamoxifen on breast cancer growth, women taking this agent should especially avoid soy.[124]

Isoflavones, such as genistein and daidzein, can also inhibit oxidative and conjugative metabolism in vitro and in vivo.[125] Notably, genistein has been shown to inhibit CYP1A, CYP2E1,[126] CYP2A6, CYP2C9, CYP2D6, CYP3A4,[127] and CYP3A7 (but not CYP3A5),[128] as well as UGT1A1, and particularly UGT2B15.[129] In 20 healthy volunteers, a 14-day course of soy extract (50 mg bid) did not alter the ratio of the amounts of 6β-hydroxycortisol and cortisol excreted in the urine, suggesting that soy is not an inducer of CYP3A4 in humans.[129] It is noteworthy, however, that genistein interacts with transporters such as P-glycoprotein,[117] MRP1,[115] and MRP2.[130] Given that these transporters are involved in the intestinal absorption and biliary secretion of several anticancer drugs,[131] it is reasonable to suspect that soy may alter drug absorption and/or disposition of such agents in humans. To our knowledge, this possibility has not been explored.

Saw Palmetto

Saw palmetto (*Serenoa repens*) is a small low-growing palm tree native to southeastern North America, particularly Florida. Saw palmetto is used in men with the hope of toning and strengthening the reproductive system, and specifically for symptoms of prostate enlargement.[132,133] It was also one of eight herbs present in PC-SPES, a preparation with estrogenic activity that is currently unavailable and that reduces serum testosterone in men with prostate cancer.[134,135] It has been reported, however, that saw palmetto is the least potent ingredient of PC-SPES to inhibit prostate cancer proliferation.[136,137] In women, the principal use of saw palmetto is to reduce ovarian enlargement and to increase the size of small, undeveloped mammary glands.[73]

The main constituents of saw palmetto include carbohydrates, fixed oils, steroids, flavonoids, resin, tannin, and volatile oil.[138] Although no drug interactions or medical contraindications with the use of saw palmetto have been reported, it would be prudent to avoid concomitant use with other hormonal therapies (eg, estrogen replacement therapy and oral contraceptives), which may provide an additive effect.

Ginseng

Although there are many types of ginseng (Siberian, Asian, American, and Japanese), the most common type used in herbal preparations is Asian ginseng (*Panax ginseng*). Ginseng's properties have reported to include sedation, hypnotic, aphrodisiac, antidepressant, and diuretic.[139] Known pharmacologic actions include stimulation of the CNS, modulation of the immune system, and increase of glycogen storage.[73] The efficacy of ginseng in the treatment of physical performance, psychomotor performance and cognitive function, immune modulation, diabetes mellitus, and herpes simplex type 2 infections has been reviewed recently.[140] Based on this analysis, it was concluded that the efficacy of ginseng is not established beyond reasonable doubt for any of these indications. However, a retrospective trial involving 4,634 patients suggested a dose-response relationship between ginseng consumption and a decrease in the risk of cancer, with a relative risk reduction of 40%.[141] Evidence also indicates that some preparations of ginseng have phytoestrogenic effects, suggesting that its use, as with soy supplementation, should be discouraged in women with breast cancer or endometrial cancer.[84]

Ginsenosides, the presumed active constituents in ginseng extracts, may be the culprit when looking at adverse effects and drug interactions with ginseng. Ginsenosides have been shown to inhibit cAMP phosphodiesterase,[142] and the central nervous excitation associated with ginseng usage may be related to increased cAMP levels, as well as known interactions with monoamine oxidase inhibitors.[143,144]

A single case report has also pointed to a possible link between ginseng consumption and an interaction resulting in a decrease in the international normalized ratio for a patient stabilized on warfarin.[145] Interestingly, rat studies have shown no effect of ginseng on absorption or elimination of warfarin, as well as no changes in steady-state prothrombin times.[146] Components of ginseng have been shown to inhibit thromboxane A_2, which might result in increased bleeding events, but no such events have ever been reported.[147,148]

Effects of ginseng on drug-metabolizing enzymes. Treatment of mice with a ginseng extract caused a marked increase in total hepatic CYP content, and the activities of NADPH-cytochrome c reductase and total carboxylesterase.[149] In vitro studies using human liver microsomes have suggested that a crude extract of ginseng as well as the various ginsenosides, at clinically relevant concentrations associated with ginseng use,[150] moderately inhibit CYP1A1, CYP1A2, CYP1B1,[151] CYP2D6,[152] CYP2C9,[95,152] CYP2C19,[152] CYP2E1,[153,154] and CYP3A4.[89] An extract of ginseng at concentrations of 0.5 mg/mL did not exhibit inductive properties toward CYP3A4 in vitro in human hepatocytes.[62] Ginseng protopanaxatriol ginsenosides

Table 5. Pharmacokinetic Interactions With Ginseng (*Panax ginseng*)

Drug	Herbal Regimen	No. of Participants	Parameter	Effects	References
Caffeine	500 mg tid/28 days	12	Paraxanthine/caffeine ratio	No significant difference	67
Cortisol	100 mg bid/14 days	20	6β-hydroxyl urine ratio	No significant difference	128
Chlorzoxazone	500 mg tid/28 days	12	6-hydroxylation ratio	No significant difference	67
Debrisoquine	500 mg tid/28 days	12	Urinary recovery	No significant difference	67
Ethanol	100 mg/8 days	14	Blood alcohol concentration	32.5% decreased*	156
Midazolam	500 mg tid/28 days	12	1-hydroxyl serum ratio	No significant difference	67
Nifedipine	200 mg/18 days	22	C_{max}	29% increased†	94

NOTE. All participants in these studies were volunteers.
Abbreviations: C_{max}, maximum concentration.
*Postulated mechanism, delayed gastric emptying by ginsenosides.
†Postulated mechanism, inhibition of CYP3A4.

moderately inhibit P-glycoprotein activity in vitro, albeit only at relatively high concentrations of > 200 μg/mL.[155]

Pharmacokinetic interactions with ginseng. The in vitro notion of CYP3A4 inhibition in human hepatocytes[89] is consistent with the finding that an 18-day course of ginseng significantly increased the peak plasma concentration of nifedipine, a CYP3A4 substrate, in healthy volunteers (Table 5).[93] As predicted by in vitro data,[62] phenotype-probe observations in humans indicated a lack of CYP3A4 induction (Table 5). Ginseng consumption has also been related to increased alcohol clearance in rats and humans,[156,157] due to delayed gastric emptying, as well as possible induction of the alcohol dehydrogenase and aldehyde dehydrogenase pathways. As observed with echinacea, substantial variability in ginsenoside content has been reported among commercial ginseng preparations, indicating that clinically significant effects on the pharmacokinetics of anticancer drugs that are metabolized by CYP3A4 could be brand-specific.[158]

St John's Wort

St John's wort (*Hypericum perforatum*), a perennial plant native to Europe, North America, and western Asia, is one of the most extensively studied herbal products.[159] Many of St John's wort's therapeutic applications, including its uses as a vulnerary, diuretic, and treatment for neurologic conditions, stem from traditional Greek medicine, originally documented by Hippocrates (ca. 460-377 B.C.).[160] Since the time of Swiss physician Paracelsus (ca. 1493-1541), it has been used to treat psychiatric disorders.[161] Currently, St John's wort is still widely used for the treatment of mild to moderate depression and other nervous conditions.[162,163] Reported cases and trials have shown varying results of therapy with St John's wort for depressive disorders. Linde et al[164] provided an analysis of 23 trials in 1,757 patients and concluded that treatment of depression with St John's wort was comparable to standard, prescription antidepressants and superior to placebo. More recently, randomized, double blind, placebo-controlled trials evaluating the safety and efficacy of St John's wort in the treatment of patients with major depressive disorders revealed that St John's wort was no more effective than placebo.[165,166]

St John's wort is a very complex mixture of more than two dozen compounds, including catechin-type tannins and condensed-type proanthocyanidins, flavonoids (mostly hyperoside, rutin, quercetin, and kaempferol), biflavonoids (eg, biapigenin), phloroglutinol derivatives like hyperforin, phenolic acids, volatile oils, and naphtodianthrones, including hypericin and pseudohypericin.[167-169] With regard to the antidepressant effects of St John's wort, many of the pharmacologic activities appear to be attributable to hypericin and hyperforin, which inhibit the reuptake of neurotransmitters in synapses,[170] although a contribution of other constituents has been proposed.[171]

Effects of St John's wort on drug-metabolizing enzymes. Various in vitro studies have shown that St John's wort is a potent inducer of CYP1A2,[172] CYP2B6,[173] CYP2C9, CYP2C19,[88] and CYP3A4,[174,175] but not of CYP2D6,[88] CYP3A5, CYP3A7, and CYP3A43.[176] The inducing effects on CYP2B6,[173] CYP2C19,[177] and CYP3A4[178-181] have been linked to hyperforin-induced ligand activation of a steroid- and xenobiotic-regulated transcription factor known as the pregnane X receptor (also known as SXR or NR1I2; Fig 2). Using cDNA-expressed models, St John's wort extracts have also been reported to inhibit the activity of several enzymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 through both competitive and noncompetitive actions.[113,128,181]

Animal studies using probe drugs have provided compelling evidence that St John's wort is also a potent modulator of CYP3A activity in vivo both in mice[182,183] and rats.[184] However, short-term treatment of St John's wort, hypericin, or hyperforin failed to induce CYP isoforms.[185,186] Human studies indicated that long-term (ie, $>$ 2 weeks') administration of St John's wort significantly induced intestinal and hepatic CYP3A4[66,84,187-191] but did

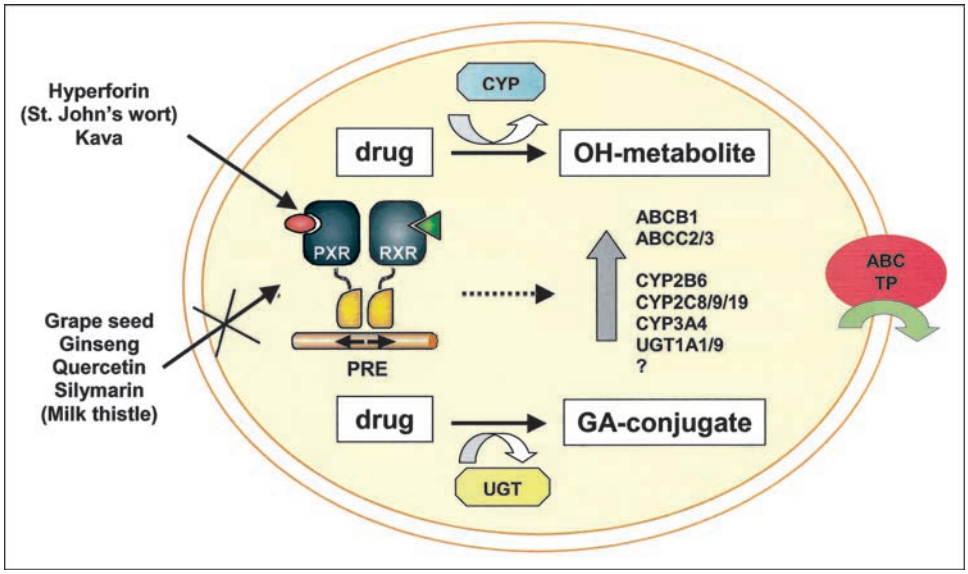

Fig 2. Induction of cytochrome P450 (CYP) isozymes, UDP glucuronosyltransferase (UGT) isozymes, and ATP binding cassette transporter proteins (ABC TP) by herbal preparations through activation of the human pregnane X receptor (PXR; also known as SXR and NR1I2). PXR binds to DNA via a pregnane response element (PRE) as a heterodimer with the 9-*cis* retinoic acid receptor (RXR), and transduces phase I metabolism (eg, oxidation), phase II metabolism (eg, glucuronic acid (GA) conjugation), and active, outward-directed transport. Illustration, T.W. Synold.

not alter CYP2C9,[189] CYP1A2,[66,189] or CYP2D6[66,189,192,193] (Table 6). As predicted from the animal experiments, induction of CYP3A4 by St John's wort is subject to the dosing regimen, and schedules involving administration of the herb for less than 8 days are unlikely to activate the pregnane X receptor.[193,200] The cited studies have also indicated that St John's wort contains both inhibitory and activating constituents for the CYP system, causing temporally distinguishable inhibition and induction depending on the dose, duration of administration, and the formulation and source of the herb.

Effects of St John's wort on drug transporters. LS-80 intestinal carcinoma cell exposed to St John's wort or hypericin have shown strong induction of P-glycoprotein in a dose-dependent fashion.[210] Similarly, the administration of St John's wort significantly increases the intestinal expression of P-glycoprotein in rats and humans,[184] as well as its expression in peripheral blood lymphocytes.[211] Given the broad substrate specificity of this protein, these findings have been used to support the importance of P-glycoprotein in addition to CYP3A4 as a mechanism to reduce oral absorption of substrate drugs given combined with St John's wort.

Pharmacokinetic interactions with St John's wort. Although St John's wort has been shown to be well tolerated, with headache and photosensitivity as its most prominent adverse reactions,[73] clinical trials are now reporting significant pharmacokinetic interactions with St John's wort and drugs from a variety of therapeutic classes (Table 6). These studies followed a number of case reports of serious interactions between St John's wort and digoxin,[212] theophylline,[213] cyslosporine,[214-222] oral contraceptives,[223,224] phenprocoumon,[225] warfarin,[223] and sertraline,[226,227] which were speculated to be secondary to enzyme induction.[34,228]

The mechanism for most of the interactions observed in subsequent clinical trials remains unclear, although for some agents, induction of CYP3A4 (eg, indinavir, midazolam, simvastatin), P-glycoprotein (eg, digoxin, fexofenadine), or both (eg, cyclosporine, tacrolimus) may explain their increased clearance. Nonetheless, although common molecular mechanisms may be involved, the quantitative aspects of CYP3A4 and P-glycoprotein induction are complex and depend on the particular drug and the relative contribution of both proteins to its absorption and disposition.[190] Another factor adding to the complexity is the recent finding that St John's wort produced significantly greater increases in CYP3A4 expression in females compared to males, which appeared to be unrelated to body mass index.[66]

Although no differences have been noted in the extent of inducibility by St John's wort among six different ethnic groups,[191] the effects of this herb remain unpredictable, especially when based on in vitro or animal studies. For example, St John's wort did not alter the pharmacokinetics of the CYP3A4 substrate carbamazepine,[197] presumably because repeated intake of the drug already maximizes enzyme induction.[31] More recently, it was shown that various transcription factors, including the pregnane X receptor, regulate constitutive expression of mouse Ugt1a1 and Ugt1a9,[229,230] and human UGT isoforms.[231] However, in a clinical study, St John's wort had no effect on the extent of glucuronidation of the irinotecan metabolite SN-38,[203] which is a known substrate for UGT1A1 and UGT1A9.[232] Regardless, the modulation of CYP3A4 and P-glycoprotein activity observed with St John's wort is particularly worrying bearing in mind its crucial role in the elimination of many important anticancer drugs.[36] This suggests that interactions between St John's wort and such agents are likely to have clinical and toxicological implications, and that rigorous testing for possible interactions is urgently needed.

Table 6. Pharmacokinetic Interactions With St. Johns Wort (*Hypericum perforatum*)

Drug	Herbal Regimen	Population	No. of Participants	Parameters	Effects	Reference
Alprazolam	300 mg tid/3 days	Volunteers	7	AUC, C_{max}, $T_{1/2}$	No significant differences	95
Alprazolam	300 mg tid/14 days	Volunteers	12	AUC	54% decreased*	194
Amitriptyline	300 mg tid/14 days	Patient with MD	12	AUC, nortriptyline AUC	22%, 44% decreased*†‖¶	195
Caffeine	300 mg tid/28 days	Volunteers	12	Paraxanthine/caffeine ratio	26% increased§	66
Caffeine	300 mg tid/8 days	Volunteers	16	Paraxanthine/caffeine ratio	No significant differences	196
Caffeine	300 mg tid/1 or 14 days	Volunteers	12	AUC, C_{max}, CL/F	No significant differences	189
Carbamazepine	300 mg tid/14 days	Volunteers	8	AUC, CL/F	No significant differences	197
Chlorzoxazone	300 mg tid/28 days	Volunteers	12	6-hydroxyl plasma ratio	110% increased‡	66
Cortisol	300 mg tid/14 days	Volunteers	13	6β-hydroxyl urine ratio	114% increased*	188
Cortisol	300 mg tid/14 days	Volunteers	50	6β-hydroxyl urine ratio	41% increased*	187
Cyclosporin A	300 mg tid/12 days	Volunteers	21	C_{max}, CL/F	28% decr, 63% incr*¶	190
Cyclosporin A	300 mg/14 days	RT patients	11	AUC, C_{max}	46%, 42% decreased*¶	198
Debrisoquine	300 mg tid/28 days	Volunteers	12	Urinary recovery	23% increased†	66
Dextromethorphan	300 mg tid/3 days	Volunteers	7	Dextrorphan urine ratio	No significant difference	193
Dextromethorphan	300 mg tid/8 days	Volunteers	16	Dextrorphan urine ratio	No significant difference	199
Dextromethorphan	300 mg tid/14 days	Volunteers	13	Dextrorphan urine ratio	No significant difference	192
Dextromethorphan	300 mg tid/1 or 14 days	Volunteers	12	Dextrorphan urine ratio	No significant difference	189
Dextromethorphan	300 mg tid/14 days	Volunteers	12	Dextrorphan urine ratio	No significant difference	194
Digoxin	300 mg tid/10 days	Volunteers	13	AUC, C_{max}	25%, 33% decreased¶	200
Digoxin	300 mg tid/14 days	Volunteers	8	AUC	18% decreased¶	184
Fexofenadine	300 mg tid/10 days	Volunteers	30	CL/F	71% increased¶	191
Fexofenadine	300 mg tid/12 days	Volunteers	21	C_{max}, CL/F	39% decreased, 94% increased¶	190
Fexofenadine	900 mg tid/1 day	Volunteers	12	C_{max}, CL/F	45% increased, 20% decreased¶	201
Fexofenadine	300 mg tid/14 days	Volunteers	12	C_{max}, CL/F	No significant difference	201
Indinavir	300 mg tid/14 days	Volunteers	8	AUC	57% decreased*	202
Irinotecan	300 mg tid/14 days	Cancer patients	5	SN-38 AUC	42% decreased*	203
Midazolam	300 mg tid/1 or 14 days	Volunteers	12	F, CL	45% decreased, 27% increased*	189
Midazolam	300 mg tid/28 days	Volunteers	12	1-hydroxyl serum ratio	98% increased*	66
Midazolam	300 mg tid/10 days	Volunteers	30	F, CL	45% decreased, 56% increased*	191
Midazolam	300 mg tid/12 days	Volunteers	21	F, CL	45% decreased, 44% increased¶	190
Mycophenolic acid	600 mg/14 days	RT patients	10	AUC	No significant difference	204
Nevirapine	Unknown	HIV patients	5	CL/F	35% increased*	205
Nifedipine	200 mg/18 days	Volunteers	22	C_{max}	53% decreased*	93
Quazepam	300 mg tid/14 days	Volunteers	13	AUC, C_{max}	25%, 25% decreased*	206
Phenprocoumon	300 mg/11 days	Volunteers	10	Unbound AUC	17.4% decreased	207
Pravastatin	300 mg tid/14 days	Volunteers	16	AUC, C_{max}	No significant differences	208
Simvastatin	300 mg tid/14 days	Volunteers	16	AUC, C_{max}	52%, 28% decreased*	208
Tacrolimus	600 mg/14 days	RT patients	10	AUC	58% decreased*¶	204
Talinolol	900 mg/12 days	Volunteers	9	AUC	36% decreased	209
Tolbutamide	300 mg tid/1 or 14 days	Volunteers	12	AUC, C_{max}, CL/F	No significant differences	189

Abbreviations: $T_{1/2}$, half-life of the terminal phase; AUC, area under the time-concentration curve; C_{max}, maximum concentration; CL, clearance; CL/F, apparent oral clearance; F, oral bioavailability; MD, mild depression; RT, renal transplant.
*Postulated mechanism, induction of CYP3A4.
†Postulated mechanism, induction of CYP2D6.
‡Postulated mechanism, induction of CYP2E1.
§Postulated mechanism, induction of CYP1A2.
‖Postulated mechanism, induction of CYP2C19.
¶Postulated mechanism, induction of ABCB1 P-glycoprotein.

Black Cohosh

The herb black cohosh (*Actaea racemosa*, formerly named *Cimicifuga racemosa*), is native to North America. The roots and rhizomes of this herb are widely used in the treatment of menopausal symptoms and menstrual dysfunction.[233,234] Studies have demonstrated that this botanic product, when standardized properly to the terpene glycoside fraction, shows promise in alleviating menopausal symptoms.[233,235] Interestingly, sales of black cohosh surged dramatically in the second half of 2002,[12] possibly as a result of a study indicating that long-term use of conventional hormone-replacement therapy may actually increase the risk of heart disease and cancer in women.[36]

The phytoconstituents of black cohosh are not completely known, but triterpene glycosides are considered the main active constituents.[237] The clinical effects of black cohosh are probably due to substances with dopaminergic activity rather than an estrogen-like activity.[238]

Adverse effects are extremely uncommon, and there are no known drug interactions.

Cranberry

Currently, there are about 150 species of cranberry in the world. The best known and most popular one is the American cranberry (*Vaccinium macrocarpon*).[239] It is a low-lying fruit plant grown mainly in North America, and the United States currently produces approximately 98% of the world's cranberries. Commercial cranberry preparations contain flavonoids (proanthocyanides and anthocyanins), considered the active ingredients, as well as a number of fatty acids, including quinic acid, and small amount of quercetin and myricetin.[240,241] The most common medicinal uses of cranberry is as a prophylaxis of urinary tract infections,[242,243] The amount of flavonoids in carnberries is probably too low to either inhibit the activity of CYP3A4,[114] or induce the expression of this protein.[62] There are no identified drug interactions associated with the consumption of cranberries or cranberry-containing preparations.

Valerian

Valerian (*Valeriana officinalis*) is a nervine, stimulant, carminative and antispasmodic of complex composition,[244,245] containing isovalerianic, formic and acetic acids, the alcohol known as borneol, and pinene.[246] The valerian root also contains two alkaloids (ie, chatarine and valerianine), which are still under investigation and concerning which relatively little is known. One of the valerian constituents, valerenic acid, has no inhibitory effects at concentrations up to 200 μmol/L on CYP1A2, CYP2D6, CYP3A4, and only very weak effects on CYP2C9, and CYP2C19, as assessed using surrogate substrates on cDNA-derived isoforms.[88] Effects of other valerian alkaloids on drug-metabolizing enzymes and pharmacokinetic interactions between valerian and conventional drugs are currently unknown.

Milk Thistle

Milk thistle (*Silybum marianum*) is one of the most common herbal therapies worldwide and has been used for more than 2,000 years as a tonic, demulcent, and antidepressant, and to assist in lactation.[247] Milk thistle tinctures have been used in the treatment of bronchitis, cough, gallstones, hemorrhage, jaundice, peritonitis, uterine congestion, and varicose veins.[248] The most important medical use of milk thistle today is for liver protection (for example, after the ingestion of poisonous mushrooms) and for treatment of such hepatic ailments as cirrhosis, hepatitis, and fatty infiltration due to alcohol consumption.[249,250] The principal constituent of milk thistle is silymarin, a mixture of flavonoids and phenylpropanoids found in the fruit of the milk thistle plant, and consists mostly of silybin (approximately 50% to 70%), but can also contain silychristin, silyydianin, and other similar flavonoligans.[251]

Effects of milk thistle on drug-metabolizing enzymes. Inhibition of certain hepatic enzymes secondary to silymarin ingestion has been reported,[252] in addition to significant reductions in the glucuronidation of bilirubin and depletion of the UDP glucuronic acid pools.[253] Furthermore, reports of reduced in vitro activity for CYP3A4 (up to 100% at 25 mmol/L),[254,255] CYP2D6, CYP2C9,[255] and UGT1A6/9[254] isozymes by milk thistle components have been published. However, at clinically achievable concentrations (about 0.6 μmol/L at peak concentration),[256,257] silybin, dehydrosylibin, silydianin, and silycristin do not substantially inhibit the activity of CYP2D6, CYP2E1, and CYP3A4 in human liver microsomes.[258] Similarly, the finding that silymarin at concentrations higher than 100 μmol/L inhibits P-glycoprotein[259] and MRP1[115] in some in vitro models is probably of unlikely clinical significance.

Pharmacokinetic interactions with milk thistle. The effect of milk thistle, administered three times a day for a period of 2 or 3 weeks, on the pharmacokinetics of the HIV protease inhibitor indinavir was recently studied indepenently in two groups of 10 volunteers.[260,261] In line with the in vitro findings, milk thistle did not significantly alter the overall exposure to indinavir, although the mean trough concentrations were 25% ($P = .0084$)[260] and 32% ($P > .05$)[261] decreased in the two studies. Indinavir is a substrate for both CYP3A4 and P-glycoprotein that is highly susceptible to enzyme inhibition and induction.[262] Overall, this suggests that milk thistle is unlikely to alter the pharmacokinetics of anticancer drugs that are predominantly eliminated by CYP3A4 or P-glycoprotein.

Evening Primrose

Evening primrose (*Oenothera biennis*) is used to treat premenstrual syndrome,[233] chronic mastalgia, diabetic peripheral neuropathy,[263] atopic eczema, rheumatoid arthritis,[264] and schizophrenia.[265] Evening primrose oil contains a complex mixture of essential fatty acids, including linoleic acid, oleic acid, palmitic acid, stearic acid, and gamma-linolenic acid.[266] *Cis*-linoleic acid moderately inhibits, in a concentration-dependent manner, the in vitro activity of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.[88] It is noteworthy that some of the fatty acids present in evening primrose are among the most highly bound compounds to human serum albumin.[267] Hence, it is possible that drug interactions with evening primrose occur at the level of competitive protein-binding displacement, which may have clinical implications for anticancer agents with a high extraction ratio and that are given intravenously.[268] Even though no cases are known of interactions of evening primrose with conventional medications, it may be prudent to closely monitor concomitant usage in patients receiving concurrent chemotherapy.

Kava

Kava (*Piper methysticum*), a member of the pepper family, is a large-leaved Pacific island plant that has been used in that region for centuries.[269] Kava is an herbal anxiolytic,[270-273] and supplements containing kava are pro-

moted for relaxation (eg, to relieve stress and tension), insomnia, and menopausal symptoms.[73] The major constituents of commercially available kava are kavalactones;[274] a mixture of more than 18 different α-pyrones, including kavain, methysticin, and demethoxyyangonin (5,6-dehydrokawain); kawain; 7,8-dihydrokawain; yangonin; dihydromethysticin; and 5,6-dehydromethysticin.[275]

In vitro, extracts of kava and several of the individual kavalactones were shown to be potent inhibitors of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4,[88,276,277] although whole kava extracts had no effect of the activity of CYP2A6, CYP2C8, and CYP2E1.[276] Since one case report described the coma of a woman after simultaneous ingestion of kava and the CYP3A4 substrate alprazolam,[278] an in vitro-in vivo correlation is possible. Although direct evidence for this relationship is lacking, caution is warranted when kava is used in combination with CYP3A4-substrate anticancer drugs. This seems also important in light of the recent finding that kava produced almost three-fold increased expression of CYP3A4 mRNA in primary cultures of human hepatocytes, as a result of pregnane X receptor activation (Fig 2).[62]

In 2002, most Western countries suspended sales of kava products following a series of reports of serious liver toxicity, including several fatal cases.[279-289] In March 2002, the US Food and Drug Administration Center for Food Safety and Applied Nutrition notified healthcare professionals and consumers in the United States of the potential risk of severe liver injury associated with the use of kava-containing dietary supplements (http://www.cfsan.fda.gov/~dms/addskava.html).[290,291]

Bilberry

Bilberry (*Vaccinium myrtillus*) is a shrubby perennial plant found in the mountains and forests of Europe and the northern United States. Bilberry fruit extracts and leaf decoctions have been used for the treatment of diabetic retinopathy,[292] diarrhea, dysentery, throat inflammations, and chronic fatigue syndrome.[293]

Several active constituents have been isolated from the berries and leaves of the bilberry plant, including anthocyanoside flavonoids (anthocyanins), quercetin, myricetin, catechins, tannins, and iridoids.[294] The anthocyanosides are considered the most important of the pharmacologically active components. The amounts of quercetin in bilberry are lower than in cranberry, and circulating concentrations are of unlikely significance with respect to the ability to modulate CYP3A4 activity in vivo.[295] Because bilberry extracts have antiplatelet aggregating properties, the use of this product should be discouraged in patients with hemorrhagic disorders and those taking anticoagulant or antiplatelet drugs.[47]

Grape Seed

Grape seed (*Vitis vinifera*) is a naturally occurring plant substance that contains a concentrated source of potent antioxidants.[296] Grape seed extracts are used primarily in the treatment of peripheral venous insufficiency, respiratory conditions, allergic rhinitis,[297] and as a cardioprotectant.[298] The chemistry of the grape seed is complex and was shown to contain flavonone compounds such as quercetin, quercitrin, catechin, epicatechin, gallocatechin, epicatechin 3-*O*-gallate, rutin, and luteolin.[299,300] The films that surrounds the seed are rich in procyanidins, a class of proanthocyanidins (condensed tannins) consisting of oligomers of catechin and epicatechin units.[301] In human hepatocytes, grape seed extract produced 270% of control CYP3A4 mRNA at a concentration of 600 ng/mL,[62] indicating the ability to induce enzyme expression in hepatocytes. However, it is implausible that these levels can be reached in humans following intake of commercial grape seed preparations.[301] Interestingly, in a reporter gene assay, grape seed exhibited negligible increases in luciferase activity, suggesting that it induces CYP3A4 by mechanisms that may not involve the human pregnane X receptor (Fig 2).[62] Although the clinical relevance of this observation requires further investigation, caution is needed when high-doses of grape seed extract are administered simultaneously with chemotherapeutic agents.

CONCLUSION AND PERSPECTIVES

In recent years, a wealth of evidence has been generated from in vitro and in vivo studies showing that many herbal preparations interact extensively with drug-metabolizing enzymes and drug transporters. A number of clinically important pharmacokinetic interactions has now been recognized, although causal relationships have not always been established. Most of the observed interactions point to the herbs affecting several isoforms of the CYP family, either through inhibition or induction. These enzymes have a crucial role in the elimination of various anticancer drugs, and concurrent use of some herbs with chemotherapy is destined to have serious clinical and toxicologic implications (Table 7). Therefore, rigorous testing for possible pharmacokinetic interactions of anticancer drugs with widely used herbs is urgently required. An additional consideration for cancer chemotherapy is that herb-mediated induction of various enzymes and transporters may also take place in tumor cells and subsequently result in resistance to anthracyclines, epipodophyllotoxins, taxanes, and vinca alkaloids.[302] Likewise, catalytic inhibition of topoisomerase IIα in tumor cells by some herbs[303] might diminish therapeutic responses to anthracyclines, dactinomycin, and etoposide.[304] Because of the high prevalence of herbal medicine use in the United States, physicians should include herb usage in their routine drug histories to have an opportunity to outline to individual patients which potential hazards should be taken into consideration.[3,84]

Note Added in Proof

Additional important work has been published since the acceptance of this paper, including the evaluation of

Table 7. Specific Herbal Remedies to Discourage and Avoid During Chemotherapy

Herb	Concurrent Chemotherapy/Condition (suspected effect)
Garlic	Avoid with decarbazine (CYP2E1 inhibition); caution with other concurrent chemotherapy (inconclusive data)
Ginkgo	Caution with camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca alkaloids (CYP3A4 and CYP2C19 inhibition); discourage with alkylating agents, antitumor antibiotics, and platinum analogues (free-radical scavenging)
Echinacea	Avoid with camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca alkaloids (CYP3A4 induction)
Soy	Avoid with tamoxifen (antagonism of tumor growth inhibition), and treatment of patients with estrogen-receptor positive breast cancer and endometrial cancer (stimulation of tumor growth)
Saw palmetto	No significant interactions expected
Ginseng	Caution with camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and Vinca alkaloids (CYP3A4 inhibition); discourage in patients with estrogen-receptor positive breast cancer and endometrial cancer (stimulation of tumor growth)
St. John's wort	Avoid with all concurrent chemotherapy (CYP2B6, CYP2C9, CYP2C19, CYP2E1, CYP3A4, and P-glycoprotein induction)
Black cohosh	No significant interactions expected
Cranberry	No significant interactions expected
Valerian	Caution with tamoxifen (CYP2C9 inhibition), cyclophosphamide, and teniposide (CYP2C19 inhibition), cyclophosphamide, and teniposide (CYP2C19 inhibition)
Milk thistle	No significant interactions expected
Evening primrose	No significant interactions expected, but caution with highly extracted drugs (serum-binding displacement)
Kava	Avoid in all patients with pre-existing liver disease, with evidence of hepatic injury (herb-induced hepatotoxicity), and/or in combination with hepatotoxic chemotherapy; caution with camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca alkaloids (CYP3A4 induction)
Bilberry	No significant interactions expected
Grape seed	Caution with camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca alkaloids (CYP3A4 induction), and with alkylating agents, antitumor antibiotics, and platinum analogues (free-radical scavenging)

Abbreviation: EGFR-TK, epidermal growth factor receptor tyrosine-kinase.

potentially significant interactions between ginkgo and alprazolam, dextromthophan,[305] and donepezil[306]; between saw palmetto and alphrazolam and destromthorphan[307]; and between St. John's wort and omeprazole,[308] oral contraceptives,[309,310] tacrolimus,[311] theophyllin,[312] verapamil,[313] and warfarin.[314]

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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