Herbs and Cytotoxic Drugs: Recognizing and Communicating Potentially Relevant Interactions

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Drug interactions are an unending concern in the pharmacologic management of many acute and chronic conditions, including cancer. More than 100,000 deaths per year in the United States can be attributed to fatal acute drug reactions, making drug reactions the sixth-leading cause of death (Lazarou, Pomeranz, & Corey, 1998). For patients with cancer, cytotoxic drugs often are a component of their treatment plans.

When patients take herbs simultaneously with cytotoxic drugs, the pharmacologic dynamics of the interactions are not well understood and may remain clinically unknown in the short term. The impact of drug interactions between herbs and cytotoxic drugs on a patient’s course of therapy can be overdosing or undertreatment, and this occurrence or series of occurrences can be additive, synergistic, or antagonistic effects, such as when cytotoxic drugs are given in combination regimens.

Pharmacokinetic interactions may occur as a result of variations in drug absorption, distribution, metabolism, or elimination. Often, metabolizing enzymes or drug transports are involved. The hepatic enzyme cytochrome P450 is the most important drug-metabolizing system, the predominant site of most drug metabolism, and the site for most drug-drug interactions. More than 100 substrates (also known as isoenzymes or isoforms) of cytochrome P450 exist, and nomenclature is based on and named for the amino acid or enzyme involved in the pharmacokinetic pathway. Enzymes responsible for the largest part of drug metabolism are CYP3A (50%), CYP2D (25%), and CYP2C (20%) (Sparreboom, Cox, Acharya, & Figg, 2004; Zhou et al., 2003).

Specifically, drug interactions arise when drugs are given simultaneously and one drug alters the metabolic clearance of the second drug in inhibition or induction of specific isoenzymes (Zhou et al., 2003). Cytotoxic agents are metabolized through the cytochrome P450 pathways involving predominantly enzyme CYP3A. Some herbs also are metabolized through the same pathway and can either induce or inhibit activity of the CYP isoenzymes on a cellular level in the liver or the intestinal epithelium (see Table 1). Herbs also may induce enzymes and transporters in tumor cells and cause resistance to some cytotoxic agents or lessen therapeutic responses to other cytotoxic agents (Sparreboom et al., 2004). Because multiple CYP isoenzymes in the P450 pathway are involved in drug metabolism in general and especially with cytotoxic agents, the concurrent use of some herbs with cytotoxic drugs may have clinical and toxicologic implications. Most cancer treatment regimens are complex (e.g., multiple cytotoxic agents, antiemetics, analgesics, and corticosteroids). Given the complexity of most treatment regimens, relatively few specific data are available to guide clinicians beyond general avoidance of herbs with known or suspected interactions in connection with cytotoxic agents.

Herb Use by Patients With Cancer Undergoing Cytotoxic Therapy

Several researchers have assessed herbal use by patients with cancer undergoing cytotoxic therapy. McCune et al. (2004) conducted a sample investigation examining
the potential of herb-cytotoxic interactions in adults over a one-month period. Of the 76 patients who completed a questionnaire, 78% of patients used herbs or vitamins while receiving cytotoxic agents. More than a quarter (27%) of the patients took herbs or vitamins that placed them at potential risk for herb-cytotoxic agent interactions. Most patients (> 85%) indicated that they would discontinue use of herbs or ask their medical oncologists for advice if a potential herb-cytotoxic agent interaction was suspected. The authors concluded that potential exists for herb-cytotoxic agent interactions and that methods to improve communication about herb and vitamin use between patients receiving chemotherapy and providers are necessary to recognize and reduce the potential risk of interactions (McCune et al.).

In a similar study conducted by Werneke et al. (2004), patients receiving cytotoxic agents in an outpatient clinic were surveyed to establish a pattern of herb or supplement use to identify potential interactions. Of the 318 patients who completed the questionnaire, almost 52% took herbs or supplements. A small portion of patients (11%) reported taking higher-than-recommended doses of herbs or supplements. The authors asserted that patients may not be aware of the potential risks of herb-cytotoxic interactions and should be encouraged to disclose their use with their healthcare providers (Werneke et al.).

Market sales of supplements, as reported by the American Botanical Council in 2005, showed that the 20 leading herbs are garlic, echinacea, saw palmetto, ginkgo, soy, cranberry, ginseng, black cohosh, St. John’s wort, milk thistle, evening primrose, valerian, green tea, bilberry, grape seed, horny goat weed, yohimbe, horse chestnut, eleuthero, and ginger (see Table 2). This applies to patients with or without cancer (Blumenthal, 2005). Of these, seven have known or suspected herb-cytotoxic interactions (garlic, echinacea, ginkgo, soy, ginseng, St. John’s wort, and grape seed). Following is a discussion of the commercial uses, metabolism, potential interactions, and implications involving the seven herbs.

### Garlic

**Scientific name:** *Allium sativum*

**Family name:** Alliaceae or Liliaceae

Garlic has been used as a culinary spice and medicinal herb for more than 5,000 years and has been cultivated in the Middle East since 510 A.D.

**Commercial uses:** Garlic is used to treat or prevent hypertension, hyperlipidemia, coronary heart disease, age-related vascular changes and atherosclerosis, earaches, and menstrual disorders. Garlic also is used to prevent and treat several types of cancer, although it is not approved by the U.S. Food and Drug Administration (FDA) for the conditions. Other uses include treatment of benign prostatic hyperplasia, diabetes, arthritis, allergies, traveler’s diarrhea, colds, and flu (Natural Medicines Comprehensive Database, 2005).

**Metabolism and interactions:** In vitro studies have revealed that garlic constituents affect various CYP enzymes, with extracts of fresh garlic and samples of garlic oil, freeze-dried garlic, and aged garlic exhibiting inhibitive effects on CYP2C9, CYP2C19, CYP3A4, CYP3A5, and CYP3A7 (Zhou, Chan, Pan, Huang, & Lee, 2004). Garlic has been shown to alter blood coagulation by increasing platelet aggregation and increasing fibrinolysis (Sparreboom et al., 2004). Additionally, garlic is considered a potential CYP3A4 inducer based on in vitro data showing that garlic decreased serum concentrations of the protease inhibitor saquinavir by about 50% (Piscitelli, Burstein, Welden, Gallicano, & Falloon, 2002).

**Implications:** General caution should be exerted with concurrent chemotherapy or other medications metabolized via the CYP 450 pathway. Garlic should be avoided in patients after surgery and by those with documented thrombocytopenia.

### Echinacea

**Scientific name:** *Echinacea angustifolia, Echinacea pallida,* and *Echinacea purpurea.*

**Family name:** Asteraceae or Compositeae
Echinacea is one of the most commonly used alternative medicines in the world and is indigenous in the central United States. Nine species exist in the genus *Echinacea*, a member of the sunflower family, of which the most common species are *E. angustifolia*, *E. purpurea*, and *E. pallida*.

**Commercial uses:** Echinacea is used to assist in upper respiratory tract infection prevention and treatment in adults and children and in general immune system stimulation.

**Metabolism and interactions:** The bulk of pharmacologic studies have been conducted using *E. purpurea* formulations made from freshly pressed juice from the flowering plant. Proposed mechanisms of action involve immune stimulation such as increased granulocyte and T lymphocyte production, cytokine activation, improved phagocytic performance, inhibition of virus proliferation, and an increase in the T4/T8 cell ratio. Theoretically, echinacea might increase levels of drugs metabolized by CYP3A4. In vitro studies have suggested that echinacea is likely to interact with cytotoxic drugs that are metabolized via the CYP3A4 pathway, and the interaction depends on the route of administration and drug interaction in the liver and intestines (Natural Medicines Comprehensive Database, 2005; Natural Standard, 2005).

**Implications:** General caution should be exerted with concurrent chemotherapy or other medications metabolized via the CYP 450 pathway.

**Ginkgo**

**Scientific name:** Ginkgo biloba

**Family name:** Ginkgoaceae

Ginkgo has been used medicinally for thousands of years and is a frequently used herb in traditional Chinese medicine for a variety of ailments.

**Commercial uses:** Ginkgo is used for claudication, dementia, cerebral insufficiency, and age-associated memory impairment (Natural Medicines Comprehensive Database, 2005).

**Metabolism and interactions:** In a randomized, double-blind clinical trial involving 219 healthy adults, ginkgo extract did not produce improvement in memory (Solomon, Adams, Silver, Zimmer, & DeVeaux, 2002). In preclinical studies, ginkgo was found to be a potential inhibitors of CYP2C9 and CYP3A4 (Sparreboom et al., 2004; Zou, Harkey, & Henderson, 2002). Several case reports have documented the development of spontaneous bleeding episodes in patients taking ginkgo (Benjamin, Muir, Briggs, & Pentland, 2001; Fessenden, Wittenborn, & Clarke, 2001). This untoward event likely is related to the presence of ginkgolide B, a principal component of ginkgo that acts as a strong antagonist of platelet-activating factor, thereby promoting bleeding.

**Implications:** General caution should be exerted with concurrent chemotherapy or other medications metabolized via the CYP 450 pathway. Ginkgo is contraindicated for patients receiving anticoagulation therapy.

**Soy**

**Scientific name:** Glycine max

**Family name:** Fabaceae or Leguminosae

**Commercial uses:** Soy is used for hyperlipidemia, menopausal symptoms, and prevention of osteoporosis. It also is used orally for hypertension, type 2 diabetes, constipation, diarrhea, and muscle soreness caused by exercise (Natural Medicines Comprehensive Database, 2005).

**Metabolism and interactions:** The isoflavones genistein and daidzein are the primary components of soy and produce weak estrogenic effects. Genistein, in particular, has been shown to negate the inhibitory effect of tamoxifen on breast cancer growth and interact with transporters such as P-glycoprotein, in addition to inhibiting CYP2E1 (Helsby, Chipman, Gescher, & Kerr, 1998), CYP2D6, CYP3A4 (Anderson, Rosito, Mohusty, & Elmer, 2003), and CYP3A7 (Foster et al., 2003). With the understanding that transporters such as P-glycoprotein are involved in the absorption of several anticancer drugs, researchers have theorized that soy may alter cytotoxic drug absorption in humans (Sparreboom et al., 2004).

**Implications:** General caution should be exerted with concurrent chemotherapy or other medications metabolized via the CYP 450 pathway. Caution is recommended when soy or soy products are given to patients with estrogen-dependent tumors because some preclinical data have indicated that soy may stimulate tumor growth in mice (Sparreboom et al., 2004).

**Ginseng**

**Scientific name:** Panax quinquefolius

**Family name:** Araliaceae

Many types of ginseng exist such as Siberian, Asian, American, and Japanese, of which the most common type is Asian ginseng.

**Commercial uses:** Ginseng is used for improving stress resistance as a general tonic, stimulant, diuretic, and digestive aid for several conditions such as anemia, diabetes, insomnia, and gastritis (Natural Medicines Comprehensive Database, 2005). Vogler, Pittler, and Ernst (1999) performed a systematic review of 16 trials related to the use of ginseng and physical performance, diabetes mellitus, immunomodulation, herpes simplex type II infections, and psychomotor performance and cognitive function. Efficacy of ginseng for the conditions was not established, and further research was recommended (Vogler et al.).
Metabolism and interactions: In vitro studies have suggested that a crude extract of ginseng, in addition to several ginsenosides, moderately inhibit CYP2D6, CYP2C19, and CYP2E1 (Henderson et al., 1999; Nguyen et al., 2000). In vitro study results have provided conflicting evidence regarding whether ginseng inhibits CYP3A4.

Implications: General caution should be exerted with concurrent chemotherapy or other medications metabolized via the CYP 450 pathway. Preparations of ginseng possess phytoestrogens that may exert an effect; as with soy and soy products, ginseng should be used with caution in patients with estrogen-dependent tumors (Weiger et al., 2002).

St. John’s Wort

Scientific name: Hypericum perforatum
Family name: Hypericaceae

St. John’s wort is obtained from the flowering tops of Hypericum perforatum, a perennial plant endemic to Europe, Asia, and the United States.

Commercial uses: Numerous studies have reported that St. John’s wort is more effective than placebo and equally as effective as tricyclic antidepressant drugs or selective serotonin reuptake inhibitors for the short-term (one to three months) treatment of mild to moderate depression (Natural Medicines Comprehensive Database, 2005). Additionally, St. John’s wort has been used in the management of anxiety and insomnia.

Metabolism and interactions: St. John’s wort is a very complex mixture of more than two dozen compounds and often is standardized to contain 0.3% hypericin or hyperforin (2%–5%). In humans, St. John’s wort is a known inducer of CYP3A4 and CYP2E1 and has been shown to decrease the plasma levels of a large range of prescribed drugs metabolized through the same pathways, with possible clinically serious consequences. Examples are chemotherapeutic agents such as the plant alkaloids, anticoagulants such as warfarin, and antiviral agents such as indinavir (Cox, Lepper, Figg, & Sparreboom, 2004; Sparreboom et al., 2004).

Implications: Although the clinical relevance of grape seed extract’s ability to induce enzyme expression requires further investigation, general caution is recommended when high doses (amounts > 300 mg per day) are administered simultaneously with chemotherapeutic agents.

Grapefruit

Scientific name: Citrus paradisi
Family name: Rutaceae

Although not technically an herb, grapefruit is an herb-cytotoxic interaction of concern because of its ability to inhibit CYP3A4. Grapefruit interactions can occur when using any part of the fruit, including juice or peel. Repeated consumption of grapefruit not only inhibits CYP3A4 but also prolongs elimination half-life for as long as three to seven days. Preliminary in vitro evidence suggests that grapefruit juice might inhibit CYP1A2, CYP2C9, and CYP2C19, although this has not been reported in humans (Natural Medicines Comprehensive Database, 2005). Thus, common medications used in cancer care that are metabolized through the same CYP pathways (e.g., ondansetron, amitriptyline, nonsteroidal anti-inflammatory drugs, warfarin, statins, proton pump inhibitors) may result in increased drug levels or added effects of the drugs when taken with grapefruit juice or peel. More specifically, grapefruit may increase the risk of bleeding when used with anticoagulants, increase side effects associated with drugs such as cyclosporine, and reduce the effectiveness of chemotherapy agents such as vinblastine, etoposide, and ifosfamide.

Implications for Nursing

Of the top 20 herbal supplements sold in the United States, 7 have potentially relevant known or suspected herb-chemotherapy reactions: garlic, echinacea, ginkgo, soy, ginseng, St. John’s wort, and grape seed. Also on the same list, herbs for which no herb-cytotoxic interactions have been reported thus far or for which no information was available at the time this article was printed are cranberry, black cohosh, milk thistle, evening primrose, valerian, green tea, bilberry, saw palmetto, horny goat weed, yohimbe, horse chestnut, eleuthero, and ginger. Not all of the herbs, except for ginger, have been studied to the extent of the previous seven herbs. This does not mean that the latter group of herbs will not interact with other medications. Thus, continued assessment, monitoring, and documentation of the comprehensive medication profile are necessary whenever individuals who are undergoing active treatment for cancer are taking herbal products concurrently. Reporting adverse events to providers and the FDA is critical, not only for the patients in whom interactions occur but also for the multitude of patients who may be taking the same or similar combinations of herbs and chemotherapy.

Any approach to communicating potentially relevant interactions requires participation of patients, providers, and pharmacists. Developing such approaches is compulsory because of the high prevalence of consumer use of herbal medicine. Oncology nurses and other healthcare providers must conduct comprehensive medication assessments as a part of intake medical histories to have an opportunity to outline to individual patients which potential hazards should be taken into consideration. Approaches need to focus on medication assessment, coordination, and teaching with attention to the following aspects.

Assessment

Goal: Conduct a comprehensive medication summary.
• Perform a comprehensive medication assessment prior to hospital admission, protocol enrollment (if applicable), clinic administration of chemotherapy, inpatient and outpatient surgery, invasive diagnostic procedures, hospital discharge, and each
time a medication type, dose, or schedule changes. Medication assessment should include the name of prescription and nonprescription medications, manufacturer names if available, doses, routes, indications, appearances, and schedules. Specific components of a comprehensive medication assessment are listed in Figure 1.

- Visually inspect nonprescription medications and medications prescribed by other providers outside of the primary treatment center. Patients can be encouraged to bring medication containers to the clinic or hospital setting along with a three-day medication history recall.
- Discuss and document patients’ ability to take medications (inhibiting factors such as taste changes or mucositis, etc.), compliance, allergies, and adverse reactions.
- Perform ongoing assessment and documentation of medications that may not be captured routinely, such as diagnostic imaging contrast, fluoride treatment in dental procedures, or local anesthesia for dermatologic procedures.

**Coordination**

**Goal:** Keep multiple providers aware of patients’ medication history.

- Establish definitive guidelines in each treatment facility for refraining from and eventual safe resumption of grapefruit juice or peel, herbs with known or suspected interaction, or any herbs.
- Collaborate with a pharmacist or pharma- cotherapy consultant who can review medication orders, collaborate with other providers (e.g., consultants, acute care providers for emergent visits outside of routine clinic visits, nutritionists), and provide information if needed to outside pharmacies that fill a patient’s prescriptions.
- Recommend that patients carry a complete, updated list of prescription and nonprescription medications (including generic and trade names, dosages, routes, indications, and schedules) at all times while undergoing cancer treatment.
- Recommend that patients return or destroy discontinued or dose-changed medications.
- Recommend eliminating grapefruit or grapefruit juice from selections on menus or refrigerators in clinics and inpatient units.

**Teaching**

**Goal:** Help patients to avoid harming themselves in the setting of known or suspected interactions.

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**Prescription Medications**

- Ear or eye drops
- Injectable medications (e.g., syringe, ambulatory pump, recent vaccines, anergy panels, immunizations, allergy testing)
- IV medications (continuous infusion and intermittent)
- Medicated patches
- Medications given via jejunostomy, gastrostomy, or nasogastric tube
- Nasal sprays and inhalation preparations (e.g., aerosols, inhalers, mist tent)
- Oral medications (e.g., tablets, capsules, liquids, lozenges, sublingual medications)
- Prescribed marijuana (inhalation form)
- Rectal or vaginal suppositories or enemas
- Topical creams, lotions, ointments, or powders

**Nonprescription Medications**

- Alcoholic beverages
- Antacids
- Cold and flu remedies
- Ear or eye drops
- Essential oils (applied topically or via aromatherapy)
- Fluid products: water or juice with additives, iced or hot teas (single or combination herbs and how they are dispensed), and drinks made in blenders
- Food supplement bars (containing soy, vitamins, and minerals)
- Herbs (single or combination products)
- Home remedies (e.g., tonics, homeopathic products)
- Medicated patches
- Medications given via jejunostomy, gastrostomy, or nasogastric tube
- Minerals (single or combination products)
- Nasal sprays and inhalation preparations (e.g., aerosols, inhalers, mist tent)
- Pain relievers
- Rectal or vaginal suppositories or enemas
- Stimulants, laxatives, and anti diarrheals
- Tobacco products (e.g., cigars, cigarettes, chew, betel nut)
- Topical creams, lotions, ointments, or powders
- Vitamins (single or combination products)

**Practice Implications**

Two immediate practice implications are apparent. The first is the need to establish universal or, at a minimum, facility-based guidelines to inform patients when to refrain from grapefruit juice or peel, herbs with known or suspected interactions, or any herbs. At present, word-of-mouth recommendations vary by facility and may include a time period ranging from (a) only during actual days of chemotherapy, (b) one to three weeks prior to chemotherapy, or (c) one month before chemotherapy. Guidelines for safe resumption of such products are needed. Currently, word-of-mouth recommendations offer various intervals for safe resumption such as (a) between cycles of chemotherapy, (b) following completion of chemotherapy as part of the treatment plan, or (c) following completion of all conventional interventions as a part of the treatment plan. In clinical trial settings, guidelines are more established. Patients are required to refrain from all herbs prior to and while on studies involving chemotherapy; yet at the same time, researchers may lack foresight in counseling patients after completion of studies. (Known or suspected herb interactions exist in the areas of radiation therapy and diagnostic imaging but are not mentioned in this article.)

The second implication is the broad establishment of informal or formal educational...
programs in facilities for patients and healthcare providers who respond to inquiries and provide reliable facts and knowledge surrounding complementary and alternative therapies. Numerous programs are in existence at this time, and smaller facilities can develop new programs that model the larger programs yet are tailored to meet the needs of patients and providers in their facilities. Programs can provide lecture and discussion sessions, books, videos, and access to pharmacists or pharmacotherapy consultants. Here is a sampling of some of the larger, integrated cancer complementary and alternative medicine programs.

- Columbia University, the Richard and Hindy Rosenthal Center for Complementary and Alternative Medicine, www.rosenthal.hs.columbia.edu
- Dana-Farber Cancer Institute, Zakim Center for Integrated Therapies, www.dana-farber.org/pat/support/zakim_default.asp
- Duke Comprehensive Cancer Center, http://cancer.duke.edu/pated/CAM.asp
- The Johns Hopkins Center for Complementary and Alternative Medicine, www.hopkinsmedicine.org/CAM
- University of Maryland School of Medicine Center for Integrative Medicine, www.commped.umm.edu/index.html
- University of Texas M.D. Anderson Cancer Center Complementary/Integrative Medicine education resources, www.mdanderson.org/departments/cimer
- University of Pittsburgh, the Alternative Medicine Home Page, www.pitt.edu/~cbw/condit.html#cancer
- University of Virginia Health System, Complementary Cancer Care Program, www.healthsystem.virginia.edu/internet/cancer/choicesinhealing.cfm

The Role of Scientific Research

Dietary supplements, as defined by the Dietary Supplemental Health and Education Act of 1994, including the herbs discussed in this article, do not fall under postmarket regulation by the FDA. The FDA is responsible, however, for taking action against unsafe products once reported. As stated previously, when patients take herbs in addition to cytotoxic agents, the impact on the course of treatment may not be known immediately or ever known to its full extent. This article would be remiss if it did not mention that factors other than herbs impact the metabolism of cytotoxic agents. Researchers continue to quantify the role of demographic, physiologic, and genetic factors that influence CYP P450 3A activity in patients with cancer (Baker et al., 2004). Added complexities are the plethora of herbal product manufacturers and variability in commercial preparations, plus the disparity in commercial versus scientific information regarding product safety and efficacy.

Well-controlled preclinical studies and human trials for herb-cytotoxic agent activity and possible interactions are imperative and currently under way. Increased attention to potential interactions in the preclinical and early clinical development phases may decrease the incidence in the postmarket setting. Oncology nurses play a pivotal role across multiple settings in recognizing and communicating effectively regarding the potential for herb-cytotoxic agent interactions.

For More Information

For more information on this topic, visit the following Web sites.

- American Holistic Nurses Association: Position on the Role of Nurses in the Practice of Complementary and Alternative Therapies, www.ahna.org/about/statements.html#role
- Also, see the following texts.

The author wishes to acknowledge the contributions of Scott Penzak, PharmD, and Barry Goldspiel, PharmD, from the National Institutes of Health, Clinical Center Pharmacy Department.

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