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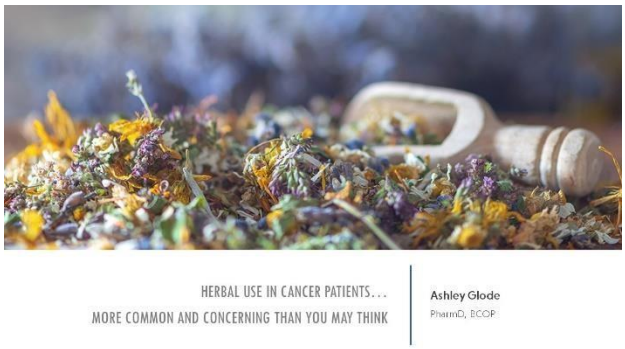
Herbal Use in Cancer Patients… More Common and Concerning Than You May Think



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A thorough medication review is essential in patients receiving cancer therapy. An important element to discuss is the use of herbal medications with cancer patients. Patients may use herbal supplements for a variety of reasons; to treat their cancer, mitigate side effects, and appease a friend or family member. This program will discuss the use of herbal supplements in cancer patients, and review some of the more common agents used focusing on potential herbal-disease and herbal-drug interactions and concerns.

Learning Objectives

Pharmacist

1 Identify examples of common herbals used by cancer patients
2 Recognize the current landscape of herbal use in cancer patients
3 Identify common drug-drug and drug-disease interactions with selected herbals
4 Identify appropriate provider and patient resources to assess use and safety of herbal supplements

Pharmacy Technician

1 Identify examples of common herbals used by cancer patients
2 Identify common drug-drug and drug-disease interactions with selected herbals
3 Recognize the current landscape of herbal use in cancer patients
4 Identify appropriate provider and patient resources to assess use and safety of herbal supplements

Nurse

1 Identify appropriate provider and patient resources to assess use and safety of herbal supplements
2 Identify examples of common herbals used by cancer patients
3 Identify common drug-drug and drug-disease interactions with selected herbals
4 Identify examples of common herbals used by cancer patients

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Pharmacists, Pharmacy Technicians, Nurses

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Introduction

The use of complementary and alternative medicine (CAM) in cancer patients is becoming better described as there is a heightened awareness of its use in the oncology community. The National Cancer Institute (NCI) defines CAM as treatment used in addition to or instead of standard therapy, and may include dietary supplements, megadose vitamins, herbal preparations, special teas, acupuncture, massage therapy, magnet therapy, spiritual healing, and meditation (NCI Dictionary). Cancer survivors report a greater use of CAM than the general population, and as many as 50-83% of adult patients and 84% of children diagnosed with cancer have reported using CAM one or more times after their cancer diagnosis (Davis 2012, Rashrash 2017). From the ASCO (American Society of Clinical Oncology) National Cancer Opinion Survey, 68% of adults with cancer believe that alternative therapies are a good supplement to standard cancer treatment(s) and 22% believe cancer can be cured solely through alternative therapies, without standard cancer treatment(s) (ASCO Survey 2018). In surveyed patients over 50 years of age, about one-third reported using herbal products and dietary supplements, which was the most common CAM approach utilized (Latte-Naor 2019). Patients may use herbal supplements for a variety of reasons including as a treatment for their cancer, to manage or prevent side effects, to have a sense of control or involvement in their care, or upon recommendation of a friend or family member. The potential for interactions of herbal supplements with conventional therapy is one of the main concerns healthcare professionals have with the use of CAM therapy in cancer patients. Some herbal therapies may be beneficial, while others may be directly harmful, or result in reduced efficacy of chemotherapy, surgery, and radiation treatment.

Landscape of Herbal Use

The National Institutes of Health classify herbal medicines as any products originating from plants and used to preserve or recover health (Rashrash 2017). Thousands of herbal products are available over the counter and are routinely being used by Americans, yet many of them are lacking scientific evidence proving efficacy and safety (Rashrash 2017). Of adults diagnosed with cancer responding to the National Cancer Opinion Survey, 17% reported using vitamins/minerals/herbs for symptom management in the past 12 months (ASCO Survey 2018). Individuals more likely to use herbal therapies are female, younger, white, and have a higher socioeconomic status than nonusers (Damery 2011, Rashrash 2017). Additional predictors of herbal medicine use include type of malignancy, stage, and disease duration (Rashrash 2017). Compared to the general population and those with other malignancies, women with breast cancer are most likely to use herbal medicines.

Patients enrolled on clinical trials are also likely to have used CAM therapy. In 2004, results were published on the use of CAM therapy in patients participating in phase I clinical trials at the Mayo Clinic Comprehensive Cancer Center (Dy 2004). Over 100 patients (n=102) were surveyed to describe CAM use in this population. All patients included had metastatic disease, with 26% diagnosed with gastrointestinal/hepatobiliary cancer, 15% lung cancer, 8% pancreatic cancer, 7% renal cancer, and 7% with head and neck malignancies (Dy 2004). Nearly all patients (88.2%) had used at least one form of CAM; 93.3% of which was pharmacologic. Nonvitamin, nonmineral supplements were used by 71.4% of patients. The most popular agents were green tea (29.8%), echinacea (13.1%), and essiac (9.5%). Almost two-thirds (61%) of patients used vitamins/minerals in addition to nonvitamin, nonmineral products. In 2011, the MD Anderson Cancer Center published on their experience in the phase I population as well (Naing 2011). This study included survey results from 309 patients. About half of study participants (52%) reported using 1 or more CAM interventions. From the CAM users (n=162), 77% reported using pharmacologic interventions. The most commonly utilized CAM interventions were vitamins (70%), prayer (57%), and herbal preparations (26%). With the high prevalence of pharmacologic CAM use reported in patients enrolling on clinical trials it is important that patients have a thorough medication and supplement review prior to initiating study therapy.

Additional vulnerable patient populations are the adolescent young adult (AYA) and geriatric patients. A retrospective study was conducted at the University of Texas MD Anderson on patients referred for an integrative oncology consultation to compare the AYA population (age 15-39 years) to a control sample of adult patients (age ≥ 40 years) (Lopez 2018). During the study period 2383 patients completed the surveys, including 286 AYA patients. The majority of the AYA group was female (73.1%), white (63.6%), and had local disease (55.8%). The most common cancer diagnoses were breast (30.1%), gastrointestinal (13.3%), and sarcoma (10.5%). The AYA group was more likely to be non-white (36.3 vs 23.5%, $p < 0.001$) and had advanced disease (44.2 vs 36.9%, $p=0.034$) when compared with the adult group. The AYA group most commonly used vitamins (45%), massage (28.4%), relaxation techniques (23.9%), and herbs (19.3%) in the year prior to their integrative oncology appointment. In the adult group, the most commonly used modalities were vitamins (50%), massage (21.1%), and herbs (19%). Both the AYA and adult group was interested in discussing herbal supplements during their appointment, 35.1% and 34.5% respectively. At the other end of the age spectrum, the senior adult (age ≥ 60 years) is also at risk for negative effects from CAM use. In this population, there is concern that the use of herbal supplements may influence polypharmacy and inappropriate medication use (Nightingale 2015). A study assessing

CAM use was evaluated at the Senior Adult Oncology Center at Thomas Jefferson University, National Cancer Institute-designated Kimmel Cancer Center. In this study, a pharmacist conducted a thorough review of all medications (prescription, nonprescription, herbals and supplements) senior adults (n=234) were taking. About one quarter (26.5%) reported CAM use which included herbal medications, minerals or other dietary supplements. A total of 86 out of 2163 medications were classified as CAM. CAM was most common in 80 year old Caucasian women. It was also highest in older adults diagnosed with breast (6%), lung (4%) and colorectal cancers (3%), and malignancies of the genitourinary tract (3%). The majority of patients (73.5%) were not taking any complementary and alternative medications, with 19% of patients taking 1 medication. The most commonly used agents in this population were vision impairment supplements (6.4%), gastrointestinal probiotics (4.3%), joint health agents (3.9%), vitamin-mineral herbal combinations (2.1%), cod liver oil (1.7%), coenzyme Q10 (1.7%), and melatonin (1.7%). This older adult population is at increased risk for disease- and drug-herb interactions considering the increased number of comorbidities and associated polypharmacy. This patient population should have a comprehensive medication assessment, including CAM use, which is documented in the patient's medical record to facilitate shared/informed decisions regarding continuing use of these therapies.

Commonly Used Herbals

Types of supplements used by patients vary by indication for use. Some patients use herbal therapy to help mitigate side effects while others use it to help treat their cancer. Commonly used supplements by patients with cancer include black cohosh, echinacea, essiac, garlic, ginger, ginseng, green tea, milk thistle, mistletoe, and turmeric (Dy 2004, Damery 2011, Tascilar 2006). Indications for use and mechanisms of action for these agents are described below.

Black Cohosh (Cimicifuga racemose)

Black cohosh is a hardy perineal wildflower native to eastern North America (NMD, MSKCC). The herb is obtained from the rhizome and root of the plant and is used to relieve symptoms of menopause and dysmenorrhea. It also has anti-osteoporotic effects and can enhance bone formation. Black cohosh is typically taken orally to manage menopausal symptoms and is possibly safe for up to a year of administration. Data are conflicting on the effectiveness of black cohosh, and a meta-analysis indicates insufficient evidence for its use to manage menopausal symptoms.

Black cohosh is reported to mimic neurotransmitters, and exerts its effect on menopausal symptoms through dopaminergic, noradrenergic, serotonergic, and GABAergic activity (NMD, MSKCC). It was believed these symptoms were relieved via estrogenic effects, but studies have revealed it has no effect of the levels of LH, FSH, prolactin or estradiol. Black cohosh also has potential anti-cancer activity and repressed the expression of cyclin D1 and ID3, and inhibited proliferation of HepGe, p53 positive liver cells; and impaired equilibrative nucleoside transporter (ENT) activity in prostate cancer cells causing impaired nucleoside uptake.

Echinacea (Echinacea purpurea, Echinacea angustifolia, Echinacea pallida)

Echinacea species are closely related to the sunflowers, daises, and ragweed and are commonly found naturally growing in areas east of the Rocky Mountains (NMD, MSKCC). There are 9 species, but only 3 are used medicinally. Extracts are made from the root and aerial parts. Specific products may vary due to the use of different species, variable plant materials or extraction methods used, and addition of other components. Echinacea is commonly used as an immunostimulant, and to prevent or treat the common cold and influenza. Based on in vitro and in vivo analysis, echinacea may have immunostimulatory and anti-inflammatory properties. Echinacea is likely safe when taken orally short-term. Data for the prevention and treatment of the common cold are conflicting.

The active components of echinacea include cichoric and caftric acids, polysaccharides, and alkylamides (NMD, MSKCC). Echinacea is reported to exert its immune-modulating effects by upregulating interleukin (IL)-2 and IL-8 and down regulating proinflammatory cytokines tumor necrosis factor (TNF)-alpha and IL-6. Alkylamides bind to human cannabinoid receptors 1 and 2 and inhibit TNF-apha.

Essiac

Essiac is a formulation of 4 different botanical products; burdock *(Arctium lappa, Arctium majus)* root, sheep sorrel *(Rumex acetosella)* root, slippery elm *(Ulmus rubra)* bark, and rhubarb *(Rheum palmatum, Rheum officinale)* root (NMD, MSKCC). It was developed by a Canadian nurse as an alternative treatment for cancer. Unfortunately, it was found to stimulate the growth of human breast cancer cells via estrogen pathways. There are also conflicting data in the management of prostate cancer. Despite unsubstantiated

claims, patients still use this product for its antioxidant and cytotoxic properties that were demonstrated in vitro.

The anthraquinones found in rhubarb and sheep sorrel stimulate secretion of mucosa and water, and stimulate peristalsis (NMD, MSKCC). Anthraquinones from rhubarb can stimulate IL-1, IL-6 and TNF in vitro and tumor necrosis against sarcoma 37, breast cancer, and Ehrlich cell lines in mice. Burdock root might have the ability to scavenge free radicals and serve as an antioxidant. Tannin extract can stimulate macrophage response and the lignin and sesquiterpene extracts in vitro have inhibited platelet activating factor (PAF).

Garlic (Allium sativum)

As a supplement, garlic is obtained from the bulb or the clove of the plant. It has many purported uses, most commonly to treat hyperlipidemia, hypertension, atherosclerosis, cancer, and infections (NMD, MSKCC). For the benefit of treating cholesterol, several placebo-controlled studies have produced mixed results, but a systematic review was supportive of garlic's ability to lower total and LDL cholesterol. Meta analyses show consistent evidence that garlic can lower cardiovascular risk factors and supplements have the potential to decrease blood pressure, regulate cholesterol, and have immunostimulatory effects. Garlic may also be used to prevent cancer as there is an inverse association with garlic intake and risk of some common cancers. Garlic is likely safe when used appropriately orally long term. Clinical studies have reported safety of use up to 7 years.

The majority of the pharmacologic activity of garlic is attributed to allicin (NMD, MSKCC). The allicin is created when the garlic bulb is crushed, ground, or cut, and the allin is converted to allicin by the enzyme allinase. The allicin is reported to have antiplatelet, antibiotic, and antihyperlipidemic activities. Garlic is thought to lower cholesterol levels by acting as an HMG-CoA reductase inhibitor. To treat atherosclerosis, it is thought to reduce oxidative stress and low-density lipoprotein oxidation and have antithrombotic effects. To treat hypertension, it is believed to cause smooth muscle relaxation and vasodilation by stimulating the production of endothelium-derived relaxation factor. Garlic also may stimulate humoral and cellular immunity through proliferation of T-cells, restoration of suppressed antibody responses and stimulation of macrophage cytotoxicity on tumor cells. Selenium absorption may be increased which lends possible protection against tumorigenesis. It also may halt cell cycle progression and induce apoptosis of cancer cells and decrease angiogenesis.

*Ginger (*Zingiber officinale, Zanzibaris rhizome)

Ginger is a perennial plant that is native to warmer parts of Asia, with the spice and medicine coming from the rhizome of the plant (NMD, MSKCC). Western culture tends to use ginger primarily for gastrointestinal symptoms such as motion sickness, morning sickness and chemotherapy-induced nausea, and respiratory conditions such as upper respiratory tract infections and cough. In vitro and animal studies support the use of ginger for its antiemetic, anticancer, anti-inflammatory, anti-drug-dependence, and hypoglycemic effects. Ginger also can promote gastric emptying and help with feelings of satiety. The use of ginger is likely safe when used appropriately orally as there are multiple clinical trials of its use.

Ginger has several different active constituents which vary among fresh, semi-dry and dry formulations. The components in ginger associated with having antiemetic properties are shogaol, gingerol, and Galan lactone (NMD, MSKCC). These constituents stimulate the flow of saliva, bile, and gastric secretions, and competitively antagonize serotonin receptors. Preclinical research also suggests that the 6-gingerol constituent can inhibit neurokinin-1, serotonin, and dopamine receptors explaining its potential activity as an antiemetic. Ginger's antiplatelet activity is exerted through inhibition of thromboxane formation and is dose and formulation dependent. Fresh ginger can stimulate mucosal cells to secrete interferon-beta to fight viral infections in vitro.

Ginkgo (Ginkgo biloba)

Ginkgo biloba is one of the oldest living tree species dating back more than 2 million years (NMD, MSKCC). Its seeds were used in traditional Chinese medicine, but more recent use typically involves leaf extracts. It is native to temperate Asia and has been grown in Europe and the US for over 200 years. In vitro ginkgo extracts have chemo preventive, anticancer, and cytotoxic effects. Despite being marketed for memory impairment, clinical studies do not support its use to improve cognitive performance or prevent Alzheimer's disease or dementia. There is limited data to support ginkgo having chemo preventive and anticancer activity. It is likely safe when used orally and this has been demonstrated in trials for several weeks up to 6 years.

The ginkgo leaf and its extracts have several active components including flavonoids, terpenoids, and organic acids (NMD, MSKCC). Ginkgo may be involved in decreasing high-glucose-induced endothelial inflammation by inhibition of IL-6 activation.

Repeated intake of ginkgo enhanced cell proliferation and neuroblast differentiation. Flavonoids have been shown to inhibit estrogen biosynthesis via inhibition of aromatase, decreased CYP19 mRNA, and induced transcriptional suppression. The flavonoids also are reported to have antioxidant and free radical scavenging abilities. The exact anticarcinogenic mechanism for ginkgo is unclear. Ginkgolides in the leaf of the plant competitively inhibit PAF which decreases platelet aggregation.

Ginseng (Panax quinquefolius)

There are several types of ginseng utilized, American, Asian, and Siberian, as an herbal supplement and each has unique medicinal properties (NMD, MSKCC). American ginseng is primarily found in North America, with most being produced in Ontario, Canada. American ginseng is used orally to improve athletic performance, strength and stamina, and to treat diabetes and cancer. It is likely safe when used orally short term, up to 12 weeks.

The ginsenosides, which are responsible for its biological effects, possess stimulatory and inhibitory effects on the central nervous system, and can alter cardiovascular tone, enhance humoral and cellular-dependent immunity, and demonstrate anticancer effects (NMD, MSKCC). American ginseng appears to activate monocytes, induce TNF-alpha, and interferon-gamma. Natural killer cell activity, IL-2, and other factors involved in cell mediated immunity are increased. It also may stimulate B-lymphocyte proliferation, serum immunoglobulin production and macrophage production of IL-1 and IL-6. Several ginsenosides have shown anticancer properties in vitro, potentially due to the activity of compound K, a metabolite of the ginsenoside Rb1.

Green tea (Camellia sinensis)

Camellia sinesis is a woody plant native to Asia, and the unfermented leaves and buds are used to produce green tea (NMD, MSKCC). Green tea has many marketed uses including improving cognitive function, regulating blood sugar, cholesterol, and blood pressure, and for weight loss and cancer prevention. Green tea is likely safe when consumed in moderate amounts as a beverage. Green tea extract is considered possibly safe when used orally.

Green tea contains polyphenols such as flavanols, flavandiols, flavonoids and phenolic acid (NMD, MSKCC). The flavanols (epigallocatechin gallate (EGCG), epigallocatechin

(EGC), epicatechin gallate (ECG), and epicatechin (EC)) are catechins which are deemed responsible for the majority of the benefits of green tea. Green tea is reported to increase HDL cholesterol, lower LDL cholesterol and triglycerides, and prevent platelet aggregation. The polyphenol content of green tea may be responsible for its anticancer activity. ECGC may inhibit enzymes responsible for cell replication and DNA synthesis.

Milk thistle (Silybum marianum, Carduus marianum)

Milk thistle is a plant native to Europe used to manage different liver diseases including liver damage from chemicals, alcohol and chemotherapy (NMD, MSKCC). The flavonoids in milk thistle are reported to have antioxidant and anticancer effects and may protect against Alzheimer's disease based on in vitro and animal studies. When milk thistle is used orally appropriately it is likely safe for prolonged periods of time.

Milk thistle seeds are the most commonly used portion of the plant medically, and standard seed extract contains 70-80% silymarin, a combination of flavonolignans (NMD, MSKCC). Silymarin has antioxidant properties which may contribute to its anticancer activity. In human leukocytes, it inhibited the release of hydrogen peroxide and production of TNF-alpha. Other studies report flavonoids in milk thistle arrest the G1 and S1 phases of the cell cycle leading to cancer cell death. Silybin, one of the flavonolignans, inhibited growth a hepatocellular carcinoma by the Notch signaling pathway in vitro. Silymarin and silybin have antioxidant and free radical scavenging activity and are thought to be important mechanisms for milk thistle's liver protective effects.

Mistletoe (Viscum album)

European mistletoes are a semi-parasitic plant found growing on various trees throughout Europe, northwest Africa, and southern and central Asia (NMD, MSKCC). Mistletoe can be administered orally, subcutaneously, intravenously and intratumorally. Typically, the injections are used for cancer. Most clinical research evaluating mistletoe has utilized the parenteral formulations which are not approved for use in the United States. Mistletoe extracts are used for many conditions including cancer and reducing side effects from chemotherapy and radiation. It is considered to be possibly safe when used orally, subcutaneously, or intravenously appropriately.

In the management of cancer, mistletoe might stimulate the immune system and exert cytotoxic effects (NMD, MSKCC). In vitro studies show that mistletoe lectins induce macrophage cytotoxicity, stimulate immune-cell phagocytosis, increase TNF-alpha, IL-1, IL-2 and IL-6 cytokine secretion, and enhance cytotoxicity. Mistletoe has been shown to reduce secretion of VEGF from breast cancer cells in vitro. There is also evidence to suggest it can exert its cancer cell killing effects through inhibiting cellular protein synthesis in vitro and in animals. The immunostimulant seen with mistletoe may be responsible for the reported improved quality of life in cancer patients.

Reishi mushroom (Ganoderma lucidum)

Reishi mushroom is a type of fungus used commonly in Traditional Chinese Medicine (NMD, MSKCC). It is used by cancer patients as an immunostimulant. In vitro and in vivo, extracts had immunomodulatory, Reno protective, anti-inflammatory, and hepatoprotective properties. Reishi has been shown to have antiproliferative and chemo preventive effects, alleviate chemotherapy induced nausea, enhance the effects of radiotherapy, and increase the sensitivity of ovarian cancer cells to cisplatin in vitro and in animal studies. It may also work to prevent cisplatin-induced nephrotoxicity. It increased plasma antioxidant capacity and enhanced immune responses in small clinical studies of cancer patients. It is possibly safe when used orally and appropriately for up to 1 year in the extract form.

The active components from reishi mushrooms are mostly polysaccharides, including beta-glucans, which have demonstrated antitumor and immunostimulant activities, and triterpenes, including ganoderic acid, which may be responsible for inhibiting tumor invasion by reducing matrix metalloproteinase expression, and tumor metastases by limiting binding to endothelial cells (NMD, MSKCC). Reishi mushroom polysaccharides appear to stimulate immune function in cancer patients. A specific extract increased IL-2, IL-6, interferon-gamma, and natural killer cell activity, and decreased IL-1 and tumor necrosis factor-alpha. Polysaccharides are also suspected to have antitumor effects potentially by stimulating cytokine production from macrophages and T lymphocytes. Some extracts may be directly cytotoxic against certain types of cancer cells.

Turmeric (Curcuma longa)

Turmeric is a perennial herb native to South Asia used as a spice, coloring agent, and in traditional medicine for improvement in circulation and digestion (NMD, MSKCC). Orally

turmeric extracts are used to improve memory, for arthritis, and cancer prevention. Curcumin is one of the major active components of turmeric, and one of the most studied. It acts as a weak phytoestrogen, and has neuroprotective, choleretic, anti-inflammatory, immunomodulatory, anti-proliferative, and chemo preventive effects. It also may have chemo sensitizing and radio sensitizing effects. Turmeric and its component curcumin haven been used safely in many trials up to 12 months and is considered to be likely safe when used orally or topically on the skin and appropriately.

Turmeric may induce cancer cell apoptosis by upregulation of p53 expression, and may inhibit angiogenesis (NMD, MSKCC). Laboratory studies show that curcumin may inhibit cellular pathways leading to tumor metastasis, invasion, and angiogenesis. Turmeric and curcumin may have antioxidant effects and have been shown to scavenge free radicals and phenolic oxidants and decrease levels of reactive oxygen species. Curcumin also may have anti-inflammatory effects possibly through inhibition of cyclooxygenase2 (COX-2), prostaglandins, leukotrienes, and other pro-inflammatory cytokines. There is preliminary evidence that turmeric and curcumin may have immunostimulatory effects.

Potential for Interactions

A study of adult patients with cancer determined that nearly one-third were at risk for herbal interactions, and almost half of those at risk were being treated with curative intent (Lee 2014). The pharmacist can play a vital role in the optimization of medication therapy management. Patients may not discuss that they are taking herbal supplements with their provider for several reasons. Most often cited are that physicians don't ask, patients anticipate the provider's disapproval, disinterest, or inability to help, or the patient perceives it is irrelevant to their care (Davis 2012). Pharmacists have the professional education, training, and skill set to thoroughly discuss and evaluate the patient's medication and herbal supplement use to identify potential interactions with their therapy and condition.

Table 1. Broad categories of potential interactions: (Latte-Naor 2019)

- High doses of products with antioxidant properties may interfere with radiation or chemotherapy efficacy
- Anticoagulant herbs may cause detrimental effects in patients with low platelet counts or when used concurrently with anticoagulants or during perioperative periods
- Phytoestrogenic herbs may interfere with hormonal therapies or exert negative effects on hormone-sensitive cancers
- Immunostimulant herbs may impact the efficacy of immunosuppressive therapy
- Direct organ toxicity (i.e. renal or hepatic injury)

- Drug-drug metabolism interactions (i.e. CYP450 or Pgp)

Drug-Drug and Drug-Disease Interactions

Black Cohosh

Black Cohosh may inhibit CY3A4 and 2D6, and OATP2B1 therefore administration with substrates should be avoided (NMD, MSKCC). Black cohosh is reported to interfere with the activity of tamoxifen. The toxicity of doxorubicin and docetaxel may be increased if these agents are given together. In an animal model, black cohosh was shown to decrease the cytotoxic effects of cisplatin, therefore patients receiving cisplatin should avoid black cohosh. Black cohosh has been associated with the development of hepatotoxicity. Upon review of 30 independent cases of reported hepatotoxicity, the United States Pharmacopeia's Botanical Expert Committee determined black cohosh products should include a cautionary statement. Due to the concern for hepatotoxicity, theoretically it would be prudent to avoid concomitant administration of drugs also known to cause hepatotoxicity.

Echinacea

Echinacea appears to inhibit CYP1A2, inhibit intestinal CYP3A4 and induce hepatic CYP3A4, inhibit CYP2C8, and inhibit Pgp (NMD, MSKCC). Medications that are substrates of these enzymes should be used with caution. In vitro studies suggest that using tamoxifen in combination with echinacea may lead to decreased systemic exposure of prodrugs therefore reducing their efficacy. In a patient receiving etoposide, more severe thrombocytopenia was noted implying the inhibition of etoposide metabolism through CYP3A4. With echinacea's immunostimulatory activity, it should be avoided in patients being treated with immunomodulating therapy, in particular immunosuppressant drugs.

Essiac

Essiac has been shown to inhibit CYP enzymes in vitro. Burdock root may reduce platelet aggregation due to its inhibition of PAF (NMD, MSKCC). Patients should avoid use with anticoagulant and antiplatelet drugs to minimize the risk of bleeding. There are no known drug interactions with sheep sorrel. Rhubarb has been shown to induce CYP3A4 and Pgp in animals, therefore substrates of these enzymes may have reduced efficacy. Rhubarb can reduce gastrointestinal transit time leading to reduced absorption of oral

drugs. Slippery elm may have the same effect due to its mucilage content. There is concern that high tannin levels in rhubarb can lead to a negative impact on the liver. In addition, there is a report of renal failure in a patient utilizing a rhubarb containing supplement. The anthraquinone constitutions are possibly to blame. Patients should avoid rhubarb containing supplements with other renal toxic medications.

Garlic

Garlic has been shown to decrease platelet aggregation and potentially increase a patient's INR (NMD, MSKCC). Therefore, it should not be used concomitantly with anticoagulants or antiplatelet agents, or in patients with platelet dysfunction. It also should be discontinued at least 7 days prior to surgery. Garlic can inhibit CYP2C9, 2C19, 2E1, and 3A4 enzymes leading to interference of drugs metabolized by these enzymes. Garlic can induce Pgp as well. Caution should be used with antihypertensive and antidiabetic medications as garlic can have an additive effect on lowering blood pressure and blood glucose respectively.

Ginger

Ginger should be held prior to surgery due to its potential antiplatelet effects (NMD, MSKCC). It should also be avoided in individuals with bleeding disorders, and not used concomitantly with anticoagulants, antiplatelet agents, and NSAIDs. Ginger also can cause hypoglycemia, so it should not be used in combination with insulin or other antidiabetic drugs. Ginger may have hypotensive and calcium-channel blocking effects, therefore patients should be monitored closely who are also taking calcium-channel blockers.

Ginkgo

Through inhibition of PAF ginkgo can decrease platelet aggregation, therefore patients on anticoagulants and antiplatelet agents should avoid use (NMD, MSKCC). Ginkgo leaf extract may inhibit CYP2C9, Pgp, and MATE1, and induce CYP2C19. There is conflicting evidence whether ginkgo inhibits or induces CYP1A2, 2D6 and 3A4, and should be used in caution with patients taking CYP3A4 substrates. It can also modulate the UGT enzyme in vitro and increase the toxicities of drugs metabolized by them.

Ginseng

American ginseng may stimulate the growth of cancer cells through estrogenic effects and patients with hormone sensitive malignancies should use ginseng with caution (NMD, MSKCC). Certain ginsenosides can induce CYP3A4 thereby decreasing the efficacy of CYP3A4 substrates. American ginseng can cause hypoglycemia and should be used in caution with patients with diabetes. American ginseng has been shown to decrease the effectiveness of warfarin therapy and should be avoided in combination. Due to its immunostimulatory properties, American ginseng may decrease the effectiveness of immunosuppressant drugs.

Green tea

Green tea may inhibit CYP3A4 and OATP, and modulate the UGT enzyme (NMD, MSKCC). Some notable substrates of OATP that may be affected include etoposide, fluoroquinolone antibiotics, irinotecan, and methotrexate. Additional agents that may be impacted by green tea include bortezomib, fluorouracil, tamoxifen, and palbociclib. The catechins in green tea are reported to have antiplatelet and anticoagulant effects, therefore patients should use these therapies with caution. There are also reports of hepatotoxicity occurring in individuals ingesting green tea, therefore concomitant hepatotoxic medications should be avoided.

Milk thistle

The silymarin found in milk thistle may bind to estrogen receptor beta and may have estrogenic effects in women with hormone sensitive diseases. Milk thistle may inhibit several CYP isoenzymes including 1A2, 2C9, 2D6, 3A4 and 3A5, and Pgp, and UGT. Substrates of these pathways should be used with caution and patients monitored. Milk thistle has been shown to lower blood sugar levels and hemoglobin A1c (HbA1c) levels in patients with type 2 diabetes. Patients should be monitored for potential additive hypoglycemic effect of milk thistle with antidiabetic medications.

Mistletoe

Mistletoe is reported to inhibit CYP3A4(NMD, MSKCC). It also may decrease the effectiveness of immunosuppressant medications due to its immunostimulatory effects. There are reports of hepatotoxicity occurring in individuals using mistletoe, therefore it should be used with caution in combination with other hepatotoxic drugs. Mistletoe may cause hypotension, therefore use cautiously and monitor patients on antihypertensive medications. There is also a report of severe hypertension occurring in one patient. Due to blood pressure effects, mistletoe should be avoided prior to surgery.

Reishi mushroom

Reishi polysaccharides are reported to inhibit CYP2E1, 1A2, and 3A4 (NMD, MSKCC). It can also increase plasma antioxidant capacity, thereby potentially interacting with medications and radiation that rely on free radicals. Reishi can enhance the immune response and caution should be used with immunosuppressants. There is reported potential for reishi mushroom to impact platelet aggregation, therefore patients should avoid concomitant use of anticoagulant/antiplatelet medications. Reishi mushrooms may have the potential to decrease blood sugar, and caution should be used with antidiabetic medications. It also may decrease blood pressure, and caution should be used with concomitant antihypertensive drugs. Hepatotoxicity may occur with the use of reishi mushrooms. Patients should be monitored, and caution used with concomitant hepatotoxic drugs.

Turmeric

In vitro evidence suggests that curcumin has the potential to competitively inhibit the binding of 3H-estradiol or beta-galactosidase with the estrogen receptor, and might have estrogenic effects (NMD, MSKCC). Women with hormone-sensitive conditions should use turmeric with caution as it may exacerbate those conditions. Curcumin may inhibit CYP3A4, 1A1, 1A2, 2A6, and 2D6, and Pgp. Turmeric has antiplatelet effects and may increase a patient's risk of bleeding. Curcumin may reduce blood sugar levels and HbA1c in patients with diabetes. Caution should be used in patients taking antidiabetic medications. There is also data on curcumin interacting with chemotherapy induced apoptosis in cancer cell lines; camptothecin, doxorubicin and mechlorethamine in breast cancer. Dietary turmeric has been shown to inhibit cyclophosphamide-induced tumor

regression in animal studies. In the presence of acetaminophen, aspirin, and ibuprofen, the cytotoxic effects of curcumin were reported to increase significantly.

Resources for the Provider and Patient

People with cancer are advised to discuss any prescription drug, over the counter medication, herbal or supplement they are taking with their healthcare provider. When providers learn of alternative medicine use there are several available resources to educate themselves and their patients. Some of the more commonly utilized tools are included in Table 2.

Table 2. Natural Product Databases (Latte-Naor 2019)

Database	Website
About Herbs, Memorial Sloan Kettering Cancer Center	https://www.mskcc.org/aboutherbs
ConsumerLab	https://www.consumerlab.com (subscription)
National Center for Complimentary and Integrative Health	https://nccih.nih.gov
Natural Medicines Comprehensive Database	http://naturaldatabase.com (subscription)
National Cancer Institute Office of Cancer Complementary and Alternative Medicine	https://cam.cancer.gov
Office of Dietary Supplements	https://ods.od.nih.gov

About Herbs and the Natural Medicines Comprehensive Database also contain patient friendly information that can be given to patients and their caregivers. In addition to English, the Natural Medicines Database has the option of printing the patient handout in Spanish or French. The Natural Medicines Database also has a drug-herb interaction checker which allows the provider to run an analysis on potential interactions without having to review each individual supplement.

If it is deemed safe and appropriate for a patient to use an herbal supplement it is prudent to verify the safety of the product being used. Since herbal products are not regulated by the FDA like prescription drugs, it is difficult to ensure product integrity and quality. Manufacturers can elect to have their products verified by the United States

Pharmacopeia (USP) and are then allowed to label their product with a USP Verified Mark (USP Verified Mark). Products with this indication on their label should be recommended as they are considered safer to use. Consumer Lab, NSF-International, and UL also test and verify product contents (Tarkan 2016). Seals from these organizations may also be seen on products to indicate their verification.

Table 3. USP Labeled Products (USP Verified Mark)

- Contain ingredients listed on the label, in the declared potency and amounts
- Do not contain harmful levels of specified contaminants
- Will break down and release into the body within a specified timeframe
- Made according to the FDA Good Manufacturing Practices using sanitary and well-controlled procedures

Conclusions

It is important for healthcare providers to be aware of CAM therapy use in cancer patients. The use of herbal supplements during cancer treatment poses a concern as it may impact the efficacy of conventional treatment, as well as lead to worsening side effects and organ toxicity. Acknowledging the increasing interest by cancer patients, several cancer centers are developing integrative oncology programs that work with patients, caregivers, and oncology care teams to develop an integrative care plan that blends conventional and non-conventional treatment in support of improving overall health throughout cancer treatment (Lopez 2018). When these specialized centers are not available, it is important for pharmacists at a minimum to be verifying and documenting what herbal therapies patients are using and assessing if they are safe to use in conjunction with their planned cancer therapy from a drug and disease interaction perspective.

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QUIZ – May 2020 • Herbal Use in Cancer Patients… More Common and Concerning Than You May Think

In order to receive credit for this activity, fill in the information below, answer all questions, and return Quiz Only for certification of participation to:

CE-PRN
341 Wellness Drive
Myrtle Beach, South Carolina 29579

WHEN YOU SEND IN QUIZZES, ALWAYS KEEP A COPY. YOU MAY MAIL, EMAIL, OR FAX THEM.
FAX #. (843) 488-5554 • EMAIL. INFO@CE-PRN.COM

NAME
_____

ADDRESS
_____

CITY _____ STATE _____ ZIP _____

☐ PHARMACIST ☐ PHARMACY TECHNICIAN

CPE Monitor ePID _____ BIRTHDATE (MM/DD) _____

IF LICENSED IN FLORIDA, FL LICENSE #
_____

EMAIL ADDRESS
_____

LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1a. PHARMACISTS ONLY: Does this lesson meet the learning objectives? (Circle choice).

Identify examples of common herbals used by cancer patients	YES	NO
Recognize the current landscape of herbal use in cancer patients	YES	NO
Identify common drug-drug and drug-disease interactions with selected herbals	YES	NO

Identify appropriate provider and patient resources to assess use and safety of herbal supplements

YES NO

2a. TECHNICIANS ONLY: Does this lesson meet the learning objectives? (Circle choice).

Identify examples of common herbals used by cancer patients YES NO

Identify common drug-drug and drug-disease interactions with selected herbals YES NO

Recognize the current landscape of herbal use in cancer patients

Identify appropriate provider and patient resources to assess use and safety of herbal supplements YES NO

YES NO

2. Was the program independent & non-commercial? YES NO

	Low Relevance						Very Relevant
3. Relevance of topic	1	2	3	4	5	6	7

4. What did you like MOST about this lesson?

_____

_____

5. What did you like LEAST about this lesson?

_____

_____

6. How would you improve this lesson?

_____

_____

Activity Test

A passing grade of 70 or higher is required to earn credit.

1. Which patient population has the highest use of herbal therapies compared with the general population?
    a. Young males diagnosed testicular cancer
    b. Young females diagnosed with breast cancer
    c. Older males diagnosed with prostate cancer
    d. Older females diagnosed with ovarian cancer

2. Which of the following herbal supplements is commonly used to relieve menopausal symptoms?
    a. Black cohosh
    b. Echinacea
    c. Ginseng
    d. Turmeric

3. Which of the following herbal supplements was developed as an alternative treatment for cancer, but found to stimulate the growth of breast cancer cells?
    a. Essiac
    b. Green tea
    c. Milk thistle
    d. Mistletoe

4. Which of the following herbal supplements is reported to have anti-inflammatory effects through inhibition of COX-2, prostaglandins, leukotrienes, and other pro-inflammatory cytokines?
    a. Garlic
    b. Ginkgo
    c. Reishi mushroom
    d. Turmeric

5. Which of the following properties of herbal supplements may interfere with the efficacy of radiation?
    a. Anticoagulant
    b. Antioxidant
    c. Immunostimulatory
    d. Phytoestrogenic

6. Which of the following herbal supplements should be avoided in patients on anticoagulation?
    a. Ginseng
    b. Milk thistle
    c. Mistletoe
    d. Reishi mushroom

7. Which of the following herbal supplements should be used cautiously in patients taking antidiabetic medications?
    a. Ginkgo
    b. Green tea
    c. Mistletoe
    d. Turmeric

8. Which of the following agents may impact the absorption of oral medications due to its slowed gastrointestinal transit time effects?
    a. Black cohosh
    b. Echinacea
    c. Essiac
    d. Garlic

9. Which agent should be used cautiously in patients on calcium-channel blockers?
    a. Echinacea
    b. Ginger
    c. Milk thistle
    d. Turmeric

10. Which of the following resources has a drug-herb interaction checker?
    a. About Herbs
    b. Consumer Lab
    c. Natural Medicines Comprehensive Database
    d. Office of Dietary Supplements