SUPPLEMENT/BOTANICAL INTERACTIONS WITH CHEMOTHERAPY AND RADIATION

Many people take supplements and botanicals during cancer treatment. The potential for side effects from concurrent use requires physicians to be aware of the risks and benefits that may arise. Some direct evidence for such interaction is defined in the literature, but much of the concern regarding botanical and supplement interactions with chemotherapy and radiation is theoretical. Interactions with chemotherapy drugs affect solubility, absorption, distribution, metabolism, and excretion.

Note: Please refer to the *Passport to Whole Health*, Chapter 15 on Dietary Supplements for more information about how to determine whether or not a specific supplement is appropriate for a given individual. Supplements are not regulated with the same degree of oversight as medications, and it is important that clinicians keep this in mind. Products vary greatly in terms of accuracy of labeling, presence of adulterants, and the legitimacy of claims made by the manufacturer.

BLEEDING RISK

Many supplements and botanicals can increase bleeding and bruising in patients. A blood thinning effect may be desired when they are used to prevent blood clots, venous thromboses, and improve circulation. The mechanisms of action include direct platelet function inhibition or interactions with drugs that are blood thinners. When used by a patient with bleeding tendencies, especially one who has anemia or thrombocytopenia, or is on blood thinner medications (aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], platelet inhibitors, warfarin, new oral anticoagulants [NOACs]), it can lead to unwanted bleeding and bruising. Patients who are on these should discontinue their use 10 days before surgery to reduce the chance of perioperative bleeding and hemorrhage.

SUPPLEMENTS AND BOTANICALS THAT MAY INCREASE BLEEDING RISK[1]

- Bilberry
- Black cohosh
- Chamomile
- Devil's claw
- Dong quai
- Fish oil
- Flax oil
- Garlic
- Ginger
- Gingko biloba
- Ginseng
- Licorice
- Policosanol
- Resveratrol
- Turmeric
- Vitamin E

CYTOCHROME P450 (CYP450) ENZYME ACTIVATORS AND INHIBITORS

Just like pharmaceutical drugs, certain botanicals and supplements activate or inhibit the CYP450 liver enzyme. The major phase I liver CYP450 enzyme is CYP3A4, which is responsible for metabolizing more than 35% of chemotherapy drugs.[2] CYP3A4 enzyme

activation during chemotherapy will reduce the half-life of the drug, thereby decreasing effectiveness. Enzyme activation increases drug half-life and may lead to more side effects or contribute to increased toxicity.

TABLE 1. SUPPLEMENTS THAT INDUCE, INHIBIT, OR HAVE NO EFFECT ON CYP3A4

Botanical	Effect on CYP3A4 Enzyme
Asian ginseng (Panax ginseng)	Weak inhibitor
Black cohosh *(Actaea racemosa)*	No effect
Black pepper *(Piper nigrum)*	Potential inhibitor
Chinese skullcap *(Scutellaria baicalensis)*	Potential inhibitor
Cranberry *(Vaccinium macrocarpon)*	No effect
Danshen *(Salvia miltiorrhiza)*	Potential inducer
Echinacea *(Echinacea spp.)*	Potential inducer
Garlic *(Allium sativum)*	Weak inhibitor
Ginkgo *(Ginkgo biloba)*	Weak inhibitor
Goldenseal *(Hydrastis canadensis)*	Strong inhibitor
Grapefruit juice *(Citrus paradise)*	Strong inhibitor (intestinal)
Grapeseed *(Vitis vinifera)*	Potential inducer (hepatic)
Green tea *(Camellia sinensis)*	No effect
Guggul tree *(Commiphora mukul)*	Potential inducer
Yun zhi *(Coriolus versicolor)*	No effect
Kava-kava *(Piper methysticum)*	No effect
Licorice *(Glycyrrhiza uralensis)*	Potential inhibitor
Milk thistle *(Silybum marianum)*	No effect
Peppermint *(Mentha piperita)*	Weak inhibitor
Saw palmetto *(Serenoa repens)*	No effect
American ginseng *(Panax quinquefolius)*	No effect
Soy *(Glycine max)*	No effect
St. John's wort *(Hypericum perforatum)*	Strong inducer
Turmeric *(Curcuma longa)*	No effect
Valerian *(Valeriana officinalis)*	No effect
Wheat bran *(Triticum aestivum)*	Potential inhibitor
Reishi *(Ganoderma lucidum)*	Inhibitor

Adapted from Abrams[2]

INTERACTIONS WITH SPECIFIC DRUGS

Several supplements and botanicals can interact with specific chemotherapy drugs to increase resistance to them or decrease their effectiveness (for more information, refer to the sections below). Some of the interactions have been proven, but many of them are theoretical. [3]

TABLE 2. SUPPLEMENT INTERACTIONS WITH SPECIFIC CHEMOTHERAPY DRUGS

Chemotherapy Drug	Supplement/Botanical	Interaction
Carboplatin, Oxaliplatin	N-acetylcysteine L-glutathione	Decrease effectiveness of chemotherapy agent

Chemotherapy Drug	Supplement/Botanical	Interaction
Cisplatin	N-acetylcysteine Black cohosh Zinc	Decrease effectiveness of chemotherapy agent
Cyclophosphamide	Quercetin Curcumin	Decrease effectiveness of chemotherapy agent
Doxorubicin	Most botanicals	Reduce conversion to active form
Doxorubicin	N-acetylcysteine Curcumin	Decrease effectiveness of chemotherapy agent
Etoposide	Most botanicals	Reduce conversion to active form
Etoposide	Vitamin K Glucosamine	Decrease effectiveness of chemotherapy agent
Fluorouracil	Beta-carotene	Decrease effectiveness of chemotherapy agent
Irinotecan	Most botanicals St. John's wort	Decrease effectiveness of chemotherapy agent
Methotrexate	Kava-kava Willow bark	Increase toxicity of chemotherapy agent
Paclitaxel, Docetaxel (taxanes)	Most botanicals	Reduce conversion to active form
Paclitaxel, Docetaxel (taxanes)	Quercetin	Decrease effectiveness of chemotherapy agent
Gemcitabine, Ifosfamide, Topotecan, Vinblastine, Vincristine	Not applicable	No interactions

Adapted from Alschuler[3]

SUPPLEMENT INTERACTIONS WITH DRUG CATEGORIES

The following list was adapted from Alschuler[3].

ANTIESTROGENS: TAMOXIFEN, RALOXIFENE, TOREMIFENE

- **Indole-3-carbinol** may increase the metabolism
- **Licorice root** has potent estrogenic activities
- Long-term use of **phytoestrogenic** herbs such as alfalfa, red clover, black cohosh, and ginkgo

AROMATASE INHIBITORS: LETROZOLE, ANASTROZOLE, EXEMESTANE

- **Soy isoflavones** in high doses stimulate estrogen receptor positive breast cancer cells
- **DHEA** levels are correlated with disease progression

LUTEINIZING HORMONE-RELEASING HORMONE (LHRH) AGENTS: LEUPROLIDE, GOSERELIN, TRIPTORELIN

- There are no supplement/botanical interactions

ANTIANDROGENS: BICALUTAMIDE, FLUTAMIDE

- There are no supplement/botanical interactions

SPECIFIC BOTANICALS TO AVOID WITH CHEMOTHERAPY DRUGS

The following list was adapted from Abrams[2].

Echinacea

Apply caution with the following:

- Camptothecins
- Cyclophosphamide
- Tyrosine kinase inhibitors
- Epipodophyllotoxins
- Taxanes
- Vinca alkaloids (CYP3A4 induction)
- Etoposide

Ginkgo

Apply caution with the following:

- Camptothecins
- Cyclophosphamide
- Tyrosine kinase inhibitors
- Epipodophyllotoxins
- Taxanes
- Vinca alkaloids (CYP3A4 induction)

Discourage with the following:

- Alkylating agents
- Antitumor antibiotics
- Platinum analogues (free-radical scavenging)

Ginseng

Discourage in patients with estrogen-receptor positive breast cancer and endometrial cancer (stimulates tumor growth)

Green tea

Discourage with erlotinib (CYP1A2 induction) and bortezomib

May cause elevated liver enzymes if taking over 800 mg of epigallocatechin gallate (EGCG) per day

Synergistic with bleomycin, 5-fluorouracil, cisplatin, tamoxifen, docetaxel, paclitaxel, and doxorubicin[4]

Soy isoflavones

Avoid with the following:

- Tamoxifen (antagonism of tumor growth inhibition)
- Treatment of patients with estrogen-receptor positive breast cancer and endometrial cancer (stimulates tumor growth)

Valerian

Apply caution with the following:

- Tamoxifen (CYP2C9 inhibition)
- Cyclophosphamide
- Teniposide (CYP2C19 inhibition)

Kava-kava

Avoid in all patients with the following:

- Preexisting liver disease
- Evidence of hepatic injury (herb-induced hepatotoxicity),

Apply caution with the following:

- Camptothecins
- Cyclophosphamide
- Tyrosine kinase inhibitors
- Epipodophyllotoxins
- Taxanes
- Vinca alkaloids (CYP3A4 induction)

Grape seed

Apply caution with the following:

- Camptothecins
- Cyclophosphamide
- Tyrosine kinase inhibitors
- Epipodophyllotoxins
- Taxanes
- Vinca alkaloids (CYP3A4 induction)

- Alkylating agents
- Antitumor antibiotics
- Platinum analogues (free-radical scavenging)

ADDITIONAL PRECAUTIONS

- Probiotics should not be taken when the white blood cell (WBC) count is lower than 2.5 as they can become the source of infection.
- Activated charcoal is contraindicated when taking oral chemotherapy drugs.
- Panax ginseng, soy isoflavones (daidzein, genistein), dong quai, gingko biloba, and licorice should be used with caution or not taken by patients with estrogen receptor-positive (ER+) breast cancer.
- Essiac tea is contraindicated in patients with breast cancer.
- Rhodiola and vitamin A should be used with caution during radiation therapy.
- St. John's wort has so many interactions that it should not be used during chemotherapy or by patients on numerous medications.

ANTIOXIDANTS

Although antioxidant-rich foods are commonly associated with reduced risks of a variety of cancers, use of antioxidant supplements during chemoradiotherapy can be associated with harm, and this has remained a controversial area. Conventional oncologists recommend against concurrent use of oral or intravenous antioxidants and chemoradiotherapy, as there is some potential for decreasing the effectiveness of conventional therapy. Most concerns are theoretical, although limited evidence for harm exists, mainly for vitamin E with head and neck patients. Experts cite large amounts of preclinical data and some human data to support use of antioxidants, such as vitamin C, coenzyme Q10, and vitamin E, for reduction of chemoradiotherapy-related toxicity.[5]

In a review of antioxidants which included glutathione, melatonin, vitamin A, an antioxidant mixture, N-acetylcysteine, vitamin E, selenium, L-carnitine, Co-Q10, and ellagic acid, 24 out of 33 studies reported decreased toxicities from the concurrent use of antioxidants with chemoradiotherapy. Only one trial with vitamin A reported a significant increase in toxicity in the antioxidant group. Five studies reported that the antioxidant group was able to complete more full doses of chemotherapy or had less-dose reduction than control groups.[6]

In an earlier review of vitamin A, beta-carotene, vitamin E, and glutathione used concurrently during chemoradiotherapy, studies repeatedly reported beneficial effects. Doses of vitamin A ranging from 30,000 IU to 500,000 IU daily to twice a week increased the treatment response rate, duration of response, and projected survival, lowered toxic side effects, and enhanced the cellular sensitivity to radiation. Two studies of beta-carotene given concurrently decreased side effects and allowed for a longer-than-expected disease-free interval. Those who received high-dose vitamin E in several studies had fewer toxicities, increased response rate, and reduced alopecia, and they were able to prevent

oral mucositis. Patients given antioxidant mixtures via total parenteral nutrition (TPN) also had fewer side effects and a higher response rate. Oral combined antioxidant regimens decreased rates of recurrence, and increased quality of life, survival rates, and partial remission rates. Concurrent intravenous glutathione therapy increased response rates, reduced side effects, prevented nephro- and neurotoxicity, and improved survival.[7,8]

There are several potential mechanisms of action thought to be responsible for the beneficial effects of concurrent antioxidant treatment and chemotherapy/radiation. Cancer cells lose their homeostasis control mechanism for the uptake of antioxidants, leading them to accumulate them excessively. This causes cancer cells to shut down the oxidative reactions necessary for generating energy. In addition, studies have found that antioxidants increase apoptosis, inhibit cancer cell growth, inhibit oncogene expression, and selectively inhibit the repair of cancer cells damaged by radiation. These changes can lead to higher rates of cancer cell death and reduced rates of cell proliferation and induction of differentiation. The changes seem to override any protective action that antioxidants have against free radical damage on cancer cells.[7,8]

The following section reviews the effects of antioxidant supplementation on cancer risk:

GENERAL EVIDENCE

A meta-analysis of 22 randomized controlled trials indicated that there is no clinical evidence to support primary or secondary prevention of cancer with antioxidant supplements.[9] Other studies confirm that there is no evidence that antioxidants prevent colorectal,[10] skin,[11] or prostate[12] cancer. A Cochrane review demonstrated increased mortality of patients with gastric cancer when supplemented with antioxidants.[13] There may be some preventive effects for cervical cancer.[14]

VITAMINS A, C, AND E

A systematic review did not find that vitamin C or vitamin E prevents or treats cancer.[15] Total intake of vitamin A and retinol could reduce breast cancer risk, but associations between vitamins C and E and breast cancer were limited.[16] Systematic reviews have shown no benefit of intravenous vitamin C therapy on patients with cancer.[17,18]

CAROTENOIDS

A systematic review found no effect of beta-carotene supplementation on the incidence of all cancers, or specifically, pancreatic, colorectal, prostate, breast, or skin cancer. The incidence of lung and stomach cancers was significantly increased in individuals supplemented with beta-carotene, in smokers and asbestos workers.[19] In a smaller meta-analysis, beta-carotene had no preventive effect on cancer incidence or mortality, while it increased the risk of bladder cancer.[20] Two reviews found that increased blood concentrations of carotenoids were associated with reduced breast cancer risk.[21,22] A Cochrane review concluded that there is insufficient evidence to either support, or refute, the use of lycopene for the prevention of prostate cancer.[23]

SELENIUM

A Cochrane review found no beneficial effect of selenium supplements in reducing cancer risk, noting that evidence offered a high certainty to make this conclusion.[24] There is no association between selenium and thyroid cancer.[25] Selenium may have a protective role against the development of prostate cancer and its progression.[26] There is an inverse relationship between selenium levels and bladder cancer risk, particularly in women.[27]

SUMMARY

There are numerous contraindications for using certain supplements and botanicals in patients undergoing cancer treatment. The most concerning interactions include those that upregulate the metabolism of a chemotherapy agent, thereby reducing its availability and effectiveness. Additionally, as patients receiving chemotherapy often have low blood counts, it is imperative to be wary of supplements that may increase bleeding or infection risk. Finally, antioxidant supplementation during chemoradiotherapy is still controversial. Until more rigorous trials are conducted, advise patients to obtain antioxidants naturally through food sources while receiving active treatment.

RESOURCE LINKS

- *Passport to Whole Health*: https://www.va.gov/WHOLEHEALTHLIBRARY/docs/Passport_to_WholeHealth_FY2020_508.pdf

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"Supplement/Botanical Interactions with Chemotherapy and Radiation" was written by Srivani Sridhar, MD (2014, updated 2020).

This Whole Health tool was made possible through a collaborative effort between the University of Wisconsin Integrative Health Program, VA Office of Patient Centered Care and Cultural Transformation, and Pacific Institute for Research and Evaluation.

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