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 ten 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
- Willow bark
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

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

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**

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

*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)

**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)

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.[4] Research behind several antioxidants is covered here.

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.[5]

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.[6,7]

There are several potential mechanisms of action thought to be responsible for the beneficial effects of concurrent antioxidant treatment and chemoradiotherapy. 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.[6,7]

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.[8] Other studies confirm that there is no evidence that antioxidants prevent colorectal,[9] skin,[10] or prostate[11] cancer. A Cochrane review demonstrated increased mortality of patients with gastric cancer when supplemented with antioxidants.[12] There may be some preventive effects for cervical cancer.[13]

**VITAMINS A, C, AND E**

A systematic review did not find that vitamin C or vitamin E prevents or treats cancer.[14] Total intake of vitamin A and retinol could reduce breast cancer risk, but associations between vitamins C and E and breast cancer were limited.[15]

**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.[16] In a smaller meta-analysis, beta-carotene had no preventive effect on cancer incidence or cancer mortality, while increasing the risk of bladder cancer.[17] Two reviews found that
increased blood concentrations of carotenoids were associated with reduced breast cancer risk.[18,19] A Cochrane review concluded that there is insufficient evidence to either support, or refute, the use of lycopene for the prevention of prostate cancer.[20]

SELENIUM

A Cochrane review of epidemiologic data found that cancer incidence was reduced and mortality rate higher with increased selenium exposure, that was more pronounced in men.[21] A meta-analysis indicates that there is evidence to support the use of selenium supplements for cancer prevention in the low baseline serum selenium level population (<125.6 ng/mL) and in the high-risk population for cancer.[22]

A meta-analysis demonstrated an inverse relationship between selenium levels and bladder cancer risk, particularly in women.[23] A Cochrane review found that selenium reduced gastrointestinal cancer occurrence.[12] Another study indicated that the chemopreventive effect is dependent on baseline selenium status: selenium supplementation may reduce risk of lung cancers in populations with lower baseline selenium (serum < 106 ng/mL), but increase risk in those with higher selenium (serum ≥ 121.6 ng/mL).[24] A study found that prostate cancer risk decreased with increasing selenium up to 170 ng/mL.[25]

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.

AUTHOR(S)

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7. Simone CB, Simone NL, Simone V, Simone CB. Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, part 2. *Altern Ther Health Med.* 2007;13(2):40-47.


