

# Herbal Medicine: Friend or Foe?

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Presenter's disclosure of conflicts of interest is found at the end of this article.

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## Abstract

Many cancer patients report the use of supplements and herbal medicines but may not always disclose their use to their health-care team. Along with potential interactions, these therapies may also affect outcomes of treatment. During JADPRO Live Virtual 2021, Roberta Bourgon, ND, emphasized the importance of opening a dialogue with patients regarding complementary and alternative medicine and guiding patients in making appropriate choices in their treatment.

The practice of naturopathic medicine is growing rapidly in the United States, with 23 states currently licensing naturopathic physicians from six approved schools in the United States. During JADPRO Live Virtual 2021, Roberta Bourgon, ND, a naturopathic physician at Billings Clinic in Montana, discussed the potential impact of complementary and alternative medicine (CAM) on oncology-related outcomes and provided guidance for patients regarding the use of CAM treatments.

## ALTERNATIVE, COMPLEMENTARY, AND INTEGRATIVE MEDICINE

As Dr. Bourgon explained, alternative medicine implies a nonconventional therapy that may or may not have evidence supporting its use and is offered or used in lieu of conventional treatment. Alternatively, complementary medicine has evidence to support its use, but it is frequently used without consultation with, or

knowledge of the oncology team. Integrative medicine, on the other hand, which is practiced at Billings Clinic, consists of nonconventional, evidence-based therapies that are used as adjuncts to conventional treatment with the knowledge of the entire team.

These distinctions are important, said Dr. Bourgon, because up to 50% of cancer patients have reported supplement use, but only one third of these patients have disclosed this use to their health-care team (Berretta et al., 2017).

“There are potential interactions that can occur with the conventional treatments and the supportive medications that are used to help alleviate some of the side effects we anticipate with chemotherapy that can adversely affect their outcomes,” she added.

## PREDICTORS OF USE

As Dr. Bourgon reported, the primary reasons for using CAM include health maintenance or disease prevention (77%), pain management

(73%), treatment of specific acute or chronic health conditions (59%), and as substitutes to conventional medicine (53%; Dossey & Keegan, 2013).

“The use of CAM is most associated with younger age and higher education,” she said. “In addition, research indicates that patients are also likely to use CAM therapies due to family pressure to do so.”

According to Dr. Bourgon, it’s important for health-care providers to determine where patients are receiving their information and who is directing their use of CAM, whether it’s driven by practitioners, family, friends, or religious leaders.

“Patients are looking for answers, and sometimes they’re frightened about the prospects of receiving chemotherapy or radiation,” Dr. Bourgon explained. “If someone offers them an alternative that will ‘cure’ their cancer that can sound appealing, it’s important for us to have a conversation about the lack of data regarding the efficacy of some of these remedies.”

“In general, if something sounds too good to be true, it probably is,” she added. “Patient safety is paramount, but honoring the patient is also imperative.”

## HERBAL MEDICINE: CHALLENGES IN THE US

According to Dr. Bourgon, herbal/botanical medicine is not as well-regulated in the US as it is in other countries, and thus, access to safe and effective herbal/botanical medicine is not guaranteed. The regulation of dietary supplements differs from that of prescription or over-the-counter drugs in that dietary supplements do not require premarket review or approval by the U.S. Food and Drug Administration (FDA). In addition, dietary supplement labels may carry certain health-related claims.

Although all claims must be followed by the words, “This statement has not been evaluated by the US Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease,” said Dr. Bourgon, “if something says that it can cure cancer, the rest of that small disclaimer gets forgotten, unfortunately.”

Moreover, while US Pharmacopeia requires testing for *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas*, *Candida*, *Aspergillus*, and *Salmonella*, herbal products and nutritional supple-

ments manufactured outside of the US may not have these assurances. Dr. Bourgon noted reports in the literature of herbal supplements from other countries containing heavy metals, pesticides, and conventional pharmaceuticals (Harris et al., 2011).

## POTENTIAL INTERACTIONS

Outside of standardization and safety, there is also the concern about how herbal/botanical medications and nutritional supplements interact with conventionally prescribed medicines and treatments. According to Dr. Bourgon, there are two main considerations: the effect on pharmacokinetics and the effect on pharmacodynamics.

CYP3A4 and P-glycoprotein are responsible for the metabolism of roughly 50% of conventionally prescribed drugs, and CYP2D6 is thought to be involved in the metabolism of roughly 20% of conventionally prescribed medications.

“The concomitant use of herbs that have significant effects on these enzymes should be considered carefully, especially with conventionally prescribed medications with narrow therapeutic windows and/or where the risk of harm from such an interaction is high,” said Dr. Bourgon.

Common chemotherapeutic agents metabolized through CYP3A4 include ifosfamide, cyclophosphamide, doxorubicin, liposomal doxorubicin, paclitaxel, docetaxel, albumin-bound paclitaxel, ixabepilone, vinblastine, vincristine, vinorelbine, bortezomib, irinotecan, topotecan, etoposide, tamoxifen, exemestane, letrozole, everolimus, erlotinib, lapatinib, sorafenib, sunitinib, and regorafenib (Hakkola et al., 2020).

Common supportive medications metabolized through CYP3A4 include aprepitant, ondansetron, granisetron, palonosetron, and dexamethasone. Percocet, Vicodin, Oxycontin, Methadone, Ambien, Xanax, Celexa, Prilosec, Nexium, and Warfarin are also metabolized through CYP3A4.

Dr. Bourgon reported “strong and consistent evidence” suggesting that ginkgo and goldenseal may inhibit CYP3A4, yielding a higher dose and potentially increased toxicity of the chemotherapeutic interventions (Table 1).

St. John’s wort has also been shown to cause a clinically significant 30% reduction in the concentration of the area under the curve for imatinib in a classical pharmacokinetic interaction study,

**Table 1. Herbs That May Interfere With CYP3A4**

Hypericum (St. John's wort)
Quercetin
Piper methysticum (Kava kava)
Hydrastis canadensis (Goldenseal)
Uncaria tomentosa (Cat's claw)
Trifolium pratense (Red clover)
Matricaria chamomilla (Chamomile)
Glycyrrhiza glabra (Licorice)
Resveratrol
Polygonum multiflorum (Chinese knotweed)
Schisandra chinensis

*Note.* Information from Hakkola et al. (2020); Izzo (2012); Meijerman et al. (2006); Wanwimolruk & Prachayasittikul (2014); Wanwimolruk et al. (2014).

leading to the recommendation that it be avoided (Frye et al., 2004).

“Prudence would dictate the avoidance of St. John’s wort in patients receiving any chemotherapy,” said Dr. Bourgon.

Resveratrol, an enzyme found in grapes, is gaining popularity as an antiaging agent and antioxidant and is being used by increasing numbers of cancer patients. In a human study, 1,000 mg per day of resveratrol taken orally for 4 weeks was shown to have a strong inhibition of CYP2D9 and CYP2C9 (Chow et al., 2010). This is significant considering that tamoxifen is metabolized through the former and warfarin the latter, said Dr. Bourgon.

“An argument can be made that the risk is high with all chemotherapeutic agents, and that such herb-drug potential interactions should be avoided,” she said.

## ARGUMENTS FOR HERBAL MEDICINE

Despite these risks, evidence exists for the safety and efficacy of certain substances (Table 2). According to Dr. Bourgon, herbal medications and supplements can be an opportunity to improve the quality and quantity of cancer patients’ lives, and multiple studies have demonstrated that cancer patients’ quality of life is predictive of survival.

### Melatonin

A systematic review and meta-analysis of 21 clinical trials (all solid tumors) showed that in trials combining melatonin with chemotherapy, melatonin decreased 1-year mortality and improved outcomes of complete response, partial response, and

stable disease (Seely et al., 2012). Melatonin also significantly reduced asthenia, leukopenia, nausea and vomiting, hypotension, and thrombocytopenia. Doses of melatonin ranged from 10 to 40 mg at bedtime.

A separate study of 22 patients with breast cancer (stages II–IV) receiving paclitaxel or docetaxel also suggested an association between 21 mg of melatonin at bedtime and a reduction in the incidence of neuropathy (Nahleh et al., 2010).

### L-Glutamine

Oral glutamine is another well-studied nutrient used for the prevention of neuropathy as well as mucositis. A study of 86 colorectal patients showed low grade 1 and 2 neuropathy after 2 cycles in the glutamine-treated group and lower incidence of grade 3 and 4 neuropathy after 4 cycles (Wang et al., 2007).

A separate systematic review also revealed that oral glutamine (30 grams per day) was effective at significantly reducing mucositis in 11 of the 15 studies reviewed (Sayles et al., 2016).

### Coenzyme Q10 and Anthracyclines

A cardioprotective effect of Coenzyme Q10 has been observed when administered with anthracyclines (Conklin, 2005), with no adverse effects on the efficacy of the drugs. CoQ10 co-administration allowed for higher doses of the drug to be obtained, said Dr. Bourgon, and no changes in cardiac function were seen in the patients receiving CoQ10 as compared with the controls (e.g., reduced cardiac output). CoQ10 doses varied from 50 to 90 mg per day.

### Omega-3 Fatty Acids and Paclitaxel

A study of patients with breast cancer randomized to omega-3 fatty acids (640 mg tid) during paclitaxel chemotherapy and continued for 1 month after completion of treatment suggests that omega-3 fatty acids may be protective against paclitaxel-induced peripheral neuropathy (Ghoreishi et al., 2012). Only 30% of the intervention group developed neuropathy compared with 70% in the placebo group.

Omega-3 fatty acids have also been shown to increase lean body mass in patients with pancreatic cancer during chemotherapy (Abe et al., 2018).

### Coriolus Versicolor (Yun Zhi)

Systemic review and meta-analysis of 13 clinical trials demonstrated a 9% absolute reduction in 5-year mortality (1 additional patient alive for every 11 patients treated) in cancer patients who supplemented with turkey tail mushroom (Eliza et al., 2012). The effects of the combination of Yun Zhi preparation on the overall 5-year survival rate was more evident in patients with breast cancer, gastric cancer, or colorectal cancer treated with chemotherapy, said Dr. Bourgon.

### Curcumin Phytosome (Meriva) and Pancreatic Cancer

There are more ongoing clinical trials of curcumin (turmeric) than nearly any other nutraceutical, said Dr. Bourgon. One study in patients with locally advanced or metastatic pancreatic cancer provided preliminary evidence that combining curcumin with gemcitabine as a single agent is as effective as the combination of nab-paclitaxel plus gemcitabine with the advantage of producing less toxicity. The study showed no neurotoxicity with the use of curcumin and lower hematologic toxicity vs. nab-paclitaxel (Pastorelli et al., 2018).

### Activated Charcoal (AC) and Irinotecan

A small trial of pediatric colorectal cancer patients receiving irinotecan showed that activated charcoal led to a significant reduction in diarrhea (Michael et al., 2004).

### Vitamin D and Colorectal Cancer

Analysis of blood samples of more than 1,000 patients with previously untreated advanced or metastatic colorectal cancer participating in a randomized phase III clinical trial of first-line chemotherapy plus biologic therapy identified a correlation between vitamin D deficiency and the incidence and severity of colorectal cancer (Yuan et al., 2019). Higher 25-hydroxy vitamin D levels were also associated with improved overall survival and progression-free survival. ●

### Disclosure

The presenter had no conflicts of interest to disclose.

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**Table 2. Resources for Herbal Medications and Complementary and Alternative Medicine**

Title	Url
Natural Medicines homepage and interaction checker	<a href="https://naturalmedicines.therapeuticresearch.com/">https://naturalmedicines.therapeuticresearch.com/</a> <a href="https://naturalmedicines.therapeuticresearch.com/tools/interaction-checker.aspx">https://naturalmedicines.therapeuticresearch.com/tools/interaction-checker.aspx</a>
Office of Dietary Supplements	<a href="https://ods.od.nih.gov/">https://ods.od.nih.gov/</a>
Health On the Net	<a href="https://www.hon.ch/">https://www.hon.ch/</a>
Examine	<a href="https://examine.com/">https://examine.com/</a>
National Center for Complementary and Integrative Health	<a href="https://nccih.nih.gov/health/atoz.htm">https://nccih.nih.gov/health/atoz.htm</a>
About Herbs, Botanicals & Other Products	<a href="https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs">https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs</a>
Complementary and Integrative Medicine	<a href="https://www.cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/more-cam-info.html">https://www.cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/more-cam-info.html</a>

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