A Botanical Approach to Symptom Management During and After Breast Cancer Treatment

By Lise Alschuler, ND, FABNO

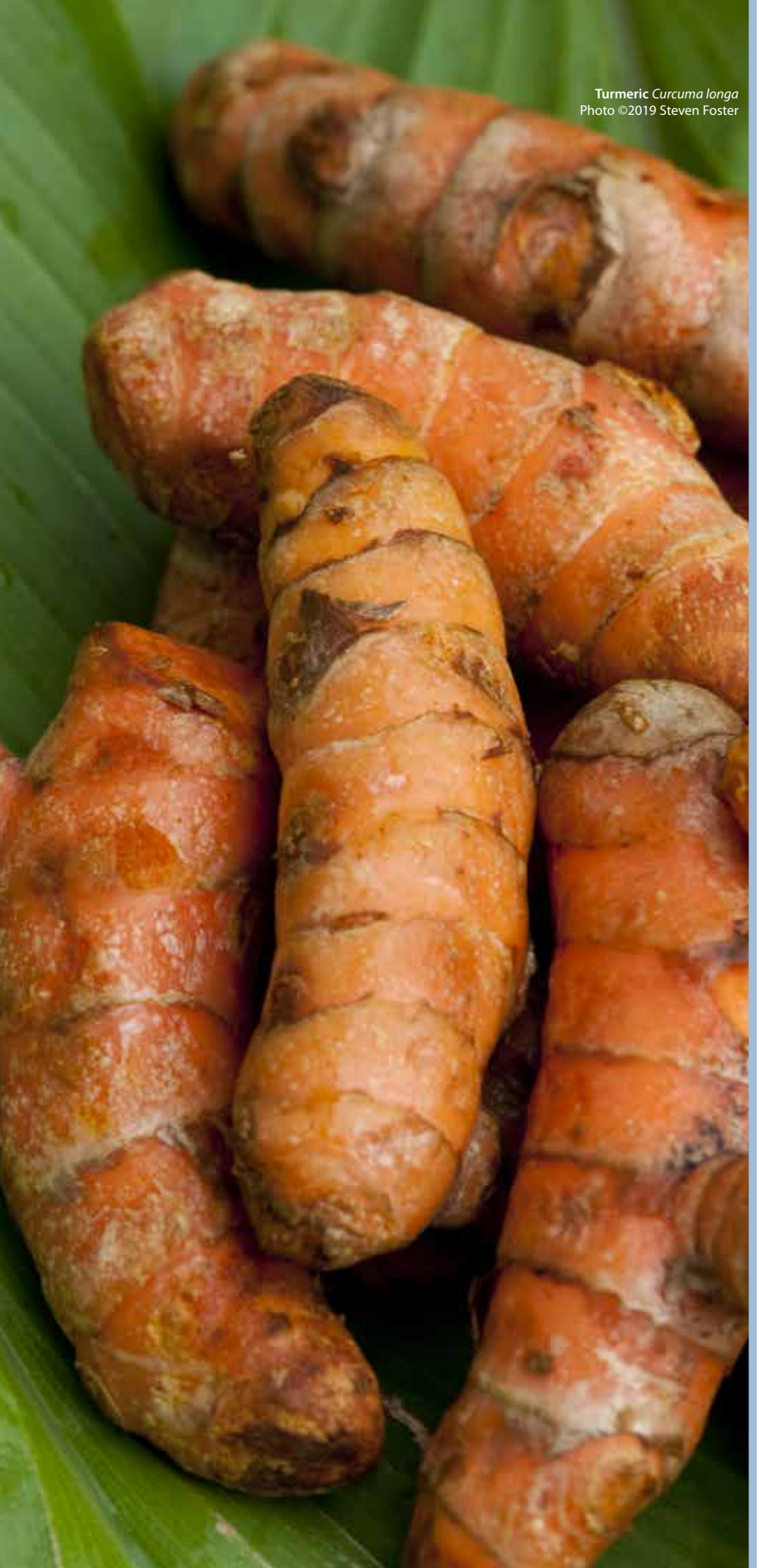
Breast cancer is the most common cancer in the United States, with 266,120 cases in women and 2,550 cases in men diagnosed in 2018.[1] In women, breast cancer represents 30% of all cancers diagnosed and is responsible for 14% of all deaths from cancer.[2] Of all breast cancers diagnosed in women, more than three-quarters are diagnosed in postmenopausal women.[3] The five-year survival rate for localized breast cancer is 99%, whereas the five-year survival for metastatic breast cancer is 27%.[4] According to the American Cancer Society, deaths from breast cancer in the United States have fallen by 30% over the past two decades.[5] This improvement is likely due in part to better screening, which results in an increased proportion of early stage diagnoses that are more amenable to treatment. Improved treatments also have contributed to this favorable trend. The majority of women diagnosed with breast cancer will undergo conventional treatment in the form of surgery, radiation, chemotherapy, and/or endocrine therapy. Many of these women seek additional integrative therapies, including botanicals, to improve their tolerance to, and the efficacy of, these conventional treatments.

While the clinical data supporting the use of botanicals concurrent with conventional treatment is far from robust, there is a body of emerging data. One area of interest is the reduction of adverse side effects, which can make conventional treatment a more tolerable experience and improve treatment adherence, thereby supporting better outcomes. This article provides an overview of the current state of evidence for selected botanicals for improving outcomes with conventional therapies.

An Integrative Approach for Women with Breast Cancer

Breast cancer is a potentially life-threatening disease, and the conventional treatments in use are effective for most women. Adjunctive integrative therapies that support a woman's well-being, while complementing and not interfering with conventional treatment efficacy or safety, may be valuable.[6] Safe, concurrent integrative botanical therapy requires nuanced knowledge of the type of breast cancer diagnosis and the conventional treatment(s) being used. For each chemotherapeutic agent, molecular targeted therapy, immune therapy, and endocrine therapy, it is important to know the class of drug, mechanism(s) of action, metabolism and terminal half-life, schedule of treatments, intent of the treatment (curative or palliative), and how each botanical or other integrative therapy might interact or interfere. For radiation therapy, the type and duration of treatment as well as the type and location of tissues within the radiation field should be ascertained in order to accurately anticipate the nature and location of potential radiation toxicities, which, in turn, can inform botanical recommendations.

It is equally important to have strong knowledge of the botanicals intended for use in a patient with breast cancer undergoing conventional treatment. Phytochemical constituents have the potential to interfere with drug metabolism, drug mechanisms of action, and/or the effects of radiation and, therefore, may modulate efficacy or increase toxicities. Botanicals may be counterproductive when used in conjunction with certain conventional treatments. For instance, the use of herbs such as *dong quai* (*Angelica sinensis*, Apiaceae)[7] and fenugreek (*Trigonella foenum-graecum*, Fabaceae) seed husks[8] that may potentially raise estradiol levels or stimulate estrogen receptor-mediated cell growth would be contraindicated during hormonal treatment with aromatase inhibitors. In addition, herbs that may have antiplatelet or anticoagulant effects, such as *dan shen* (*Salvia miltiorrhiza*, Lamiaceae),[9] should be used judiciously in patients with low platelet counts (less than 25,000), a relatively common effect of certain chemotherapeutics and found in some women with advanced disease. Finally, choosing high-quality botanicals is of utmost importance in order to avoid the introduction of potential adulterants, contaminants, excessive extraction residues, or other compounds with potentially toxic effects.



Turmeric *Curcuma longa*
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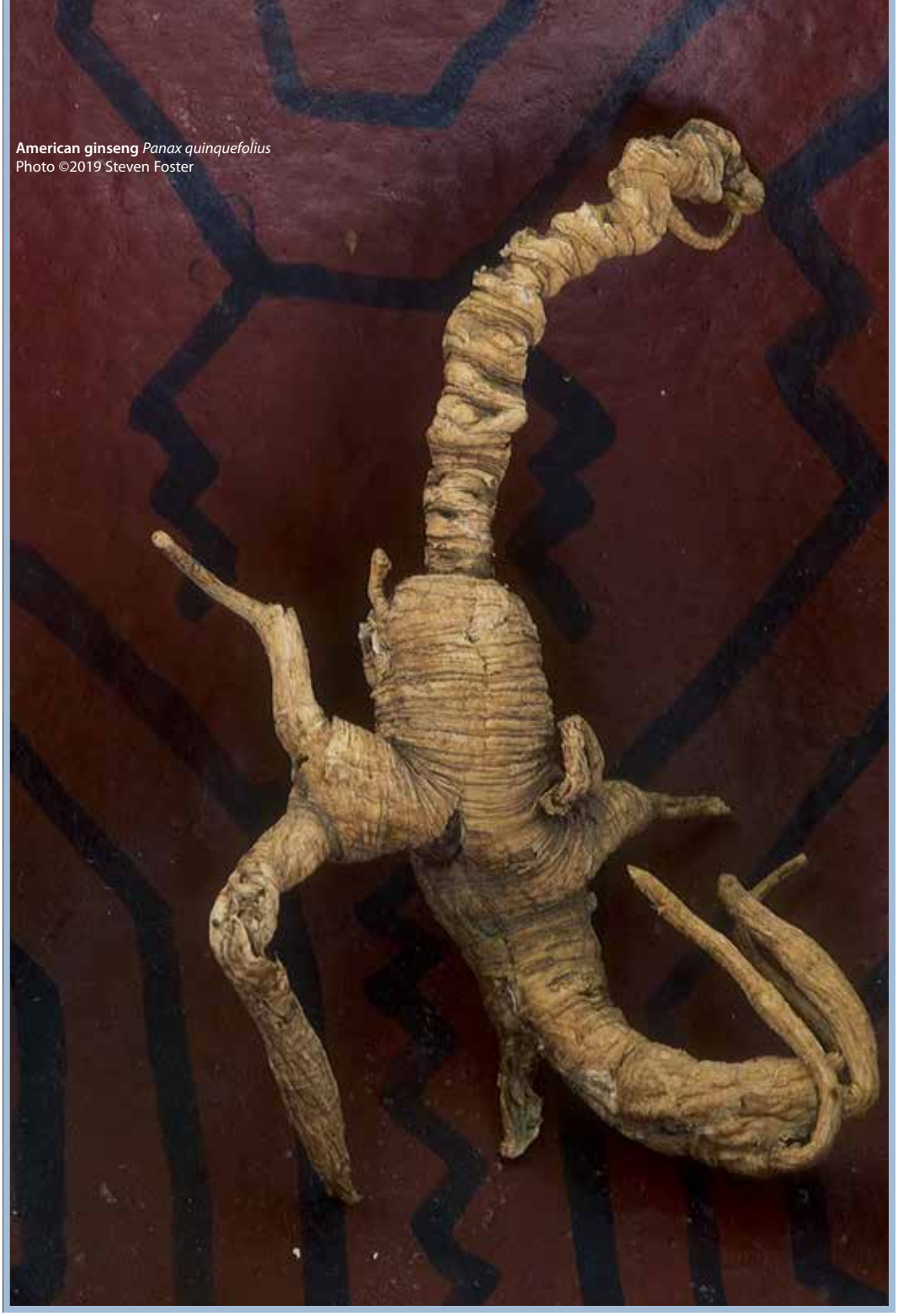
The primary focus of this discussion of herbal medicine in integrative oncology is to mitigate symptoms during conventional treatment. Given the lethality of cancer, it is essential to use an evidence-informed treatment approach. While the evidence base for botanicals in this regard is small, women are asking questions about the use of botanicals, and clinicians should be aware of the evidence for specific herbs that may aid in symptom management during active conventional treatment.

Botanicals during Chemotherapy

Turmeric

Turmeric (*Curcuma longa*, Zingiberaceae) is a well-known herb with anti-inflammatory actions. Systemic inflammation underlies many cancer- and treatment-related symptoms and is also a risk factor for disease progression and poor outcomes.[10] A randomized, double-blind, placebo-controlled eight-week trial of 98 adults with solid tumors (primarily breast, colorectal, and gastric) assessed the impact of curcumin supplementation on systemic inflammation.[11] The intervention was 300 mg phytosomal curcumin (Meriva; Indena SpA; Milan, Italy) three times daily, providing 180 mg curcuminoids daily. Chemotherapy regimens that were commonly used for these cancers were docetaxel-cisplatin-5-fluorouracil (5-FU) (gastric cancer and breast cancer), topotecan-cyclophosphamide-etoposide (breast cancer), cyclophosphamide-methotrexate-5-FU (breast cancer), and 5-FU-based regimens (colorectal cancer). Curcumin supplementation resulted in significantly greater improvements in quality of life (QoL) after eight weeks compared with placebo ($P < 0.001$). Additionally, various biomarkers of systemic inflammation reduced significantly in the curcumin group, including tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta



American ginseng *Panax quinquefolius*
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(TGF-β), high-sensitivity C-reactive protein (hs-CRP), and calcitonin gene-related peptide (CGRP). The phytosomal, or liposomal, form of curcumin used in this trial may minimize the risk of herb-drug interactions, as compared to turmeric/curcumin products containing piperine (an alkaloid derived from black pepper [*Piper nigrum*, Piperaceae]).[12]

Capecitabine, another commonly used chemotherapeutic, is associated with a 40% to 50% incidence of hand-foot syndrome (HFS), a form of peripheral neuropathy. In a six-week pilot study of 40 patients (80% were female and 52% had breast cancer) receiving capecitabine, 4 g of turmeric (95% curcumin extract), taken as two capsules 12 hours apart, was associated with a reduced incidence of all grades of HFS, specifically 27.5% incidence after the first cycle of capecitabine treatment and 34% after the second cycle. The incidence of grade 2 or higher HFS (more severe) was only 10% after the first and second cycles of capecitabine, as compared to observed rates of 29% to 38% in placebo groups reported in other trials.[13] While these data are encouraging, this study is limited by its small size and the lack of a control group.

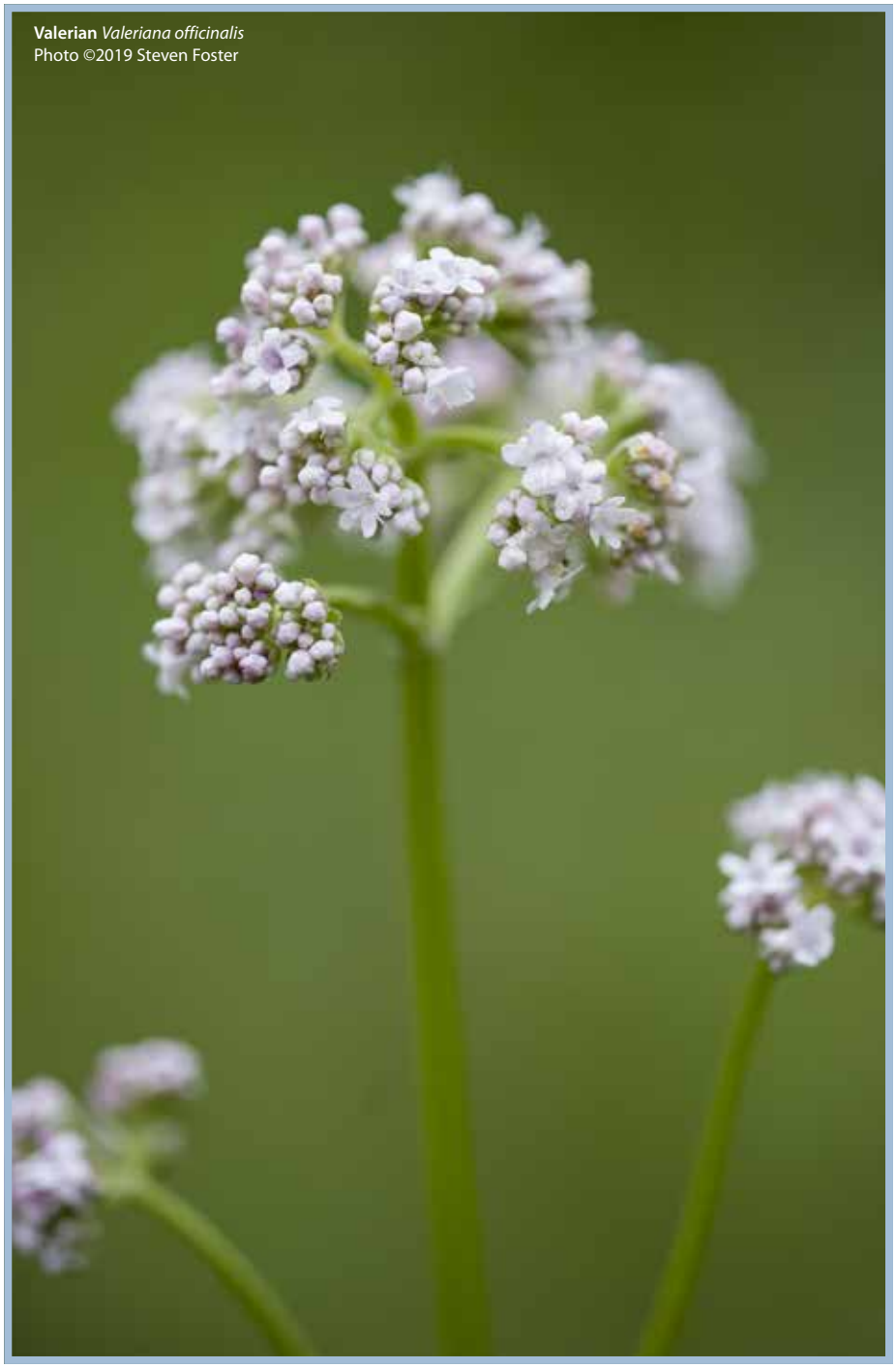
American Ginseng

Patients undergoing chemotherapy often experience fatigue. American ginseng (*Panax quinquefolius*, Araliaceae) is reputed to have anti-fatigue effects and has been a botanical of interest for this purpose. An eight-week, placebo-controlled clinical trial randomly assigned 364 adults actively receiving, or having recently completed, curative-intent treatment for cancer (all cancers were included except brain or central nervous system lymphoma) to 2 g American ginseng root extract (3% ginsenosides) or placebo daily to assess effects on fatigue.[14] Compared to the placebo group, ginseng supplementation was associated with a significant improvement in fatigue after eight weeks of treatment ($P = 0.003$). A subgroup analysis comparing patients undergoing treatment versus those who had completed treatment found significant improvements in fatigue at both four weeks ($P = 0.02$) and eight weeks ($P = 0.01$) in the ginseng patients undergoing treatment, compared to those undergoing treatment in the placebo group.

American ginseng has been shown to downregulate inflammation and modulate cortisol levels in stressed individuals, which may explain its potential benefit in fatigued patients. American ginseng does not have significant effects on cytochrome P450 enzymes, according to an in vitro assay, though further study is required.[15] Furthermore, water-extracted American ginseng and the crude root have not been shown to have estrogenic properties,[16] and in vitro data suggest American ginseng may have an inhibitory effect on the growth of breast cancer cells.[17] While these results need to be replicated in other studies, given the lack of any pharmacologic treatments for cancer-related fatigue, and the low risk presented by *P. quinquefolius*, this herb may be a reasonable option for patients.

Valerian

Sleep disruption is common among patients undergoing conventional cancer treatment, particularly chemotherapy. Poor sleep contributes to fatigue and reduced QoL during treatment. Valerian (*Valeriana officinalis*, Caprifoliaceae) root was studied in a phase III randomized, placebo-controlled trial of 227 patients undergoing



Valerian *Valeriana officinalis*
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cancer treatment who had difficulty sleeping.[18] More than 66% of participants had breast cancer and were receiving chemotherapy. The subjects were randomly assigned to receive 450 mg valerian root standardized to 0.8% valerenic acid or placebo one hour before bedtime each day for eight weeks. The Pittsburgh Sleep Quality Index (PSQI) and other sleep-quality questionnaires were used to evaluate response. While there was no significant improvement in overall sleep quality in the valerian group, the investigators reported improvements in several secondary outcomes including fatigue, sleep latency, amount of sleep per night, and drowsiness. However, these findings also lacked statistical validity. There were no serious toxicities reported. It should be noted that most studies of valerian root for insomnia use 450-900 mg of an ethanolic extract of valerian with an herb-extract ratio of 4-7:1. The use of 450 mg crude valerian root powder in this study is on the low end of typical doses.

Although there are several preclinical studies that demonstrate valerian's effect on various cytochrome P450 enzymes, clinical studies have failed to find any relevant interactions with anticancer drugs.[19] There seems to be no evidence that valerian raises serum estrogen levels or has significant stimulatory effects on the estrogen receptor.

Ginger

Clinical studies have yielded varying results for the antiemetic effect of ginger (*Zingiber officinale*, Zingiberaceae) on chemotherapy-induced nausea.[20] One positive trial was a double-blind, multisite prospective clinical study that included 744 participants with various types of cancer (74% breast cancer) receiving chemotherapy.[21] The subjects were assigned to either placebo or to one of three different daily doses of ginger: 0.5 g, 1 g, or 1.5 g. All subjects took the treatment for six days beginning three days prior to the start of each chemotherapy treatment. All patients also received an antiemetic (5-HT_3 receptor antagonist) and dexamethasone (a steroid) with each chemotherapy cycle. While all doses of ginger reduced nausea compared to placebo on the first day of chemotherapy (P = 0.003 overall), the two smallest doses (0.5 g and 1 g) reduced nausea the most (P = 0.017 and P = 0.036, respectively).

Ginger is purported to have antithrombotic actions at high doses, although in a systematic review, the majority of studies did not find an inhibitory effect on platelet aggregation at the 3.6-5 g dosage range.[20] Caution may be warranted with the concurrent use of ginger and chemotherapeutics metabolized by cytochrome P2C9 or cytochrome P3A4, as ginger has been shown to inhibit these enzymes in vitro.[22] The rapid half-life of key compounds in ginger may, however, mitigate the risk of herb-drug interactions.

Botanicals during Endocrine Therapy

Black Cohosh

Hot flashes are a common symptom in women taking endocrine therapies (tamoxifen citrate, anas-

Ginger *Zingiber officinale*
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trozole, exemestane, letrozole, and fulvestrant). Since the aim of endocrine therapy is to lower estrogen levels, the use of estrogenic substances is ill-advised. Numerous studies have evaluated the effects of black cohosh (*Actaea racemosa*, Ranunculaceae) for menopausal hot flashes, making it an herb of interest for patients and clinicians. Black cohosh does not contain phytoestrogens and does not stimulate the estrogen receptor.[23] In fact, some research suggests that black cohosh may inhibit the proliferation of estrogen receptor-positive (and estrogen receptor-negative) breast cancer cells.[24] Though clinical trials on black cohosh for hot flashes are mixed, the plant might be helpful for some women. The effect on hot flashes appears to be due to the impact of various plant components acting on the central endogenous opioid system[25] and the hypothalamus with dopaminergic, noradrenergic, serotoninergic, and GABAergic effects.[26]

In a study of 136 women taking tamoxifen (20 mg daily), a majority of the 90 patients who also took a black cohosh extract (Klimadynon, now sold as Monopret; Bionorica AG; Neumarkt, Germany; a 10:1 58% ethanol extract yielding 2.8 mg proprietary extractant) had reduced hot flashes after the intervention.[27] Specifically, after 12 months of 20 mg Klimadynon daily, 50% were free of hot flashes compared to only 26% in the tamoxifen-only group. In addition, only 25% of the women who took black cohosh extract experienced severe hot flashes. No serious adverse events were reported. The study was limited by the fact that it was open-label, there was no placebo arm, and there were twice as many women in the tamoxifen-plus-black cohosh extract group than in the tamoxifen-only group.

In addition to its potential benefit in reducing hot flashes, black cohosh may be associated with reduced risk of breast cancer recurrence. In an observational retrospective cohort study of 1,102 women previously diagnosed with breast cancer and taking tamoxifen, the use of black cohosh was associated with a 17% reduced risk of recurrence.[28] Another retrospective study of 949 patients with breast cancer and 1,524 controls found that the use of black cohosh was associated with a 53% reduced risk of recurrent breast cancer.[29]

Black cohosh has no known clinically relevant effects on cytochrome P450 enzymes,[30] or any known hepatotoxic effects. However, there have been some reported cases of hepatotoxicity associated with black cohosh dietary supplement products. A United States Pharmacopeia review in 2010 recommended a caution label on black cohosh products, but a subsequent examination of these cases suggested that the hepatotoxicity might be the result of quality problems, likely adulteration with other *Cimicifuga* species, and that black cohosh itself does not appear to pose a risk of hepatoxicity.[31,32] A 2018 study found that, when tested, only seven of 36 (19%) commercial black cohosh products contained true *Actaea racemosa*; the other 29 products indicated adulteration.[33] Clinicians should be aware of the quality issues surrounding black cohosh in the marketplace and counsel women appropriately.

Black cohosh *Actaea racemosa*
Photo ©2019 Steven Foster

Botanicals during Radiation Therapy

Calendula

One of the most common adverse effects associated with radiation therapy for breast cancer is radiation dermatitis. Radiation dermatitis is painful and, when severe, can interrupt radiotherapy. In a phase III non-blinded, randomized study of 254 patients with breast cancer receiving postoperative radiation therapy, application of topical calendula (*Calendula officinalis*, Asteraceae) ointment (Pommade au Calendula par Digestion; Boiron Ltd.; Messimy, France) to radiation-exposed skin resulted in 22% lower incidence of grade 2 or higher dermatitis compared to treatment with trolamine cream.[34] The subjects applied the ointments twice daily at least two hours before each radiation treatment.

However, in a larger randomized, double-blinded phase III study that compared the use of topical calendula (Calendula Weleda cream, 10% calendula; Weleda; Arlesheim, Switzerland) to an aqueous cream in 411 women with breast cancer undergoing radiation, no differences between the groups in patient-reported symptoms (pain, burning, itching, pulling, tenderness) were noted at any of the evaluation points. The incidence of severe acute radiation skin reactions of grade 2 or lower at the follow-up visit was 23% in the calendula group and 19% in the aqueous cream (placebo) group.[35] The cream was applied twice daily, and subjects were advised not to apply the cream within two hours of each radiation treatment.

Green Tea

Green tea (*Camellia sinensis*, Theaceae) preparations sometimes are used topically to minimize radiation dermatitis. Epigallocatechin gallate (EGCG), a key catechin in green tea, scavenges superoxide anions, hydroxyl radicals, and hydrogen peroxide, and can bind free radicals, protecting DNA from radiation-induced damage. This benefit was demonstrated in a single arm, prospective phase II clinical trial of 49 patients with breast cancer who received radiation therapy over four weeks.[36] All patients receiving radiation therapy began treatment when they developed grade 1 dermatitis. Treatment consisted of a solution of 660 mmol of 95% EGCG per liter saline sprayed onto the exposed skin three times daily. In this group of patients, the maximum grade of dermatitis over a mean duration of treatment of four weeks was mild (grade 1) in 71%, moderate (grade 2) in 29%, and no patients experienced more severe (grades 3-4) dermatitis. EGCG also improved dermatitis and improved pain in 85.7% of patients, burning in 89.8%, itching in 87.8%, and skin pulling in 71.4%. While this was an open study without a placebo arm, the results suggest that topical EGCG may limit the severity and symptoms of radiation dermatitis. The solution used

Calendula *Calendula officinalis*
Photo ©2019 Steven Foster

Green tea *Camellia sinensis*
Photo ©2019 Steven Foster

in this study can be approximated by mixing sufficient green tea standardized extract powder to obtain 350 mg EGCG with 1 liter of saline solution. The solution can then be sprayed onto skin with a nasal or throat mister.

Turmeric and Curcuminoids

Curcuminoids, the pigmented compounds found in turmeric rhizome, also have been studied for radiation dermatitis. In a randomized, double-blind, placebo-controlled trial of 30 patients with breast cancer receiving radiation therapy over four to seven weeks, 2 g turmeric containing 95% curcuminoids (Curcumin C3 Complex; Sabinsa; East Windsor, NJ) taken orally three times daily reduced the severity of radiation dermatitis at the end of treatment compared to placebo (radiation dermatitis scores of 2.6 vs. 3.4; $P = 0.008$).[37] Significantly, only 28.6% of the curcuminoid-treated patients developed moist desquamation (skin thinning and oozing as a result of radiation-induced damage to the epithelium) compared to 87.5% of the placebo-treated patients.

In addition to the potential protective effect of curcumin on the skin, there is in vitro evidence of a radiosensitizing effect from curcumin on breast cancer cells.[38] In spite of these positive results, a multisite double-blind, placebo-controlled trial of 686 patients with breast cancer failed to find benefit in the prevention of radiation dermatitis with 2 g of the previously mentioned turmeric product when taken orally three times daily over placebo throughout the course of radiation treatment plus one week after treatment.[39]

Mushrooms

Not a class of botanicals, mushrooms are in the kingdom Fungi. A proprietary processed liquid fermentation of the turkey tail mushroom (*Coriolus versicolor* or *Trametes versicolor*, Polyporaceae) known as Polysaccharide Krestin (PSK) has been shown in an adjuvant randomized trial of 914 women to increase disease-free survival in patients with node-negative, ER-negative, and stage IIA T2N1 breast cancer. The dose used in the study was 3 g per day.[40] Similar effects were observed in a randomized trial of 227 patients with operable breast cancer with vascular invasion of the tumor and/or of metastatic lymph nodes. The survival curve was improved in the group who took a daily dose of 3 g PSK concurrent with chemotherapy (5-FU, cyclophosphamide, mitomycin C, and prednisolone [FEMP]) compared to chemotherapy alone ($P = 0.0739$).[41]

The survival impact from the addition of *T. versicolor* to conventional treatment was assessed in a 2012 meta-analysis of 13 clinical trials with 2,587 subjects being treated for various solid tumors. Subjects with breast, gastric, or colorectal cancer who took *T. versicolor* extracts (PSK, PSP [Chinese product equivalent of PSK], and mycelium extracts were all included) typically dosed at 3 g daily had a 9% absolute five-year overall survival benefit, resulting in one additional patient alive after five years for every 11 patients treated with the mushroom.[42] There are no known herb-drug interactions with turkey tail mushroom.

Conclusion

Conventional breast cancer treatments offer women the most desirable disease outcomes, including, for many, remission. However, the treatments can be difficult to tolerate due to the many accompanying side effects. A broader integrative approach may optimize treatment tolerance and, therefore, success. Women are pursuing adjunctive therapies, including botanicals, while clinicians are faced with trying to provide evidence-informed counsel on their use. While the body of evidence supporting the inclusion of botanicals in integrative breast cancer care continues to expand, studies that evaluate the efficacy and impact of botanicals on the main outcome of conventional treatment are limited. Additionally, the content and quality of botanical supplements may vary, confounding conclusions from clinical trials. This state of evidence has led the Society for Integrative Oncology, in its 2018 guidelines on the use of integrative therapies during and after breast cancer treatment, to conclude that there is no strong evidence to support the use of ingested dietary supplements (including herbs) in the management of treatment-related toxicities.[43] Therefore, patients with cancer should only use these botanicals with the guidance of health care professionals. Future clinical efficacy studies may generate greater clarity on the specific indications for botanicals in the integrative treatment of breast cancer. HG

Turkey tail mushroom *Trametes versicolor*
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Lise Alschuler, ND, FABNO, *is the executive director of TAP Integrative, a nonprofit web-based educational resource for integrative medicine practitioners. Alschuler also is a professor of clinical medicine at the University of Arizona School of Medicine, where she is on the faculty of the Arizona Center for Integrative Medicine. She practices naturopathic oncology out of Naturopathic Specialists, LLC. In addition, Alschuler co-hosts a radio show, "Five To Thrive Live!" and is a co-founder of the iTHRIVE Plan, a lifestyle app for cancer survivors. She is a co-author of* Definitive Guide to Cancer *(Celestial Arts, 2010), now in its third edition, and* Definitive Guide to Thriving After Cancer *(Ten Speed Press, 2013). Alschuler is a member of the American Botanical Council Advisory Board.*

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