HHS Public Access

Author manuscript

Cancer J. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

Cancer J. 2019 ; 25(5): 357–366. doi:10.1097/PPO.0000000000000403.

Practical Application of *"ABOUT HERBS"* website: Herbs and Dietary Supplement Use in Oncology Settings

Hou Yen-Nien, PharmD, DiplOM, Lac, **Gary Deng, MD, PhD**, **Jun J Mao, MD, MCSE**

Integrative Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

The Integrative Medicine Service at Memorial Sloan Kettering Cancer Center developed and maintains *About Herbs* (www.aboutherbs.com), which provides summaries of research data including purported uses, adverse effects, and herb-drug interactions for about 284 dietary supplements. Using Google Analytics, we found the website registered over 26,317,000 hits since November 2002. The 10 most searched-for herbs/supplements of 2018 are chaga mushroom, turmeric, ashwagandha, reishi mushroom, graviola, AHCC, boswellia, dandelion, green tea, and *Coriolus versicolor*. Here we discuss their safety, herb-drug interactions, and appropriate uses in the oncology setting, based on literature searches in PubMed. Over the past 16 years, the evidence for use of these supplements is based mostly on preclinical findings, with few well-designed studies and limited trials conducted in cancer patients. It is important to familiarize healthcare professionals about popular supplements, so patients can be informed to make decisions that maximize benefits and minimize risks.

Keywords

About Herbs; dietary supplements; herb-drug interactions; chaga mushroom; turmeric; ashwagandha; reishi mushroom; graviola; AHCC; boswellia; dandelion; green tea; *Coriolus versicolor*

INTRODUCTION

Surveys show that 50% of American adults take dietary supplements.[1,2] One-third of all cancer survivors reportedly use complementary medicine or herbal products.[3-5] The reasons cited for such use include symptom relief, preventing cancer recurrence, and improving quality of life. Public perception that dietary supplements are natural and safe has remained unchanged over the last few decades. A major concern with dietary supplement use is the potential for herb-drug interactions (HDIs) that may lead to serious adverse drug events, extended hospitalization, and even death.[6] Such interactions may also alter the efficacy of cancer treatments[7-9] including chemotherapeutic agents and targeted therapies, such as

Correspondence Yen-Nien (Jason) Hou, PharmD, DiplOM, LAc, Manager, *About Herbs* Website, Integrative Medicine Service, Bendheim Center for Integrative Medicine, Memorial Sloan Kettering Cancer Center, 1429 First Avenue, New York, NY, 10021, Tel: 646-888-0822, Fax: 212-717-8534, houy@mskcc.org.

Conflicts of Interest

The authors have no conflicts of interest to report.

tyrosine-kinase inhibitors. Additional interactions include anticancer hormonal therapies with phytoestrogenic supplements[10] or supplements that increase serum testosterone.

Also concerning is the lack of reliable information about dietary supplements. In a large survey, 40–45% of respondents reported the internet and news media as their primary sources.[11] However, when compared to rigorous scientific data, web-based information can often be inaccurate or misleading.[12-14] The knowledge gap about dietary supplements among American physicians does not prepare them for clinical encounters when patients approach them for information,[15,16] whether it be the appropriateness of supplement use or advice about a better alternative for symptom management.

We have attempted to develop an evidence-based practical approach for safe use of herbs and dietary supplements in oncology settings. The Memorial Sloan Kettering Cancer Center's *About Herbs* website is a database which provides reliable and objective information about 284 dietary supplements that include herbs, vitamins, and minerals commonly used by cancer patients. We identified the top 10 monographs that were frequently accessed in 2018 (Table 1). Based on available preclinical and clinical data from literature searches on PubMed, we assessed the safety of the above supplements along with the potential for their interactions with common treatments including chemotherapy, radiation, and immunotherapies, as well as targeted and hormonal therapies.

Preclinical and clinical data needs to be evaluated differently if we want to use the data to guide clinical practice. For example, orally ingested curcumin, one of the most popular searched-for supplements, has poor bioavailability. Oral ingestion of 1 g of curcumin usually leads to serum levels of conjugated curcumin at around C_{max} of 0.2 μM and around 1 μM in rectal mucosa.[17] Many in vitro studies used curcumin at 10 μM, a concentration too high to be realistically achieved by oral ingestion, and thus irrelevant in clinical settings. Proper advice to patients needs to be guided by data from clinical studies. Unfortunately, clinical data is often not available. In those cases, we may have to make a clinical judgement based on the totality of preclinical data, the mechanisms of action and pharmacokinetics of a specific supplement, and patients' values and preferences.

We hope the information presented here will be useful to oncologists and cancer patients, and facilitate physician-patient communication on this important topic.

Chaga mushroom (*Inonotus obliquus*)

Chaga is the Russian name given to a sclerotium or mass of mycelium of the fungus *I. obliquus*. As a parasite on birch or other trees, it typically grows in subarctic regions around the world. Chaga has traditionally been used in Russia since the 12th century for various maladies.[18] In vitro studies have demonstrated that chaga exhibits antiplatelet[19] and antidiabetic[20] properties. In animal studies, chaga has also displayed anti-inflammatory[21] as well as antidiabetic[22] effects. Anti-inflammatory effects in colitis models were related to suppression of tumor necrosis factor-alpha (TNF-α), iNOS, and interleukin (IL)-1beta.[21]

In preclinical cancer studies, chaga extracts have demonstrated inhibitory and proapoptotic effects against colon[23-25] and lung[26] cancer cells, and inhibited melanoma cell growth in

vivo.[27] Inotodiol, a major constituent, exerted antitumor effects against cervical cancer cells.[28] To date, no clinical trials have been conducted to assess chaga's safety and efficacy for disease prevention or for the treatment of cancer, cardiovascular disease, or diabetes.

Chaga mushrooms are high in oxalates and excessive intake may have toxic effects,[29] especially in patient with renal disease. Chaga extract inhibited platelet aggregation in a murine model,[19] and thus may have synergistic effects when used with anticoagulant or antiplatelet drugs in mice. Clinical data is lacking. In vitro, chaga extract has shown alpha-glucosidase inhibitory activity similar to acarbose, a drug for diabetes,[20] suggesting concurrent use should be monitored in patients who are on oral antihyperglycemic agents.

Practical application: This product is popular among patients of Russian or Eastern European heritage. Medicinal mushrooms all showed similar immunomodulatory effects in preclinical studies. However, other mushroom extracts have been better studied and have more clinical data than *I. obliquus.* Physicians should explain to patients the paucity of clinical data on this mushroom extract and caution patients about its potential adverse effects in the setting of chronic kidney disease, diabetic on treatment, and for bleeding or low platelet counts.

Turmeric (*Curcuma longa, Curcuma domestica*)

Turmeric is part of the ginger family. It has long been used as a spice in culinary cultures across Asia and is the most commonly known major ingredient in curry powder. In traditional medicines, turmeric is valued for its anti-inflammatory and antioxidant properties, and is also used to improve circulation and digestion.

Several studies have been conducted on the effects of turmeric for inflammatory diseases. *C. domestica* extract, taken as 500 mg of curcuminoids three times daily x 4 weeks, was found equally as effective as ibuprofen to treat osteoarthritis of the knee in a randomized control trial.[30] Most products on the market are curcumin, a major curcuminoid constituent in *C. longa*. A meta-analysis of randomized controlled trials determined that curcumin significantly reduced serum concentrations of TNF-α, a chief inflammatory mediator.[31]

About 30% of patients taking curcumin in the osteoarthritis trial reported adverse events, similar to those taking ibuprofen. Potential side effects with turmeric supplementation can include gastrointestinal issues such as abdominal pain/distension, dyspepsia, and loose stools.[30] An in vitro study showed inhibitory effects of curcumin on platelet aggregation, although at a concentration that was not clinically relevant.[17,32,33] A study in rats showed similar effects of turmeric oil. [30] However, the main constituent in turmeric oil is turmerone, not curcumin. A clinical study showed a possible increase in urinary oxalate concentrations, leading to increased risk of kidney stone formation.[34]

Curcumin has been evaluated in small clinical trials with cancer patients. In advanced breast cancer patients on docetaxel, the maximum tolerated oral dose of curcumin was identified as 8 g per day.[35] In a phase II trial of oral curcumin in patients with advanced pancreatic cancer, two of 21 evaluable patients had clinically relevant biological activity with no observed treatment-related toxic effects, 8 g of oral curcumin was well tolerated despite poor

absorption,[36] and coadministration with gemcitabine was safe and feasible.[37] Another safety trial is currently evaluating curcumin in patients with inoperable colorectal cancer undergoing a standard FOLFOX regimen.[38] In a pilot study on its potential to alleviate inflammatory side effects of capecitabine treatment, lower rates of hand-foot syndrome were observed with oral curcumin at 4 g daily.[39]

Curcumin has known HDIs with human liver cytochrome P450 enzymes [40-43]and may interfere with chemotherapy drugs such as doxorubicin and cyclophosphamide.[44] It may also interact with drug classes like tyrosine kinase inhibitors, which strongly inhibit CYP3A4.[45] The potential for HDIs specifically with CYP2C9, according to a pre-clinical study showed an inhibitory concentration (IC_{50}) of 4.3 μM,[46] which can be an achievable curcumin serum level. However, a small-scale clinical study did not show a significant decrease in metabolite levels of the CYP3A4 probe drug midazolam, even with piperine-prepared curcuminoids at a 4 g one-time dose.[47]

Practical application: An important traditional Ayurvedic and Chinese medicine, turmeric and its main active constituent curcumin are among the most well-studied dietary supplements. Curcumin has been shown to be generally safe and to possess anti-inflammatory activity, and even possible cancer inhibitory activity in small clinical studies. Although it has poor oral bioavailability, most curcumin products are formulated with either piperine (black pepper extract) or liposomes to improve its bioavailability. Based on currently available data, it is prudent for patients with oxalate kidney stones not to take curcumin. Although there are studies showing interactions between curcumin and CYP3A4, the concentration needed is unlikely to be achieved by oral ingestion.

Ashwagandha (*Withania somnifera*)

Also known as Indian ginseng, ashwagandha is among the most well-known Ayurvedic herbs. In the United States, it is often marketed for stress, strain, and fatigue. Ashwagandha is also used as a general tonic to improve health, energy levels, and longevity.[48]

Preclinical studies suggest immunomodulating, cytotoxic,[49] chemopreventive,[50] and radiosensitizing effects,[51] as well as enhanced chromosomal stability.[52] Withaferin A, a major constituent, enhanced oxaliplatin effects in human pancreatic cancer cells.[53] In a murine study, an aqueous extract of *W. somnifera* reversed paclitaxel-induced neutropenia.[54]

Small-scale human studies suggest that ashwagandha may promote growth in children and improve hemoglobin level and red blood cell count.[48] In adult patients with knee joint pain, use of a standardized ashwagandha extract resulted in chondroprotective, anti-inflammatory, and analgesic effects.[55] In an open-label nonrandomized study of breast cancer patients, adjuvant ashwagandha improved chemotherapy-induced fatigue and improved quality of life.[56] Although results seem positive, larger well-designed clinical trials are needed to confirm these findings.

Ashwagandha is generally safe, and does not interact with CYP3A4 or CYP2D6 enzymes in human liver microsomes.[57] However, ashwagandha may increase testosterone levels, and should be avoided in patients with prostate cancer.[58] Pregnant women should also avoid

ashwagandha as it may induce abortion at higher doses.[59] In addition, patients who take anticonvulsants, barbiturates, and benzodiazepines should avoid ashwagandha due to sedating properties and GABAnergic effects in preclinical models.[59]

Practical application: In Ayurveda, ashwagandha translates to "smell of horse," emitted from the fresh root. The traditional belief is that if taken, one would take on the strength and vitality of a horse. Due to its safety profile, ashwagandha can be a useful supplement in addressing symptoms such as stress and/or fatigue. However, avoid using ashwagandha in prostate cancer patients, as clinical studies have shown it may increase serum testosterone levels in men.

Reishi mushroom (*Ganoderma lucidum*)

Deeply rooted in Asian cultures for its longevity properties,[60] reishi has been used in folk medicine for more than 4000 years. In Japanese, reishi has a literal translation of "spiritual mushroom." It is also known as lingzhi in Chinese. In vitro and in vivo studies indicate that beta glucans and triterpenes, major constituents in reishi, have immunomodulatory[61] and chemopreventive[62] effects.

In healthy subjects, reishi increased plasma antioxidant capacity.[63,64] It also enhanced immune responses in cancer patients[65,66] and appeared to suppress development of colorectal adenomas.[67] In a few cases, remission of hepatocellular carcinoma was observed.[68] However, there are other case reports of elevated CA72–4 serum levels in gastrointestinal cancer patients who used reishi mushroom spore supplements.[69] Therefore, despite popular cultural beliefs there is no evidence from clinical trials for the use of reishi in first-line cancer treatment or to prolong long-term cancer survival. Its popularity for cardiovascular health also did not find support in a systematic review of reishi to address cardiovascular risk factors associated with type 2 diabetes.[70] However, preliminary evidence suggests it may have a role in stimulating host immunity and enhancing tumor response.[71]

Reishi may increase bleeding risk when used in combination with anticoagulants or antiplatelets.[72] Due to its antioxidant capacity, reishi may theoretically interact with chemotherapeutic agents that rely on free radical formation.[63] In vitro, reishi polysaccharides inhibited CYP2E1, CYP1A2, and CYP3A.[73] It could therefore affect intracellular concentrations of drugs metabolized by these enzymes, although clinical relevance is not known.

Practical application: In traditional Chinese medicine, lingzhi is believed to be the "herb of longevity," and is not only used to prevent disease, but also to cultivate one's virtues. Preliminary evidence suggests immunomodulation effects exhibited by reishi occurs via host immunity stimulation and enhanced tumor response. However, there is currently no evidence of prolonged long-term cancer survival with reishi use. Caution should be taken in patients who are also taking anticoagulants, as reishi extracts may increase bleeding risk.

Graviola (*Annona muricata*)

Graviola is a heart-shaped tropical fruit that is grown around the tropical regions of the world. It has many names: graviola in Brazil, guanábana in Spanish-speaking countries, fengli shijia in Taiwan, and soursop in the United States. The fruit, seeds, leaves, stems, and roots are used in traditional medicine for symptoms associated with infection and inflammation. In some Caribbean countries, it is part of their cultural belief that using graviola as an herbal remedy is helpful to treat cancer, especially prostate, breast, and colorectal cancers.[74]

Purported health benefits from graviola have been attributed to antioxidant properties.[75] Annonaceous acetogenins are among the active phytochemicals extracted from the fruit, leaves, bark, and twigs. [76] In animal models, graviola extracts have exhibited analgesic,[77] anti-inflammatory,[78] and antiulcer[79] effects. In other preclinical studies, graviola extracts appear to be active against various cancers, including those of the breast,[80] lung,[81] colon,[82] and pancreas.[83] However, clinical research on graviola products in cancer patients is lacking, with safety and efficacy as yet undetermined.

Potential HDIs with graviola are suggested in murine models, demonstrating additive effects with antidiabetic drugs leading to hypoglycemic effects,[84] or hypotensive episodes when taken with antihypertensive medications.[85] The clinical relevance of these interactions has yet to be determined.

Practical application: Graviola has many names in tropical regions around the world, and its consumption is driven by strong cultural influence. Therefore, it is paramount for physicians to understand patient backgrounds and expectations. Many cultures revere graviola as a cure-all, even for cancer. Although preclinical data has shown graviola extract has anticancer properties, most data were not subjected to clinical trials. Therefore, purported safety and efficacy as a cancer treatment cannot be inferred.

Active hexose correlated compound (AHCC)

AHCC is a nutritional supplement that is derived from shiitake mushroom (*Lentinula edodes*) mycelia. It shares a number of constituents that may overlap with other mushrooms, such as beta glucans.[86] However, it is also rich in oligosaccharides, particularly those that contain alpha-1,4-glucans, to which enhanced biologic activities are attributed.[87]

Animal studies suggest AHCC has antioxidant properties and may protect against disorders induced by oxidative stress.[88] It also has anti-inflammatory effects against colitis,[89] and may improve resistance to bacterial[90] and viral infection.[91] Data from preclinical cancer studies suggest AHCC may improve the therapeutic effects of various chemotherapies.[92-94] In mice treated with cisplatin, AHCC also reduced chemotherapy-induced side effects.[95]

In healthy humans, AHCC improved response to influenza vaccine,[96] and increased T-cell immune response[97] and dendritic cell number and function.[98] A few studies of AHCC have also been conducted in the oncology setting. Among patients who received curative resection for hepatocellular carcinoma, those who took AHCC postoperatively experienced

improved prognosis.[99] In smaller studies of patients with advanced cancers, AHCC reduced adverse effects from chemotherapy.[86,100]

Despite some studies on the adjuvant use of AHCC with chemotherapy, HDIs may occur with certain medications. AHCC is an inducer of CYP2D6, which may decrease the activity of doxorubicin or ondansetron.[101] In murine models, AHCC did not change activity of tamoxifen, a prodrug activated by CYP2D6; but it did interact with letrozole in breast cancer mouse models with COMT variant genotype.[102] In addition, AHCC may render aromatase inhibitors less effective by inducing the aromatase enzyme,[102] although clinical relevance has not been determined.

Practical application: Active hexose correlated compound (AHCC) is a supplement extracted from shiitake mushroom, with high amounts of α−1,4-glucan oligosaccharides. AHCC is generally safe and exhibits immunomodulating effects by increasing T cell and dendritic cell number and function. AHCC can help alleviate chemotherapy-associated adverse effects in patients with advanced cancers such as those with unresectable pancreatic ductal adenocarcinoma on gemcitabine. However, caution is warranted in breast cancer patients who are placed on doxorubicin, ondansetron, and/or aromatase inhibitors such as letrozole.

Boswellia (*Boswellia serrata*)

Boswellia is commonly referred to as Indian frankincense, and well known in Ayurvedic medicine for treating inflammatory diseases such as arthritis, ulcerative colitis, and sores. Not to be confused with guggul or myrrh, the resin or olibanum is produced by removing the bark of *B. serrata*, a tree that is prevalent in North Africa, the Middle East, and India. In the United States, the supplement is often marketed for joint health and mobility.

The major constituent of boswellia is boswellic acid.[103] It inhibits the enzyme 5-lipoxygenase, which is involved in the production of inflammatory leukotrienes, with dose-dependent anti-inflammatory and anti-arthritic effects.[103,104] In preclinical studies conducted in glioma cell lines, boswellia exhibited cytotoxicity[105-107] and radio-enhancing properties.[108]

A few studies have also been conducted in humans. In osteoarthritis of the knee, one trial suggested benefit from supplementation with an enriched boswellic acid extract.[109] In another double-blind pilot, patients who received a *B. serrata* supplement following radiation therapy had significantly reduced MRI-measured cerebral edema.[110] As for prevention of skin damage caused by radiation therapy in breast cancer patients, application of a boswellia-based cream was found to be effective while reducing topical corticosteroid use.[111]

Although generally well tolerated,[112] contact dermatitis was reported following the topical application of a cream containing *B. serrata* extract.[113] An alcohol extract of boswellia may increase risk of bleeding by inhibiting platelet aggregation, but the same effect was not seen in a water extract.[114]

Practical application: Ru Xiang (*B. carterii*) in traditional Chinese medicine is similar to Śallakī (*B. serrata*) in Ayurveda, with the same active ingredient. In TCM, it is commonly used to alleviate pain and invigorate "Qi" or energy. Boswellia is generally safe and frequently marketed for bone and joint health. Besides a few cases of contact dermatitis, boswellia appears to be well tolerated. Even though there is a clinical study showing significant reduction in cerebral edema in patients who received the supplement following radiation therapy for brain tumors, larger trials are needed to confirm this finding.

Dandelion (*Taraxacum mongolicum, Taraxacum officinale*)

Known as pu gong ying in traditional Chinese medicine, dandelion has been used to reduce abscesses, especially in the breast and intestines.[115] It is also used to promote lactation. The flower, leaf, and root of this plant are used for their diuretic, blood glucose-lowering, and appetite-stimulating properties.[116,117]

In preclinical studies, dandelion root extract has exhibited anticancer effects in various cancer types, including melanoma,[118] pancreatic,[119] and colorectal[120] cancer cell lines. A dandelion root extract was also found to selectively induce apoptosis in aggressive and resistant chronic myelomonocytic leukemia (CMML) cells.[121] There are also a few case reports of stable or improved hematological parameters in patients with CMML that have been related in part to dandelion root extract.[122] However, clinical trials have not been conducted.

In vitro and animal models suggest that dandelion has estrogenic activity, as evidenced by increased proliferation of MCF-7 cells, and an increase in uterine weight in immature female rats.[123] Other preclinical models suggest that dandelion may inhibit CYP1A2[124] and CYP3A4[125] activities, which may alter blood levels of substrate drugs. Due to its diuretic and blood glucose-lowering properties,[116,117] dandelion may induce additive effects when patients are already on diuretics and hypoglycemic agents.

Practical application: Dandelion is part of traditional medicinal systems in Native America, China, and the Middle East, with broad uses as a general tonic and diuretic to the treatment of specific ailments such as gastrointestinal and skin issues. The whole plant can be used and is an excellent source of vitamin A. Preclinical data suggest that dandelion root extract may be helpful in aggressive and resistant CMML. Although generally considered safe, it should be avoided in hormone-sensitive breast cancer patients.

Green tea (*Camellia sinensis*)

Green tea is the unfermented preparation of *C. sinensis* leaves, as opposed to black tea, which is processed or fermented. Green tea is widely consumed as a steeped hot beverage around the world, especially in China and Japan. Active constituents include the polyphenol epigallocatechin-3-gallate (EGCG), caffeine, and theanine. Green tea extract supplements are marketed to maintain cardiovascular health, for weight management, and as an antioxidant. Patients may also be interested in green tea for cancer prevention.

Several preliminary studies of various green tea extracts have been conducted. Whether green tea extract has cancer-preventive effects in humans is inconclusive. In a randomized

controlled chemopreventive study of 97 men, powered to detect a drop in prostate cancer risk in 1 year from 30% to 9%, EGCG 400 mg daily was not significantly more effective than placebo, but did significantly lower serum prostate-specific antigen (PSA) and was well tolerated.[126] In a phase II trial of green tea extract (2 g twice daily x 6 months) in 42 chronic lymphocytic leukemia (CLL) patients, 31% of patients had ≥20% reduction in absolute lymphocyte count and 69% with palpable adenopathy had ≥50% reduction in the sum of the lymph node products.[127] At this unusually high dose, grade 3 transaminitis, abdominal pain, or fatigue was reported in 2.5% of patients for each adverse reaction.[127] In a randomized placebo-controlled trial, 199 prostate cancer patients who were under primary active surveillance or watchful waiting following previous interventions were given a whole food supplement containing green tea, turmeric, pomegranate, and broccoli for 6 months. Those taking the supplement had significantly slower rates of PSA increase compared with those taking placebo.[128] Additional studies are needed to confirm this short-term benefit.

Although the FDA includes tea on their list of Generally Recognized As Safe (GRAS), high-dose green tea extract can cause liver toxicity[129] and may pose a risk for potential HDIs. In general, 1 cup of green tea contains about 100 mg to 200 mg of EGCG. When taken in a fasting state, it can reach a C_{max} 5–10 times higher than when taken with food.[130] Preclinical studies also show a unique antagonizing effect of EGCG at a dose equivalent to 1 g oral ingestion in humans on boronic acid-based proteasome inhibitors, such as bortezomib.[131] Tamoxifen is a prodrug that gets metabolized into its active metabolites by CYP2D6. EGCG inhibits CYP2D6 at an IC_{50} of 25 ug/mL,[132] while human oral consumption of 20 mg/kg green tea leaves or 2 mg/kg EGCG extract resulted in C_{max} of around 80 ng/mL[133] and around 1 ug/mL at a much higher green tea dose.[134] Therefore, oral EGCG even at 3 g, is unlikely to have significant inhibition on CYP2D6 in human enzymes.

Practical application: Green, black, and oolong teas are all derived from *C. sinensis* leaves. As one of the most well-studied polyphenols, epigallocatechin-3-gallate (EGCG) alone, or in a combination formulation, has been shown in clinical studies to have potential effects against CLL or prostate cancer. However, high doses equivalent to 5–10 cups of green tea taken in a fasting state, is associated with liver toxicity.[129] It should also be avoided in patients who are on bortezomib. It is also advisable to always drink green tea or take EGCG supplements with food.

Turkey tail mushroom (Coriolus versicolor, Trametes versicolor)

Frequently referred to as yunzhi, Chinese for “cloud mushroom,” *Coriolus or Trametes versicolor* is used in traditional Chinese medicine as a tonic. Polysaccharide peptides (PSP) and polysaccharide-K (PSK) isolated from Coriolus are the most studied preparations, with the latter being approved for clinical use in Japan. They are also available as dietary supplements.

Studies in the oncology setting suggest benefit with adjuvant PSK to improve survival rates in patients with gastric[135,136] and colorectal[137-139] cancers. It may also benefit patients with esophageal cancer.[140] A clinical study of PSP used in conjunction with chemotherapy also suggests patients with advanced non-small cell lung cancer may benefit.[141] In addition,

clinical studies using Coriolus extract alone or in combination with other botanicals suggest positive immunomodulatory effects.[142,143] However, studies in breast cancer,[144] hepatocellular carcinoma,[145,146] and leukemia[147] have produced mixed results.

Coriolus extracts are generally well tolerated and safety data are well established from PSK use in Japan since the mid-1970s, although minor adverse effects, such as gastrointestinal upset, have been reported.[137,148] Because of its immunomodulatory activities, it may interact with immunosuppressants, at least in theory. Many over-the-counter Coriolus products contain only mycelium, not the extracts used in the clinical studies. It is unclear whether they have the same activities as reported in the above studies.

Practical application: Commonly known as turkey tail mushroom, Coriolus has a long history of medicinal use in China and Native America. Based on available clinical data and chemical structure of the constituents, Coriolus polysaccharide extracts are generally safe and have a low risk for HDIs. Among all the medicinal mushrooms, Coriolus extract appears to be the one supported by the most clinical data for patients with esophageal, gastric, and colon cancer. It is generally well tolerated but is best avoided in patients who are on immunosuppressants.

SUMMARY

Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, dietary supplements are regulated by the FDA. Unlike prescription drugs however, they are not subject to scientific rigor before they become available to the consumer. The FDA does not mandate quality or batch-to-batch consistency of the aforementioned dietary supplements in this review paper. It is up to the consumer to carefully choose the products, or rely on third-party independent testing laboratory, such as Consumer Labs or the United States Pharmacopeial Convention Dietary Supplement Verification Program, to help verify the quality and consistency of these products.

To be truly patient-centered, physicians should be aware of the popular dietary supplements that patients care about and be able to engage in conversations with an open mind. By having a blanket statement discouraging use of herbal supplements, physicians may miss opportunities to be mindful of patients' concerns. Most patients may heed physician advice about stopping dietary supplement use, but some may choose to continue taking them without the physician's knowledge leading to problems including HDIs or suspending conventional cancer treatments.

By providing the latest scientific research, summarized at aboutherbs.com, we hope to equip oncologists with tools that foster better physician-patient relationships. Physicians can then help patients make informed decisions about using herbal and dietary supplements in oncology settings.

Acknowledgments

The authors thank Ingrid Haviland and Jyothirmai Gubili at the MSK Integrative Medicine Service for their editorial assistance and Angela Donato for her artwork created for *About Herbs*.

Funding

This work was supported by funding from the NIH/NCI Cancer Center Support Grant P30 CA008748 and the Laurance S. Rockefeller Fund at Memorial Sloan-Kettering Cancer Center.

REFERENCES

1. Wu CH, Wang CC, Tsai MT, Huang WT, Kennedy J. Trend and pattern of herb and supplement use in the United States: results from the 2002, 2007, and 2012 national health interview surveys. Evid Based Complement Alternat Med 2014;2014:872320. [PubMed: 25574184]
2. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: national health interview survey, 2012. Vital Health Stat 10 2014:1–161. [PubMed: 24819891]
3. Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. J Clin Oncol 2008;26:665–673. [PubMed: 18235127]
4. Giovannucci E, Chan AT. Role of vitamin and mineral supplementation and aspirin use in cancer survivors. J Clin Oncol 2010;28:4081–4085. [PubMed: 20697066]
5. Anderson JG, Taylor AG. Use of complementary therapies for cancer symptom management: results of the 2007 National Health Interview Survey. J Altern Complement Med 2012;18:235–241. [PubMed: 22420737]
6. Ekor M The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol 2014;4:177. [PubMed: 24454289]
7. D'Andrea GM. Use of antioxidants during chemotherapy and radiotherapy should be avoided. CA Cancer J Clin 2005;55:319–321. [PubMed: 16166076]
8. Sparreboom A, Cox MC, Acharya MR, Figg WD. Herbal remedies in the United States: potential adverse interactions with anticancer agents. J Clin Oncol 2004;22:2489–2503. [PubMed: 15197212]
9. Meijerman I, Beijnen JH, Schellens JH. Herb-drug interactions in oncology: focus on mechanisms of induction. Oncologist 2006;11:742–752. [PubMed: 16880233]
10. Posadzki P, Watson L, Ernst E. Herb-drug interactions: an overview of systematic reviews. Br J Clin Pharmacol 2013;75:603–618. [PubMed: 22670731]
11. Rozga MR, Stern JS, Stanhope K, Havel PJ, Kazaks AG. Dietary supplement users vary in attitudes and sources of dietary supplement information in East and West geographic regions: a cross-sectional study. BMC Complement Altern Med 2013;13:200. [PubMed: 23899171]
12. Alnemer KA, Alhuzaim WM, Alnemer AA, et al. Are Health-Related Tweets Evidence Based? Review and Analysis of Health-Related Tweets on Twitter. J Med Internet Res 2015;17:e246. [PubMed: 26515535]
13. Goldacre B Preventing bad reporting on health research. BMJ 2014;349:g7465. [PubMed: 25498123]
14. Cooper BE, Lee WE, Goldacre BM, Sanders TA. The quality of the evidence for dietary advice given in UK national newspapers. Public Underst Sci 2012;21:664–673. [PubMed: 23832153]
15. Frenkel M, Ben-Arye E, Baldwin CD, Sierpina V. Approach to communicating with patients about the use of nutritional supplements in cancer care. South Med J 2005;98:289–294. [PubMed: 15813155]
16. Tarn DM, Paterniti DA, Good JS, et al. Physician-patient communication about dietary supplements. Patient Educ Couns 2013;91:287–294. [PubMed: 23466249]
17. Asher GN, Xie Y, Moaddel R, et al. Randomized Pharmacokinetic Crossover Study Comparing 2 Curcumin Preparations in Plasma and Rectal Tissue of Healthy Human Volunteers. J Clin Pharmacol 2017;57:185–193. [PubMed: 27503249]
18. Shikov AN, Pozharitskaya ON, Makarov VG, Wagner H, Verpoorte R, Heinrich M. Medicinal plants of the Russian Pharmacopoeia; their history and applications. J Ethnopharmacol 2014;154:481–536. [PubMed: 24742754]
19. Hyun KW, Jeong SC, Lee DH, Park JS, Lee JS. Isolation and characterization of a novel platelet aggregation inhibitory peptide from the medicinal mushroom, Inonotus obliquus. Peptides 2006;27:1173–1178. [PubMed: 16289471]

20. Ying YM, Zhang LY, Zhang X, et al. Terpenoids with alpha-glucosidase inhibitory activity from the submerged culture of Inonotus obliquus. Phytochemistry 2014;108:171–176. [PubMed: 25446238]
21. Mishra SK, Kang JH, Kim DK, Oh SH, Kim MK. Orally administered aqueous extract of Inonotus obliquus ameliorates acute inflammation in dextran sulfate sodium (DSS)-induced colitis in mice. J Ethnopharmacol 2012;143:524–532. [PubMed: 22819687]
22. Wang J, Hu W, Li L, et al. Antidiabetic activities of polysaccharides separated from Inonotus obliquus via the modulation of oxidative stress in mice with streptozotocin-induced diabetes. PLoS One 2017;12:e0180476. [PubMed: 28662169]
23. Lee SH, Hwang HS, Yun JW. Antitumor activity of water extract of a mushroom, Inonotus obliquus, against HT-29 human colon cancer cells. Phytother Res 2009;23:1784–1789. [PubMed: 19367670]
24. Kang JH, Jang JE, Mishra SK, et al. Ergosterol peroxide from Chaga mushroom (Inonotus obliquus) exhibits anti-cancer activity by down-regulation of the beta-catenin pathway in colorectal cancer. J Ethnopharmacol 2015;173:303–312. [PubMed: 26210065]
25. Lee HS, Kim EJ, Kim SH. Ethanol extract of Innotus obliquus (Chaga mushroom) induces G1 cell cycle arrest in HT-29 human colon cancer cells. Nutr Res Pract 2015;9:111–116. [PubMed: 25861415]
26. Baek J, Roh HS, Baek KH, et al. Bioactivity-based analysis and chemical characterization of cytotoxic constituents from Chaga mushroom (Inonotus obliquus) that induce apoptosis in human lung adenocarcinoma cells. J Ethnopharmacol 2018;224:63–75. [PubMed: 29800742]
27. Youn MJ, Kim JK, Park SY, et al. Potential anticancer properties of the water extract of Inonotus [corrected] obliquus by induction of apoptosis in melanoma B16-F10 cells. J Ethnopharmacol 2009;121:221–228. [PubMed: 19041933]
28. Zhao LW, Zhong XH, Yang SY, Zhang YZ, Yang NJ. Inotodiol inhabits proliferation and induces apoptosis through modulating expression of cyclinE, p27, bcl-2, and bax in human cervical cancer HeLa cells. Asian Pac J Cancer Prev 2014;15:3195–3199. [PubMed: 24815470]
29. Kikuchi Y, Seta K, Ogawa Y, et al. Chaga mushroom-induced oxalate nephropathy. Clin Nephrol 2014;81:440–444. [PubMed: 23149251]
30. Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, et al. Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. Clin Interv Aging 2014;9:451–458. [PubMed: 24672232]
31. Sahebkar A, Cicero AFG, Simental-Mendia LE, Aggarwal BB, Gupta SC. Curcumin downregulates human tumor necrosis factor-alpha levels: A systematic review and meta-analysis ofrandomized controlled trials. Pharmacol Res 2016;107:234–242. [PubMed: 27025786]
32. Prakash P, Misra A, Surin WR, et al. Anti-platelet effects of Curcuma oil in experimental models of myocardial ischemia-reperfusion and thrombosis. Thromb Res 2011;127:111–118. [PubMed: 21144557]
33. Jantan I, Raweh SM, Sirat HM, et al. Inhibitory effect of compounds from Zingiberaceae species on human platelet aggregation. Phytomedicine 2008;15:306–309. [PubMed: 17913483]
34. Tang M, Larson-Meyer DE, Liebman M. Effect of cinnamon and turmeric on urinary oxalate excretion, plasma lipids, and plasma glucose in healthy subjects. Am J Clin Nutr 2008;87:1262–1267. [PubMed: 18469248]
35. Bayet-Robert M, Kwiatkowski F, Leheurteur M, et al. Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. Cancer Biol Ther 2010;9:8–14. [PubMed: 19901561]
36. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin Cancer Res 2008;14:4491–4499. [PubMed: 18628464]
37. Kanai M, Yoshimura K, Asada M, et al. A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. Cancer Chemother Pharmacol 2011;68:157–164. [PubMed: 20859741]
38. Irving GR, Iwuji CO, Morgan B, et al. Combining curcumin (C3-complex, Sabinsa) with standard care FOLFOX chemotherapy in patients with inoperable colorectal cancer (CUFOX): study protocol for a randomised control trial. Trials 2015;16:110. [PubMed: 25872567]

39. Scontre VA, Martins JC, de Melo Sette CV, et al. Curcuma longa (Turmeric) for Prevention of Capecitabine-Induced Hand-Foot Syndrome: A Pilot Study. J Diet Suppl 2018;15:606–612. [PubMed: 29095653]
40. Zhang W, Lim LY. Effects of spice constituents on P-glycoprotein-mediated transport and CYP3A4-mediated metabolism in vitro. Drug Metab Dispos 2008;36:1283–1290. [PubMed: 18385293]
41. Chen Y, Liu WH, Chen BL, et al. Plant polyphenol curcumin significantly affects CYP1A2 and CYP2A6 activity in healthy, male Chinese volunteers. Ann Pharmacother 2010;44:1038–1045. [PubMed: 20484172]
42. Zhang W, Tan TM, Lim LY. Impact of curcumin-induced changes in P-glycoprotein and CYP3A expression on the pharmacokinetics of peroral celiprolol and midazolam in rats. Drug Metab Dispos 2007;35:110–115. [PubMed: 17050652]
43. Al-Jenoobi FI, Al-Thukair AA, Alam MA, et al. Effect of Curcuma longa on CYP2D6- and CYP3A4-mediated metabolism of dextromethorphan in human liver microsomes and healthy human subjects. Eur J Drug Metab Pharmacokinet 2015;40:61–66. [PubMed: 24510399]
44. Somasundaram S, Edmund NA, Moore DT, Small GW, Shi YY, Orlowski RZ. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. Cancer Res 2002;62:3868–3875. [PubMed: 12097302]
45. Teo YL, Ho HK, Chan A. Metabolism-related pharmacokinetic drug-drug interactions with tyrosine kinase inhibitors: current understanding, challenges and recommendations. Br J Clin Pharmacol 2015;79:241–253. [PubMed: 25125025]
46. Appiah-Opong R, Commandeur JN, van Vugt-Lussenburg B, Vermeulen NP. Inhibition of human recombinant cytochrome P450s by curcumin and curcumin decomposition products. Toxicology 2007;235:83–91. [PubMed: 17433521]
47. Volak LP, Hanley MJ, Masse G, et al. Effect of a herbal extract containing curcumin and piperine on midazolam, flurbiprofen and paracetamol (acetaminophen) pharmacokinetics in healthy volunteers. Br J Clin Pharmacol 2013;75:450–462. [PubMed: 22725836]
48. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): a review. Altern Med Rev 2000;5:334–346. [PubMed: 10956379]
49. Davis L, Kuttan G. Effect of Withania somnifera on CTL activity. J Exp Clin Cancer Res 2002;21:115–118.
50. Prakash J, Gupta SK, Dinda AK. Withania somnifera root extract prevents DMBA-induced squamous cell carcinoma of skin in Swiss albino mice. Nutr Cancer 2002;42:91–97. [PubMed: 12235655]
51. Devi PU. Withania somnifera Dunal (Ashwagandha): potential plant source of a promising drug for cancer chemotherapy and radiosensitization. Indian J Exp Biol 1996;34:927–932. [PubMed: 9055640]
52. Panjamurthy K, Manoharan S, Menon VP, Nirmal MR, Senthil N. Protective role of withaferin-A on 7,12-dimethylbenz(a)anthracene-induced genotoxicity in bone marrow of Syrian golden hamsters. J Biochem Mol Toxicol 2008;22:251–258. [PubMed: 18752311]
53. Li X, Zhu F, Jiang J, et al. Synergistic antitumor activity of withaferin A combined with oxaliplatin triggers reactive oxygen species-mediated inactivation of the PI3K/AKT pathway in human pancreatic cancer cells. Cancer Lett 2015;357:219–230. [PubMed: 25444914]
54. Gupta YK, Sharma SS, Rai K, Katiyar CK. Reversal of paclitaxel induced neutropenia by Withania somnifera in mice. Indian J Physiol Pharmacol 2001;45:253–257. [PubMed: 11480235]
55. Ramakanth GS, Uday Kumar C, Kishan PV, Usharani P. A randomized, double blind placebo controlled study of efficacy and tolerability of Withaina somnifera extracts in knee joint pain. J Ayurveda Integr Med 2016;7:151–157. [PubMed: 27647541]
56. Biswal BM, Sulaiman SA, Ismail HC, Zakaria H, Musa KI. Effect of Withania somnifera (Ashwagandha) on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. Integr Cancer Ther 2013;12:312–322. [PubMed: 23142798]
57. Savai J, Varghese A, Pandita N, Chintamaneni M. Investigation of CYP3A4 and CYP2D6 Interactions of Withania somnifera and Centella asiatica in Human Liver Microsomes. Phytother Res 2015;29:785–790. [PubMed: 25684704]

58. Lopresti AL, Drummond PD, Smith SJ. A Randomized, Double-Blind, Placebo-Controlled, Crossover Study Examining the Hormonal and Vitality Effects of Ashwagandha (Withania somnifera) in Aging, Overweight Males. Am J Mens Health 2019;13:1557988319835985. [PubMed: 30854916]
59. Shukla SD, Bhatnagar M, Khurana S. Critical evaluation of ayurvedic plants for stimulating intrinsic antioxidant response. Front Neurosci 2012;6:112. [PubMed: 22855669]
60. Guggenheim AG, Wright KM, Zwickey HL. Immune Modulation From Five Major Mushrooms: Application to Integrative Oncology. Integr Med (Encinitas) 2014;13:32–44.
61. Wang C, Shi S, Chen Q, et al. Antitumor and Immunomodulatory Activities of Ganoderma lucidum Polysaccharides in Glioma-Bearing Rats. Integr Cancer Ther 2018;17:674–683. [PubMed: 29607690]
62. Wu K, Na K, Chen D, Wang Y, Pan H, Wang X. Effects of non-steroidal anti-inflammatory drug-activated gene-1 on Ganoderma lucidum polysaccharides-induced apoptosis of human prostate cancer PC-3 cells. Int J Oncol 2018;53:2356–2368. [PubMed: 30272272]
63. Wachtel-Galor S, Szeto YT, Tomlinson B, Benzie IF. Ganoderma lucidum ('Lingzhi'); acute and short-term biomarker response to supplementation. Int J Food Sci Nutr 2004;55:75–83. [PubMed: 14630595]
64. Wachtel-Galor S, Tomlinson B, Benzie IF. Ganoderma lucidum ("Lingzhi"), a Chinese medicinal mushroom: biomarker responses in a controlled human supplementation study. Br J Nutr 2004;91:263–269. [PubMed: 14756912]
65. Gao Y, Zhou S, Jiang W, Huang M, Dai X. Effects of ganopoly (a Ganoderma lucidum polysaccharide extract) on the immune functions in advanced-stage cancer patients. Immunol Invest 2003;32:201–215. [PubMed: 12916709]
66. Sun LX, Li WD, Lin ZB, et al. Protection against lung cancer patient plasma-induced lymphocyte suppression by Ganoderma lucidum polysaccharides. Cell Physiol Biochem 2014;33:289–299. [PubMed: 24525691]
67. Oka S, Tanaka S, Yoshida S, et al. A water-soluble extract from culture medium of Ganoderma lucidum mycelia suppresses the development of colorectal adenomas. Hiroshima J Med Sci 2010;59:1–6. [PubMed: 20518254]
68. Gordan JD, Chay WY, Kelley RK, Ko AH, Choo SP, Venook AP. "And what other medications are you taking?". J Clin Oncol 2011;29:e288–291. [PubMed: 21245436]
69. Yan B, Meng X, Shi J, Qin Z, Wei P, Lao L. Ganoderma lucidum spore induced CA72–4 elevation in gastrointestinal cancer: a five-case report. Integr Cancer Ther 2014;13:161–166. [PubMed: 24282100]
70. Klupp NL, Chang D, Hawke F, et al. Ganoderma lucidum mushroom for the treatment of cardiovascular risk factors. Cochrane Database Syst Rev 2015:Cd007259. [PubMed: 25686270]
71. Jin X, Ruiz Beguerie J, Sze DM, Chan GC. Ganoderma lucidum (Reishi mushroom) for cancer treatment. Cochrane Database Syst Rev 2016;4:Cd007731. [PubMed: 27045603]
72. Tao J, Feng KY. Experimental and clinical studies on inhibitory effect of ganoderma lucidum on platelet aggregation. J Tongji Med Univ 1990;10:240–243. [PubMed: 2098581]
73. Wang X, Zhao X, Li D, Lou YQ, Lin ZB, Zhang GL. Effects of Ganoderma lucidum polysaccharide on CYP2E1, CYP1A2 and CYP3A activities in BCG-immune hepatic injury in rats. Biol Pharm Bull 2007;30:1702–1706. [PubMed: 17827724]
74. Clement YN, Mahase V, Jagroop A, et al. Herbal remedies and functional foods used by cancer patients attending specialty oncology clinics in Trinidad. BMC Complement Altern Med 2016;16:399. [PubMed: 27769229]
75. George VC, Kumar DR, Suresh PK, Kumar RA. Antioxidant, DNA protective efficacy and HPLC analysis of Annona muricata (soursop) extracts. J Food Sci Technol 2015;52:2328–2335. [PubMed: 25829616]
76. Qazi AK, Siddiqui JA, Jahan R, et al. Emerging therapeutic potential of graviola and its constituents in cancers. Carcinogenesis 2018;39:522–533. [PubMed: 29462271]
77. de Sousa OV, Vieira GD, de Jesus RGdPJ, Yamamoto CH, Alves MS. Antinociceptive and anti-inflammatory activities of the ethanol extract of Annona muricata L. leaves in animal models. Int J Mol Sci 2010;11:2067–2078. [PubMed: 20559502]

78. Ishola IO, Awodele O, Olusayero AM, Ochieng CO. Mechanisms of analgesic and anti-inflammatory properties of Annona muricata Linn. (Annonaceae) fruit extract in rodents. J Med Food 2014;17:1375–1382. [PubMed: 25133801]

79. Moghadamtousi SZ, Rouhollahi E, Karimian H, Fadaeinasab M, Abdulla MA, Kadir HA. Gastroprotective activity of Annona muricata leaves against ethanol-induced gastric injury in rats via Hsp70/Bax involvement. Drug Des Devel Ther 2014;8:2099–2110.

80. Dai Y, Hogan S, Schmelz EM, Ju YH, Canning C, Zhou K. Selective growth inhibition of human breast cancer cells by graviola fruit extract in vitro and in vivo involving downregulation of EGFR expression. Nutr Cancer 2011;63:795–801. [PubMed: 21767082]

81. Moghadamtousi SZ, Kadir HA, Paydar M, Rouhollahi E, Karimian H. Annona muricata leaves induced apoptosis in A549 cells through mitochondrial-mediated pathway and involvement of NF-kappaB. BMC Complement Altern Med 2014;14:299. [PubMed: 25127718]

82. Zorofchian Moghadamtousi S, Karimian H, Rouhollahi E, Paydar M, Fadaeinasab M, Abdul Kadir H. Annona muricata leaves induce G(1) cell cycle arrest and apoptosis through mitochondria-mediated pathway in human HCT-116 and HT-29 colon cancer cells. J Ethnopharmacol 2014;156:277–289. [PubMed: 25195082]

83. Torres MP, Rachagani S, Purohit V, et al. Graviola: a novel promising natural-derived drug that inhibits tumorigenicity and metastasis of pancreatic cancer cells in vitro and in vivo through altering cell metabolism. Cancer Lett 2012;323:29–40. [PubMed: 22475682]

84. Adeyemi DO, Komolafe OA, Adewole OS, Obuotor EM, Adenowo TK. Anti hyperglycemic activities of Annona muricata (Linn). Afr J Tradit Complement Altern Med 2008;6:62–69. [PubMed: 20162043]

85. Nwokocha CR, Owu DU, Gordon A, et al. Possible mechanisms of action of the hypotensive effect of Annona muricata (soursop) in normotensive Sprague-Dawley rats. Pharm Biol 2012;50:1436–1441. [PubMed: 22950673]

86. Ito T, Urushima H, Sakaue M, et al. Reduction of adverse effects by a mushroom product, active hexose correlated compound (AHCC) in patients with advanced cancer during chemotherapy--the significance of the levels of HHV-6 DNA in saliva as a surrogate biomarker during chemotherapy. Nutr Cancer 2014;66:377–382. [PubMed: 24611562]

87. Suknikhom W, Lertkhachonsuk R, Manchana T. The Effects of Active Hexose Correlated Compound (AHCC) on Levels of CD4+ and CD8+ in Patients with Epithelial Ovarian Cancer or Peritoneal Cancer Receiving Platinum Based Chemotherapy. Asian Pac J Cancer Prev 2017;18:633–638. [PubMed: 28440968]

88. Ye SF, Ichimura K, Wakame K, Ohe M. Suppressive effects of Active Hexose Correlated Compound on the increased activity of hepatic and renal ornithine decarboxylase induced by oxidative stress. Life Sci 2003;74:593–602. [PubMed: 14623030]

89. Mascaraque C, Suarez MD, Zarzuelo A, Sanchez de Medina F, Martinez-Augustin O. Active hexose correlated compound exerts therapeutic effects in lymphocyte driven colitis. Mol Nutr Food Res 2014;58:2379–2382. [PubMed: 25186628]

90. Aviles H, Belay T, Fountain K, Vance M, Sun B, Sonnenfeld G. Active hexose correlated compound enhances resistance to Klebsiella pneumoniae infection in mice in the hindlimb-unloading model of spaceflight conditions. J Appl Physiol (1985) 2003;95:491–496. [PubMed: 12692142]

91. Wang S, Welte T, Fang H, et al. Oral administration of active hexose correlated compound enhances host resistance to West Nile encephalitis in mice. J Nutr 2009;139:598–602. [PubMed: 19141700]

92. Yagita A, Maruyama S, Wakasugi S, Sukegawa Y. H-2 haplotype-dependent serum IL-12 production in tumor-bearing mice treated with various mycelial extracts. In Vivo 2002;16:49–54.

93. Suenaga S, Kuramitsu Y, Kaino S, et al. Active hexose-correlated compound down-regulates HSP27 of pancreatic cancer cells, and helps the cytotoxic effect of gemcitabine. Anticancer Res 2014;34:141–146. [PubMed: 24403454]

94. Kuhara K, Tokuda K, Kitagawa T, et al. CUB Domain-containing Protein 1 (CDCP1) Is Down-regulated by Active Hexose-correlated Compound in Human Pancreatic Cancer Cells. Anticancer Res 2018;38:6107–6111. [PubMed: 30396925]

95. Hirose A, Sato E, Fujii H, Sun B, Nishioka H, Aruoma OI. The influence of active hexose correlated compound (AHCC) on cisplatin-evoked chemotherapeutic and side effects in tumor-bearing mice. Toxicol Appl Pharmacol 2007;222:152–158. [PubMed: 17555784]

96. Roman BE, Beli E, Duriancik DM, Gardner EM. Short-term supplementation with active hexose correlated compound improves the antibody response to influenza B vaccine. Nutr Res 2013;33:12–17. [PubMed: 23351405]

97. Yin Z, Fujii H, Walshe T. Effects of active hexose correlated compound on frequency of CD4+ and CD8+ T cells producing interferon-gamma and/or tumor necrosis factor-alpha in healthy adults. Hum Immunol 2010;71:1187–1190. [PubMed: 20732368]

98. Terakawa N, Matsui Y, Satoi S, et al. Immunological effect of active hexose correlated compound (AHCC) in healthy volunteers: a double-blind, placebo-controlled trial. Nutr Cancer 2008;60:643–651. [PubMed: 18791928]

99. Matsui Y, Uhara J, Satoi S, et al. Improved prognosis of postoperative hepatocellular carcinoma patients when treated with functional foods: a prospective cohort study. J Hepatol 2002;37:78–86. [PubMed: 12076865]

100. Yanagimoto H, Satoi S, Yamamoto T, et al. Alleviating Effect of Active Hexose Correlated Compound (AHCC) on Chemotherapy-Related Adverse Events in Patients with Unresectable Pancreatic Ductal Adenocarcinoma. Nutr Cancer 2016;68:234–240. [PubMed: 26847832]

101. Mach CM, Fugii H, Wakame K, Smith J. Evaluation of active hexose correlated compound hepatic metabolism and potential for drug interactions with chemotherapy agents. J Soc Integr Oncol 2008;6:105–109. [PubMed: 19087767]

102. Mathew L, Gaikwad A, Gonzalez A, Nugent EK, Smith JA. Evaluation of Active Hexose Correlated Compound (AHCC) in Combination With Anticancer Hormones in Orthotopic Breast Cancer Models. Integr Cancer Ther 2017;16:300–307. [PubMed: 28438054]

103. Dahmen U, Gu YL, Dirsch O, et al. Boswellic acid, a potent antiinflammatory drug, inhibits rejection to the same extent as high dose steroids. Transplant Proc 2001;33:539–541. [PubMed: 11266947]

104. Safayhi H, Boden SE, Schweizer S, Ammon HP. Concentration-dependent potentiating and inhibitory effects of Boswellia extracts on 5-lipoxygenase product formation in stimulated PMNL. Planta Med 2000;66:110–113. [PubMed: 10763581]

105. Glaser T, Winter S, Groscurth P, et al. Boswellic acids and malignant glioma: induction of apoptosis but no modulation of drug sensitivity. Br J Cancer 1999;80:756–765. [PubMed: 10360653]

106. Jing Y, Nakajo S, Xia L, et al. Boswellic acid acetate induces differentiation and apoptosis in leukemia cell lines. Leuk Res 1999;23:43–50. [PubMed: 9933134]

107. Winking M, Sarikaya S, Rahmanian A, Jodicke A, Boker DK. Boswellic acids inhibit glioma growth: a new treatment option? J Neurooncol 2000;46:97–103. [PubMed: 10894362]

108. Conti S, Vexler A, Edry-Botzer L, et al. Combined acetyl-11-keto-beta-boswellic acid and radiation treatment inhibited glioblastoma tumor cells. PLoS One 2018;13:e0198627. [PubMed: 29969452]

109. Sengupta K, Alluri KV, Satish AR, et al. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. Arthritis Res Ther 2008;10:R85. [PubMed: 18667054]

110. Kirste S, Treier M, Wehrle SJ, et al. Boswellia serrata acts on cerebral edema in patients irradiated for brain tumors: a prospective, randomized, placebo-controlled, double-blind pilot trial. Cancer 2011;117:3788–3795. [PubMed: 21287538]

111. Togni S, Maramaldi G, Bonetta A, Giacomelli L, Di Pierro F. Clinical evaluation of safety and efficacy of Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial. Eur Rev Med Pharmacol Sci 2015;19:1338–1344. [PubMed: 25967706]

112. Holtmeier W, Zeuzem S, Preiss J, et al. Randomized, placebo-controlled, double-blind trial of Boswellia serrata in maintaining remission of Crohn's disease: good safety profile but lack of efficacy. Inflamm Bowel Dis 2011;17:573–582. [PubMed: 20848527]

113. Acebo E, Raton JA, Sautua S, Eizaguirre X, Trebol I, Perez JL. Allergic contact dermatitis from Boswellia serrata extract in a naturopathic cream. Contact Dermatitis 2004;51:91–92. [PubMed: 15373853]
114. Kokkiripati PK, Bhakshu LM, Marri S, et al. Gum resin of Boswellia serrata inhibited human monocytic (THP-1) cell activation and platelet aggregation. J Ethnopharmacol 2011;137:893–901. [PubMed: 21771654]
115. Bensky D, Clavey S, Stöger E. Chinese Herbal Medicine, Materia Medica. 3rd ed. Seattle, WA: Eastland Press, Inc; 2004.
116. Clare BA, Conroy RS, Spelman K. The diuretic effect in human subjects of an extract of Taraxacum officinale folium over a single day. J Altern Complement Med 2009;15:929–934. [PubMed: 19678785]
117. Martinez M, Poirrier P, Chamy R, et al. Taraxacum officinale and related species-An ethnopharmacological review and its potential as a commercial medicinal plant. J Ethnopharmacol 2015;169:244–262. [PubMed: 25858507]
118. Hata K, Ishikawa K, Hori K, Konishi T. Differentiation-inducing activity of lupeol, a lupane-type triterpene from Chinese dandelion root (Hokouei-kon), on a mouse melanoma cell line. Biol Pharm Bull 2000;23:962–967. [PubMed: 10963304]
119. Ovadje P, Chochkeh M, Akbari-Asl P, Hamm C, Pandey S. Selective induction of apoptosis and autophagy through treatment with dandelion root extract in human pancreatic cancer cells. Pancreas 2012;41:1039–1047. [PubMed: 22647733]
120. Ovadje P, Ammar S, Guerrero JA, Arnason JT, Pandey S. Dandelion root extract affects colorectal cancer proliferation and survival through the activation of multiple death signalling pathways. Oncotarget 2016;7:73080–73100. [PubMed: 27564258]
121. Ovadje P, Hamm C, Pandey S. Efficient induction of extrinsic cell death by dandelion root extract in human chronic myelomonocytic leukemia (CMML) cells. PLoS One 2012;7:e30604. [PubMed: 22363452]
122. Rahmat LT, Damon LE. The Use of Natural Health Products Especially Papaya Leaf Extract and Dandelion Root Extract in Previously Untreated Chronic Myelomonocytic Leukemia. Case reports in hematology 2018;2018:7267920. [PubMed: 30662779]
123. Oh SM, Kim HR, Park YJ, Lee YH, Chung KH. Ethanolic extract of dandelion (Taraxacum mongolicum) induces estrogenic activity in MCF-7 cells and immature rats. Chinese journal of natural medicines 2015;13:808–814. [PubMed: 26614455]
124. Maliakal PP, Wanwimolruk S. Effect of herbal teas on hepatic drug metabolizing enzymes in rats. J Pharm Pharmacol 2001;53:1323–1329. [PubMed: 11697539]
125. Dufay S, Worsley A, Monteillier A, et al. Herbal tea extracts inhibit Cytochrome P450 3A4 in vitro. J Pharm Pharmacol 2014;66:1478–1490. [PubMed: 24824478]
126. Kumar NB, Pow-Sang J, Egan KM, et al. Randomized, Placebo-Controlled Trial of Green Tea Catechins for Prostate Cancer Prevention. Cancer Prev Res (Phila) 2015;8:879–887. [PubMed: 25873370]
127. Shanafelt TD, Call TG, Zent CS, et al. Phase 2 trial of daily, oral Polyphenon E in patients with asymptomatic, Rai stage 0 to II chronic lymphocytic leukemia. Cancer 2013;119:363–370. [PubMed: 22760587]
128. Thomas R, Williams M, Sharma H, Chaudry A, Bellamy P. A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer--the U.K. NCRN Pomi-T study. Prostate Cancer Prostatic Dis 2014;17:180–186. [PubMed: 24614693]
129. Chow HH, Hakim IA, Vining DR, et al. Effects of dosing condition on the oral bioavailability of green tea catechins after single-dose administration of Polyphenon E in healthy individuals. Clin Cancer Res 2005;11:4627–4633. [PubMed: 15958649]
130. Naumovski N, Blades BL, Roach PD. Food Inhibits the Oral Bioavailability of the Major Green Tea Antioxidant Epigallocatechin Gallate in Humans. Antioxidants (Basel, Switzerland) 2015;4:373–393.

131. Golden EB, Lam PY, Kardosh A, et al. Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors. Blood 2009;113:5927–5937. [PubMed: 19190249]

132. Misaka S, Kawabe K, Onoue S, et al. Effects of green tea catechins on cytochrome P450 2B6, 2C8, 2C19, 2D6 and 3A activities in human liver and intestinal microsomes. Drug Metab Pharmacokinet 2013;28:244–249. [PubMed: 23268924]

133. Lee MJ, Maliakal P, Chen L, et al. Pharmacokinetics of tea catechins after ingestion of green tea and (−)-epigallocatechin-3-gallate by humans: formation of different metabolites and individual variability. Cancer Epidemiol Biomarkers Prev 2002;11:1025–1032. [PubMed: 12376503]

134. Yang CS, Chen L, Lee MJ, Balentine D, Kuo MC, Schantz SP. Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. Cancer Epidemiol Biomarkers Prev 1998;7:351–354. [PubMed: 9568793]

135. Nakazato H, Koike A, Saji S, Ogawa N, Sakamoto J. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. Study Group of Immunochemotherapy with PSK for Gastric Cancer. Lancet 1994;343:1122–1126. [PubMed: 7910230]

136. Niimoto M, Hattori T, Tamada R, Sugimachi K, Inokuchi K, Ogawa N. Postoperative adjuvant immunochemotherapy with mitomycin C, futraful and PSK for gastric cancer. An analysis of data on 579 patients followed for five years. Jpn J Surg 1988;18:681–686. [PubMed: 3150019]

137. Ohwada S, Ikeya T, Yokomori T, et al. Adjuvant immunochemotherapy with oral Tegafur/Uracil plus PSK in patients with stage II or III colorectal cancer: a randomised controlled study. Br J Cancer 2004;90:1003–1010. [PubMed: 14997197]

138. Mitomi T, Tsuchiya S, Iijima N, et al. Randomized, controlled study on adjuvant immunochemotherapy with PSK in curatively resected colorectal cancer. The Cooperative Study Group of Surgical Adjuvant Immunochemotherapy for Cancer of Colon and Rectum (Kanagawa). Dis Colon Rectum 1992;35:123–130. [PubMed: 1735313]

139. Torisu M, Hayashi Y, Ishimitsu T, et al. Significant prolongation of disease-free period gained by oral polysaccharide K (PSK) administration after curative surgical operation of colorectal cancer. Cancer Immunol Immunother 1990;31:261–268. [PubMed: 2198088]

140. Ogoshi K, Satou H, Isono K, Mitomi T, Endoh M, Sugita M. Immunotherapy for esophageal cancer. A randomized trial in combination with radiotherapy and radiochemotherapy. Cooperative Study Group for Esophageal Cancer in Japan. Am J Clin Oncol 1995;18:216–222. [PubMed: 7747709]

141. Tsang KW, Lam CL, Yan C, et al. Coriolus versicolor polysaccharide peptide slows progression of advanced non-small cell lung cancer. Respir Med 2003;97:618–624. [PubMed: 12814145]

142. Wong CK, Tse PS, Wong EL, Leung PC, Fung KP, Lam CW. Immunomodulatory effects of yun zhi and danshen capsules in health subjects--a randomized, double-blind, placebo-controlled, crossover study. Int Immunopharmacol 2004;4:201–211. [PubMed: 14996412]

143. Wong CK, Bao YX, Wong EL, Leung PC, Fung KP, Lam CW. Immunomodulatory activities of Yunzhi and Danshen in post-treatment breast cancer patients. Am J Chin Med 2005;33:381–395. [PubMed: 16047556]

144. Iino Y, Yokoe T, Maemura M, et al. Immunochemotherapies versus chemotherapy as adjuvant treatment after curative resection of operable breast cancer. Anticancer Res 1995;15:2907–2911. [PubMed: 8669887]

145. Suto T, Fukuda S, Moriya N, et al. Clinical study of biological response modifiers as maintenance therapy for hepatocellular carcinoma. Cancer Chemother Pharmacol 1994;33 Suppl:S145–148. [PubMed: 8137477]

146. Chay WY, Tham CK, Toh HC, et al. Coriolus versicolor (Yunzhi) Use as Therapy in Advanced Hepatocellular Carcinoma Patients with Poor Liver Function or Who Are Unfit for Standard Therapy. J Altern Complement Med 2017;23:648–652. [PubMed: 28375640]

147. Ohno R, Yamada K, Masaoka T, et al. A randomized trial of chemoimmunotherapy of acute nonlymphocytic leukemia in adults using a protein-bound polysaccharide preparation. Cancer Immunol Immunother 1984;18:149–154. [PubMed: 6391658]

148. Kidd PM. The use of mushroom glucans and proteoglycans in cancer treatment. Altern Med Rev 2000;5:4–27. [PubMed: 10696116]

TABLE 1.

Snapshot of Top 10 Monographs Accessed from the *About Herbs* Database in 2018

Depiction	Common Name	Scientific or Expanded Name	Origin	Key Properties	Key Interaction Concerns*	Avoid in*
	1. Chaga	*Inonotus obliquus*	Russia; subarctic regions	Antiplatelet Antidiabetic Anti-inflammatory	High in oxalates Anticoagulants Antiplatelets Antihyperglycemic agents	Renal disease Diabetic patient on treatment (acarbose)
	2. Turmeric	*Curcuma longa Curcuma domestica*	China India	Anti-inflammatory	High in oxalates CYP2C9 enzyme	Renal disease
	3. Ashwagandha	*Withania somnifera*	India	Tonic Energy level Longevity	Increase testosterone levels in men	Prostate cancer
	4. Reishi mushroom	*Ganoderma lucidum*	China Japan	Antioxidant Immune-modulating	Anticoagulants Antiplatelets	Radiation therapy

Depiction	Common Name	Scientific or Expanded Name	Origin	Key Properties	Key Interaction Concerns*	Avoid in*
	5. Graviola	*Annona muricata*	Hispanic cultural food; tropical regions	Analgesic Anti-inflammatory Anti-ulcer	Antihyperglycemic agents	Diabetic patient on treatment
	6. AHCC	Active hexose correlated compound	Japan	Immune-modulating Antioxidant Anti-inflammatory	CYP2D6 enzyme (inducer)	Breast cancer patients on doxorubicin, zofran and aromatase inhibitor (letrozole)
	7. Boswellia	*Boswellia serrata*	India	Anti-inflammatory Reduce RT-induced cerebral edema	Unknown	Contact dermatitis
	8. Dandelion	*Taraxacum mongolicum* *Taraxacum officinale*	China USA	Reduce abscesses Promote lactation Chronic myelomonocytic leukemia (CMML)	CYP1A2 enzyme Diuretic Antihyperglycemic agents Estrogenic activity	Hormone-sensitive breast cancer
	9. Green tea	*Camellia sinensis*	Asia (China, Japan) USA	Antioxidant Prostate cancer Chronic lymphocytic leukemia (CLL)	High doses or taken on an empty stomach can cause liver toxicity Bortezomib	Elevated liver function tests

Cancer J. Author manuscript; available in PMC 2020 September 01.

Depiction	Common Name	Scientific or Expanded Name	Origin	Key Properties	Key Interaction Concerns*	Avoid in*
	10. *Coriolus versicolor*	*Coriolus versicolor* *Trametes versicolor*	Asia (Japan, China)	Immune-modulating Gastric and colorectal cancers	Unknown	Patient on immunosuppressant (in theory)

* For a clinical summary and a more comprehensive assessment of potential side effects, interactions, and cautions, visit the *About Herbs* database at mskcc.org/aboutherbs.

Artwork by Angela Donato for *About Herbs.*