Herbal Medicines as Adjuncts to Cancer Chemotherapy—Part 1: Immunomodulators

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Abstract

Immunomodulating herbs that have been studied in patients undergoing chemotherapy for cancer are reviewed in depth. *Trametes versicolor* (turkey tail, yún zhī) mushroom, formerly known as *Coriolus versicolor*, *Astragalus membranaceus* (astragalus, huáng qí) root, *Panax ginseng* (Asian ginseng, rén shēn) root, and *Viscum album* (European mistletoe) injectable extracts are reviewed in depth. These represent the four best-studied natural herbal immune adjuncts to chemotherapy. Various reports of these agents' abilities to reduce adverse effects and improve survival in cancer patients are discussed in depth. Other less well studied herbal immunomodulators are also mentioned more briefly. Part 2 of this article will focus on herbal therapies for other specific adverse effects of chemotherapy such as nausea, mucositis, neuropathies, and organ damage.

Keywords: herbal medicine, chemotherapy, cancer, immunomodulator, *Trametes versicolor*, *Panax ginseng*

Introduction

Chemotherapy remains a mainstay of the conventional approach to many types of cancer. While in some cancers it is dubious to what degree chemotherapy is helpful (e.g., late-stage pancreatic or colon cancers), in others it is often life-saving (e.g., leukemias and lymphomas).[1] New agents, such as biologics and checkpoint inhibitors, continue to appear on a regular basis, driven in part by the enormous profitability of new drugs for cancer. Some of these drugs show exciting promise, while others, particularly given their extremely high price tags and the resulting poor cost-effectiveness (some drugs cost $>$$1 million/quality-adjusted year of life gained), are dubious at best.[2]

Even effective chemotherapy agents tend to have quite significant and often severe adverse effects. In this article, the first of a two-part series, the use of herbal immunomodulators in combination with cancer chemotherapy drugs will be reviewed. Almost all chemotherapy drugs cause immune suppression, bone-marrow suppression, organ damage, or some combination of these. Immunomodulators tend to protect against or correct all these problems or, by some combination of these benefits or other as yet undetermined properties, extend the life of patients on chemotherapy for cancer. Part 2 will review herbal therapies for other complications of chemotherapy, including nausea, vomiting, anorexia, mucositis, xerostomia, neuropathy, and myopathy.

Trametes versicolor, Wonder Mushroom

Suppression of immune function, including the very dangerous situation of neutropenia, is a common complication of cancer chemotherapy.[3] Cancer in part works by hijacking normal immunosuppressive mechanisms that would normally work to prevent proliferation of undifferentiated cells; it can also hide itself from normal immune recognition mechanisms.[4] Improved immune function has repeatedly been shown to correlate with the efficacy of a broad range of cancer chemotherapy drugs.[5] Newer cancer chemotherapy drugs, most notably the checkpoint inhibitors such as ipilimumab, specifically target failure of immune surveillance due to cancer and are showing great promise. Botanical and fungal immunomodulators offer a safe and effective solution to both chemotherapy-induced immunosuppression and cancer escape from immunosurveillance. These herbs and fungi have particularly been shown to support immune reconstitution post chemotherapy and to correct cancer's subversion of the immune system, in some cases leading to dramatic improvement in overall survival. Several of the best-studied agents for these purposes are reviewed here.

Trametes versicolor (turkey tail, yún zhī), formerly *Coriolus versicolor*, is a mushroom with a long history of use in Asian traditional medicines (Fig. 1). Two aqueous extracts of turkey tail have been the subject of most research in cancer patients: polysaccharide Krestin (PSK) from the fruiting body and polysaccharide peptides (PSP) isolated from the mycelium.

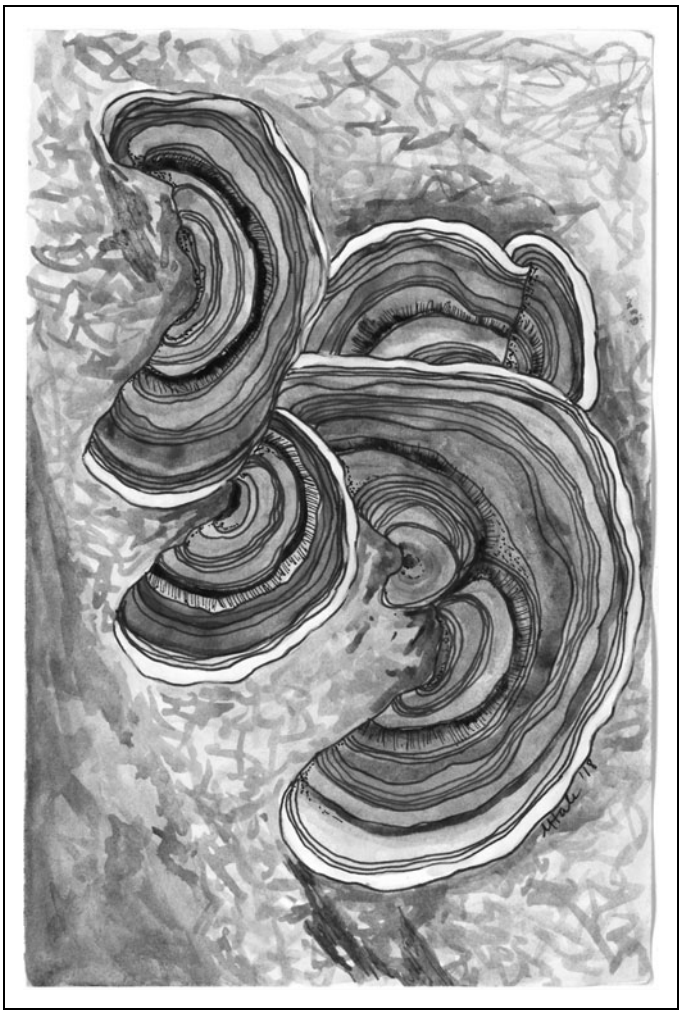

Figure 1. ***Trametes versicolor*****. Drawing by Meredith Hale and reprinted with permission.**

PSK has received the most research attention of these two. Other preparations are likely effective, though heat processing appears very important for turkey tail mushroom to be clinically effective.

A meta-analysis of eight randomized, controlled, clinical trials assessed the efficacy of PSK in Japanese gastric cancer patients who had undergone resection with curative intent.[6] Patients who were treated with chemotherapy alone (mitomycin C, carbazilquinone, carmofur, and/or tegafur) or PSK plus the same chemotherapy were compared. Five-year survival was significantly better in the group concomitantly treated with PSK. Another meta-analysis reviewed three randomized, controlled, clinical trials of PSK after curatively resected colorectal cancer.[7] As in the previous paper, the patients in these trials were all Japanese. Patients were again treated with chemotherapy alone (5-fluorouracil, carboquone, mitomycin C, tegafur with or without uracil, carmofur, and/or capecitabine) or the same regimens plus PSK. Again, five-year survival was significantly better in the PSK-treated patients compared to chemotherapy-only controls. A third meta-analysis of 12 double-blind, randomized trials using any extract of turkey tail in multiple cancers found a 9% increase in survival at five years, suggesting a number needed to treat of 11 to save one life.[8] The ethnic makeup of patients in the trials analyzed could not be determined, but likely they were mostly Japanese, as almost all PSK research has been done in Japan.

Clinical trials on PSP have been less rigorous and only followed short-term outcomes, have largely been published in conference proceedings or books and not peer-reviewed journals, and are often not available in English, making assessing their methodology difficult.[9] One modern, double-blind clinical trial randomized 68 Chinese patients with inoperable non-small-cell lung cancer (NSCLC) to either PSP or placebo.[10] All were treated with paclitaxel and carboplatin. Subjects were followed for just four weeks, but white blood cell (WBC) counts, serum antibody levels, and percent body fat were all significantly better in the PSP group compared to placebo. While it appears that PSP may offset immunosuppression and other adverse effects due to chemotherapy in breast, gastric, and colorectal cancer, more rigorous studies are needed to document this. Its relative efficacy compared to PSK also needs to be established in high-quality, head-to-head trials.

One open clinical trial examined the use of PSP 50 mg/kg/day combined with a hot water extract of *Salvia miltiorrhiza* (red sage, dān shēn) 20 mg/kg/day in capsules for six months in Chinese women with breast cancer, 80% of whom had undergone chemotherapy and 71% were on tamoxifen.[11] All subjects were normopenic at baseline. There was a significant increase in absolute T-helper lymphocytes, ratio of T-helper/T suppressor + cytotoxic lymphocytes, and the percentage and the absolute counts of B-lymphocytes compared to baseline. There was a decrease in plasma soluble interleukin-2 receptor concentration with PSP/red sage compared to baseline. Other clinical trials support that PSK works, at least in part, through immunologic mechanisms.[12]

The usual doses of PSK and PSP are 1–2 g t.i.d. A Phase I clinical trial examined the safety and maximum tolerable dose of an otherwise uncharacterized freeze-dried mycelial powder in women (of unstated ethnicity, but likely mostly of European descent) with stage I–III breast cancer after radiation therapy treatment.[13] A dose of 9 g/day was tolerable, although the study did not examine higher doses. This preliminary research suggests a faster immune recovery after radiotherapy, possibly explained by improvement in lymphocyte number and natural killer cell tumoricidal activity. Overall, turkey tail extracts are extremely safe with no known common adverse effects. In particular, they have also been shown to be helpful in patients with autoimmune diseases, eliminating concern that they might aggravate such conditions.[14]

Astragalus, A Life-Giving Root

In Chinese medicine, *Astragalus membranaceus* (astragalus, huáng qí) root has been used concurrently with cancer chemotherapy, particularly in lung cancer patients. It is traditionally viewed as a *qi* tonic, and much research supports that it

is immunomodulating (including specifically in cancer patients).[15,16] Its antioxidant, kidney-, liver-, and heart-protective effects, antifibrotic activity, and inflammation-modulating actions all suggest potential benefit in offsetting the adverse effects of various chemotherapy agents.[17,18] Polysaccharides, flavonoids, and steroidal saponins, most notably astragaloside IV, are believed to contribute substantially to the actions of astragalus. Some in vitro work suggests that astragaloside IV augments the activity of cisplatin and gefitinib, along with inhibition of the immune checkpoint-related molecule B7-H3 (CD276).[19,20]

A meta-analysis analyzed 34 purportedly randomized trials of this Fabaceae family plant by itself or in a range of herbal formulas (some given orally, some extracts by intravenous injection), combined with platinum-based chemotherapy (and, in one study, hydroxycamptothecin, fluorouracil, and leucovorin) for patients with NSCLC.[21] The quality of these trials was generally very low, with only one rating more than a 3 on the Jadad quality scale. Overall survival at 24 months was significantly increased when chemotherapy was combined with astragalus-containing products compared to chemotherapy alone. Performance status was improved in the astragalus adjunct group compared to controls without astragalus, suggesting overall clinical symptoms improved.

A later similar meta-analysis found 65 clinical trials that investigated astragalus-based herbal medicine (oral or intravenous) for patients with NSCLC.[22] Again, researchers found that most of the trials were low quality, but reported increased overall survival with astragalus-based medicines added to chemotherapy at 36 months compared to chemotherapy alone. Yet another meta-analysis assessed the efficacy of astragalus-based medicines combined with chemotherapy in patients with hepatocellular carcinoma in 26 randomized clinical trials.[23] The results were not surprisingly quite similar: increased overall survival at 36 months by adding astragalus-based medicines to chemotherapy compared to chemotherapy alone. This analysis did not look at the effect of treatment on clinical symptoms. Study quality was also rated quite low in this analysis. Large robust clinical trials of astragalus and astragalus-based herbal formulas in cancer patients undergoing chemotherapy are warranted.

A meta-analysis of 13 clinical trials involving intravenous administration of an astragalus ethanolic extract investigated whether this extract could improve leukocyte counts.[24] However, only six of these trials involved patients with chemotherapy-related leukopenia; the rest were due to other drugs, radiation therapy, or infectious diseases. Overall, astragalus extract injection did significantly raise WBC counts compared to standard-of-care Western medicine only. Of the five trials that reported adverse effects, none occurred with the extract.

Astragalus is thus a very safe herbal medicine for patients receiving various kinds of chemotherapy. Traditional use and modern research support such use. There is no reason to think it will interact negatively with any known chemotherapy agent yet determined. There are a few chemotherapy drugs that are substrates for cytochrome (CYP) 3A4 (docetaxel, irinotecan, sorafenib, sunitinib, tamoxifen, and vincristine). So far, results in vitro and in rodents have given conflicting reports as to whether astragalus induces or inhibits CYP3A4.[25–27] Combining a formula containing astragalus with the CYP3A4 substrate drug atazanavir enhanced the protease-inhibiting activity of this herb without increased toxicity in one rodent study.[28] Astragalus has shown no effect on P-glycoprotein.[29] The many trials that show astragalus extends life in patients with cancer undergoing chemotherapy further discredit the common but erroneous idea that anything with antioxidant properties is to be avoided in chemotherapy, as it will interfere. A typical dose of the tincture or glycerite is 3–5 mL t.i.d. Of granules or crude root in tea, the dose is 1–5 g t.i.d.

Ginseng and Chemotherapy

Panax ginseng (Asian ginseng, rén shēn) root, in the Araliaceae family, is perhaps the best known of all Chinese herbs. Like other *qi* tonics, it has been found to be immunomodulating in modern research. This action, its many organ-protective effects (including bone-marrow protection), and its anticancer properties make Asian ginseng an excellent candidate to combine with chemotherapy.[30] Polysaccharides known as panaxans and triterpenoid glycosides known as ginsenosides are crucial for all of these actions. Many preclinical studies provide support that Asian ginseng is safe and helpful combined with a wide range of chemotherapy agents (see Table 1). Preliminary clinical research supports Asian ginseng's role with chemotherapy, though it is not as well studied as turkey tail or astragalus.

In an open trial, 60 inoperable NSCLC patients undergoing gemcitabine and cisplatin chemotherapy were randomized to either an extract of fermented red ginseng 3 g q.d. or no additional treatment for 60 days.[31] Red ginseng is steamed then dried, causing it to turn red compared to just drying the root, which results in white ginseng. Several questionnaires documented less fatigue and less severe symptoms in patients receiving fermented red ginseng compared to those who were not. Leukopenia, thrombocytopenia, neuropathies, nausea, and vomiting were all significantly less in the ginseng group compared to controls. The short duration of the trial did not permit an analysis of any survival benefits.

A much larger double-blind trial randomized 414 patients with stage III or IV NSCLC to ginsenoside Rg3 at an unknown dose or placebo.[32] All patients were undergoing the same chemotherapy regimen. Overall survival was significantly better (by a median of 3.5 months) in the ginsenoside group compared to placebo controls. Anemia and leukopenia occurred in both groups but were significantly less severe in the ginsenoside Rg3 group compared to placebo.

A higher-dose, randomized, double-blind trial looked at the effect of 4.5 g of red ginseng daily compared to placebo in 49 patients with gastric cancer undergoing chemotherapy after surgery.[33] All patients were treated with 5-fluorouracil and cisplatin for six months, along with either the red ginseng or

Table 1. Preclinical Safety and Efficacy of Combination of *Panax ginseng* with Major Chemotherapy Drugs

Chemotherapy agent	Model and treatment form	Effect	Citation
Cisplatin	Ferrets, red ginseng aqueous extract	Reduced nausea and vomiting	Kim 2005[a]
	Rats, red ginseng aqueous extract	Reduced nausea and vomiting	Raghavendran 2011[b]
	Rats, red ginseng extract	Reduced cachexia	Lobina 2014[c]
	Multiple models, multiple extracts and isolated ginsenosides	Prevented nephrotoxicity	Park 2015[d]
	Mice, Asian ginseng fruit anthocyanins	Prevented nephrotoxicity	Qi 2017[e]
	Mice, American ginseng leaf saponins	Prevented nephrotoxicity	Ma 2017[f]
	Mice, Asian ginseng-containing formula	Enhances activity of cisplatin in lung cancer (by inhibiting efflux pumps)	Jin 2017[g]
	Rats, red ginseng extract	Prevented ototoxicity	Olgun 2016[h]
5-Fluorouracil (5-FU)	Rats and gastric cancer cells in vitro, Asian ginseng aqueous extract	Increased elimination half-life of 5-FU by 60%; enhanced anticancer activity of 5-FU in vitro	Gu 2013[i]
	Rats, American ginseng ethanol extract	No effect on 5-FU pharmacokinetics	He 2015[j]
	Colon cancer cells in vitro, red and white ginseng extracts	Red ginseng synergistically killed colon cancer cells combined with 5-FU	Fishbein 2009[k]
	Rats, red ginseng aqueous extract	Prevented myelosuppression; prevented widespread organ damage	Park 2012[l]
Paclitaxel	Mice, red ginseng acidic polysaccharide	Enhanced anti-melanoma effects of paclitaxel	Shin 2004[m]
	Breast cancer cells in vitro, ginsenoside Rg3	Enhanced anticancer effects of paclitaxel	Yuan 2017[n]
	Paclitaxel-resistant ovarian cancer cells in vitro, ginsenoside Rb1	Re-sensitized cells to paclitaxel	Deng 2017[o]
	Rats, red ginseng extract	Increased bioavailability and cancer cell penetration of paclitaxel	Bae 2017[p]
Docetaxel	Colon cancer cells in vitro, ginsenoside Rg3	Enhanced susceptibility of colon cancer cells to paclitaxel	Kim 2009[q]
Bleomycin	Rats, ginsenoside Rg1	Prevented pulmonary fibrosis	Zhan 2016[r]
Doxorubicin	Rats, Asian ginseng extract	Prevented cardiotoxicity	You 2005[s]
	Rats, ginseng intestinal metabolite-1	Prevented testicular toxicity	Kang 2002[t]
	Leukemia cells in vitro, various ginsenosides	Increased cellular uptake of doxorubicin by inhibiting MDR	Choi 2003[u]
	Mice, ginsenoside Rg3	Sensitized HCC cells to doxorubicin	Kim 2014[v]
Vinblastine	Leukemia cells in vitro, protopanaxatriol, ginsenoside Rh2, compound K	Reversed vinblastine resistance	Hasegawa 1995[w]

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[g]Jin L, Xu M, Luo XH, Zhu XF. *Stephania tetrandra* and ginseng-containing Chinese herbal formulation NSENL reverses cisplatin resistance in lung cancer xenografts. Am J Chin Med 2017;45:385–401.
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[k]Fishbein AB, Wang CZ, Li XL, et al. Asian ginseng enhances the anti-proliferative effect of 5-fluorouracil on human colorectal cancer: Comparison between white and red ginseng. Arch Pharm Res 2009;32:505–513.
[l]Park HJ, Han JM, Kim HG, et al. Anti-myelosuppression effects of Korean red ginseng in SD rat injected with 5-fluorouracil. J Korean Oriental Med 2012;33:47–55.
[m]Shin HJ, Kim YS, Kwak YS, et al. Enhancement of antitumor effects of paclitaxel (Taxol) in combination with red ginseng acidic polysaccharide (RGAP). Planta Med 2004;70:1033–1038.
[n]Yuan Z, Jiang H, Zhu X, et al. Ginsenoside Rg3 promotes cytotoxicity of paclitaxel through inhibiting NF-κB signaling and regulating Bax/Bcl-2 expression on triple-negative breast cancer. Biomed Pharmacother 2017;89:227–232.
[o]Deng S, Wong CKC, Lai HC, Wong AST. Ginsenoside-Rb1 targets chemotherapy-resistant ovarian cancer stem cells via simultaneous inhibition of Wnt/β-catenin signaling and epithelial-to-mesenchymal transition. Oncotarget 2017;8:25897–25914.
[p]Bae JK, Kim YJ, Chae HS, et al. Korean red ginseng extract enhances paclitaxel distribution to mammary tumors and its oral bioavailability by P-glycoprotein inhibition. Xenobiotica 2017;47:450–459.
[q]Kim SM, Lee SY, Yuk DY, et al. Inhibition of NF-kappaB by ginsenoside Rg3 enhances the susceptibility of colon cancer cells to docetaxel. Arch Pharm Res 2009;32:755–765.
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[w]Hasegawa H, Sung JH, Matsumiya S, et al. Reversal of daunomycin and vinblastine resistance in multidrug-resistant P388 leukemia in vitro through enhanced cytotoxicity by triterpenoids. Planta Med 1995;61:409–413.
HCC, hepatocellular carcinoma; MDR, multidrug resistance pump.

placebo. Lymphopenia was reduced or completely reversed (depending on the lymphocyte subpopulation in question) by red ginseng, a significant difference compared to placebo. Overall survival was significantly better in the ginseng group compared to controls (76% vs. 39%, respectively). No significant adverse effects were associated with the ginseng extract.

Another double-blind trial randomized 30 patients with ovarian cancer who had undergone surgery and completed adjuvant chemotherapy to either red ginseng 500 mg/day or placebo for three months.[34] Between-group statistical analyses were unfortunately not provided, except to show there was no difference in overall survival between them with prolonged observation of the study subjects. An assay for blood micronuclei (a marker of systemic chemotherapy toxicity) was significantly better in the ginseng patients compared to baseline, which was not the case in the placebo group. Similarly, health-related quality of life improved only in the ginseng group compared to baseline, not in the placebo group. There was no difference in adverse effects between the groups.

Asian ginseng's cousin *Panax quinquefolius* (American ginseng) is another revered immunomodulator and adaptogen. It too has been studied in patients undergoing chemotherapy, though in an even more limited way. A preliminary double-blind trial randomized 290 adults with various types of cancer to placebo or one of three doses of an American ginseng extract with 5% ginsenosides, 500, 1000, or 2000 mg/day.[35] Forty percent of participants were undergoing chemotherapy during the trial. There were nonsignificant trends toward improved fatigue at all doses of American ginseng compared to placebo. A follow-up double-blind trial by the same group randomized 364 adults with cancer, again many of whom were undergoing chemotherapy, to either 2 g American ginseng extract or placebo for eight weeks.[36] This time, there was a statistically significant improvement in fatigue in the American ginseng group compared to placebo. Adverse effects did not differ between the treatment groups.

Mistletoe: Promise Unfulfilled?

Injectable *Viscum album* (European mistletoe) extracts are one of the most widely used complementary cancer therapies in Europe. This unique plant is hemiparasitic on a range of trees, and its host can change the chemistry of the plant and extracts from it. Its lectins are believed to account for much of its activity when given by intradermal or intravenous injection. Injected mistletoe extracts are primarily believed to act as

Table 2. Trials of Other Immunomodulating Herbs and Formulas with Chemotherapy

Herb/formula(s)	Cancer	Chemotherapy	Study details	Citation
Multiple traditional Chinese formulas (particularly those containing astragalus, *Hedyotis diffusa* [oldenlandia], and *Scutellaria baicalensis* [Baical skullcap])	Colorectal	FOLFOX or XELOX	Meta-analysis of 42 randomized trials; improved response rate (no survival data)	Chen 2016[a]
Ganoderma lucidum (reishi, líng zhī) water-soluble polysaccharides	Lung	Multiple	Open trial, $n = 36$, 5.4 g q.d., 12 weeks, some patients had improved immune function	Gao 2015[b]
	Colorectal	Multiple	Open trial, $n = 47$, 5.4 g q.d., 12 weeks, no immune benefits	Chen 2006[c]
Aloe arborescens (tree aloe) gel	Lung, colorectal, gastric, pancreatic	Cisplatin, etoposide, vinorelbine, oxaliplatin, 5-FU, and/or gemcitabine	DBRPC, $n = 240$, 10 mL t.i.d., increased three-year overall survival	Lissoni 2009[d]
Withania somnifera (ashwagandha) root extract	Breast	Docetaxel, doxorubicin, cyclophosphamide, 5-FU, and/or epirubicin	Open trial, $n = 100$, 2 g t.i.d., fatigue and QOL improved by ashwagandha versus no additional treatment	Biswal 2013[e]

[a]Chen MH, May BH, Zhou IW, et al. Meta-analysis of oxaliplatin-based chemotherapy combined with traditional medicines for colorectal cancer. Integr Cancer Ther 2016;15:40–59.
[b]Gao YH, Tang WB, Dai XH, et al. Effects of water-soluble *Ganoderma lucidum* polysaccharides on the immune functions of patients with advanced lung cancer. J Med Food 2005;8:159–168.
[c]Chen X, Hu ZP, Yang XX, et al. Monitoring of immune responses to a herbal immuno-modulator in patients with advanced colorectal cancer. Int Immunopharm 2006;6;499:508.
[d]Lissoni P, Rovelli F, Brivio F, et al. A randomized study of chemotherapy versus biochemotherapy with chemotherapy plus *Aloe arborescens* in patients with metastatic cancer. In Vivo 2009;23:171–176.
[e]Biswal BM, Sulaiman SA, Ismail HC, et al. 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.
5-FU, 5-fluorouracil; DBRPC, double-blind, randomized, placebo-controlled; FOLFOX, oxaliplatin +5-fluorouracil + leucovorin; QOL, quality of life; XELOX, oxaliplatin + capecitabine.

immunomodulators; they may have other actions that make them ideal as adjuncts to chemotherapy. Oral use of European mistletoe has no actions that would help patients with cancer and is not interchangeable with use of injected extracts.

Many studies have examined the effects of injectable mistletoe on patients undergoing cancer chemotherapy. A randomized but open trial investigated two mistletoe extracts: one grown on apple trees and the other on fir trees.[37] The trial involved 95 women with breast cancer undergoing chemotherapy with doxorubicin, cyclophosphamide, and 5-fluorouracil. A control group had chemotherapy with no mistletoe. The authors contended that a placebo could not match the local erythema and hardness that develops with mistletoe injections. Mistletoe injections were given three times weekly during the 18 weeks of chemotherapy. While these treatments were safe, improved appetite, and reduced pain scores, there was no difference in five-year survival or leukopenia between mistletoe-treated and control patients. A similar trial in 57 women with breast cancer undergoing the same chemotherapy regimen also found that mistletoe extracts did not increase overall survival at five years.[38]

On the other hand, a trial structured very similarly in 220 patients with metastatic or locally invasive pancreatic cancer undergoing chemotherapy found that injectable mistletoe doubled median overall survival from 2.7 months in the control group to 4.8 months.[39] In patients with the best and worst prognoses, overall survival was significantly higher in the mistletoe group compared to controls. No significant adverse effects accompanied the use of mistletoe injections.

In one meta-analysis of 26 randomized trials of mistletoe injectable extracts in cancer patients, 13 involved patients simultaneously undergoing chemotherapy, radiation therapy, or cancer surgery.[40] There was a significant improvement in quality of life in patients receiving mistletoe therapy compared to controls in the pooled results of these trials. Improvements were primarily due to reduced fatigue, nausea, vomiting, depression, anxiety, and insomnia. Overall, mistletoe therapy was well tolerated in these trials, other than causing local injection site reactions (which are essential to the activity of these extracts, and represent a type IV hypersensitivity reaction that is part of the anticancer immune effects of the medicine).

Clearly, more prospective trials are needed on this therapy to determine what its role is in patients undergoing chemotherapy. Future trials should probably focus on intravenous or intratumor trials that can have a true placebo control. Preliminary trials show that such routes of injection are safe, including in children.[41–43] Low-grade fever is common with intravenous injection and may be essential to activity of the medicine, indicating systemic immune effects are occurring.

Conclusion

Immunomodulating herbs and fungi, also sometimes called adaptogens, show great promise as adjunct therapies for patients undergoing cancer chemotherapy. Besides the herbs discussed in depth above, other studies suggest a range of other immunomodulators may also be beneficial (see Table 2). All these herbs may reduce or prevent adverse effects of chemotherapy, reduce resistance to it, and improve overall survival. While clearly more research is needed, the excellent safety and efficacy record for at least turkey tail, astragalus, and Asian ginseng strongly recommends their adoption into practice. It is hoped these adjunct therapies can enhance the lives of many more cancer patients over time.

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