Immune System Effects of Echinacea, Ginseng, and Astragalus: A Review

Keith I. Block, MD, and Mark N. Mead, MS

Traditional herbal medicine provides several remedies for strengthening the body's resistance to illness through effects on immune system components. This review article examines 3 popular herbal immune stimulants that are often of interest to cancer patients. Echinacea, a native of North America, is widely used to prevent, or provide early treatment for, colds. Preclinical studies lend biological plausibility to the idea that echinacea works through immune mechanisms. Numerous clinical trials have been carried out on echinacea preparations: it appears that the extracts shorten the duration and severity of colds and other upper respiratory infections (URIs) when given as soon as symptoms become evident. However, trials of long-term use of echinacea as a preventive have not shown positive results. Ginseng has been studied in some depth as an antifatigue agent, but studies of immune mechanisms have not proceeded so far. Preclinical evidence shows some immune-stimulating activity. There have been several clinical trials in a variety of different diseases. Astragalus is the least-studied agent. There are some preclinical trials that show intriguing immune activity. The herbs discussed appear to have satisfactory safety profiles. Cancer patients may wish to use these botanicals to inhibit tumor growth or to boost resistance to infections. However, passive immunotherapy with herbs, with no mechanism to expose tumor antigens, is unlikely to be effective in inhibiting tumor growth. Although the margin of safety for these herbs is large, more research is needed to demonstrate the clear value of using herbs to improve resistance to infections.

Keywords: ginseng; echinacea; astragalus; immune system; cancer; upper respiratory infections

In recent years, natural products from the plant kingdom have been investigated for their immune-modulating potential against infectious and neoplastic diseases. Herbal therapy, or "phytomedicine," the therapeutic use of plants, plant parts, or plant-derived substances, is generally considered a form of complementary medicine.[1,2] Herbal agents can comprise the whole plant as well as any of its component parts: leaves, flowers, stems, seeds, roots, fruits, bark, or other parts used for therapeutic impact, food flavoring, or fragrance. In traditional medical systems different plant parts are believed to have specific medicinal properties that were identified over centuries of trial-and-error observation.[3] Among these properties are the ability to stimulate the body's disease-fighting mechanisms, including those now considered facets of the immune system.

Within the US population, there is widespread interest in the therapeutic and preventive potential of herbal agents.[4,5] Recent estimates of the size of the US herbal market range from $3.2 billion to $5.1 billion.[6,7] From 1993 to 1998, according to surveys conducted by Eisenberg and colleagues, the proportion of Americans who sought out a provider of herbal medicine grew from 10.2% to 15.1%.[8,9] The proportion of people who self-prescribe is considerably larger, as herbs are commonly perceived by the public as having a high margin of safety.[10] The potential impact on public health is unknown but could be substantial, given that these products can be readily purchased at health food stores, pharmacies, and supermarkets.[11] Several national polls in 1997 and 1998 reported that 32% to 37% of Americans use herbal agents in any given year.[6,12] These percentages appear to be much higher in Germany and other European countries where consumer demand has been more vigorous and where herbal agents are more widely accepted by medical professionals.[13,14] Ginseng and echinacea are among the herbs reported to be used most widely. For instance, a recent study of women aged 40 to 60 years at an urban university hospital found that 18% reported use of ginseng, and 15% use of echinacea.[15] Use of complementary medicine in cancer patients undergoing conventional cancer treatment in the

KIB is at the Institute for Integrative Cancer Care and Block Center for Integrative Cancer Care, Evanston, Illinois; the Department of Family Practice, University of Illinois College of Medicine, Chicago, Illinois; and the Program for Collaborative Research in the Pharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago. MNM is at the Institute for Integrative Cancer Care and Block Center for Integrative Cancer Care, Evanston, Illinois.

Correspondence: Keith I. Block, MD, Institute for Integrative Cancer Care and Block Center for Integrative Cancer Care, 1800 Sherman Avenue, Suite 515, Evanston, IL 60201. E-mail: research@blockmedical.com.

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United States is high, with some studies reporting as many as 80% of cancer patients using complementary and alternative medicine practices, including 54% reporting use of herbal products. Echinacea was among the herbal products most frequently used.[16]

From the perspective of Western herbal medicine systems, herbal remedies that affect the immune system may be classified as either adaptogens or immunostimulants, or both. *Adaptogens* include substances that are reputed to increase the body's resistance to physical, chemical, and biological stressors. *Immunostimulants* (immunopotentiators, immune enhancers), as opposed to immunosuppressors, are agents that activate the body's nonspecific defense mechanisms against infectious organisms (notably viral and bacterial pathogens) or against neoplastic cells. The primary goal of immunotherapy is to stimulate the activity of immunologic cells that are in direct local contact with neoplastic cells or infectious agents.[17] In general, it is claimed that herbal immunostimulants have minimal effects on the normal immune response, but may help rectify the moderately compromised cell-mediated immune response.[18,19]

Herbal agents are claimed to have therapeutic efficacy for a variety of immune-related problems, ranging from upper respiratory infections (URIs) to autoimmune and neoplastic disorders. Based on early studies, some of these plant extracts appear to affect humoral (acquired) immunity, but most appear to enhance cellular (innate or natural) immunity. Changes in humoral immunity would include mitogenic effects on B lymphocytes (increased proliferation) and production of specific types of antibodies. Changes in cell-mediated immunity, the more common outcome in phytomedicinal studies, are measured in terms of natural killer (NK) cell number and activity, lymphokine-activated killer (LAK) cell activity, macrophage activation, phagocytic activity, and proliferation of specific T-lymphocyte subsets. The relevance of each of these parameters to specific diseases is beyond the scope of this article. However, there is some evidence that natural immune mechanisms can be modulated to impede the development and progression of certain infectious and neoplastic diseases.[20,21] Cancer patients commonly seek complementary and alternative medicine (CAM) remedies to "boost the immune system," sometimes with the notion that this will retard tumor growth. However, other than for cancers known to be affected by the immune system, such as renal cancer and melanoma, the impact of the immune system on malignancy is questionable.[22] Active immunotherapy utilizing tumor antigen exposure and presentation to immune cells, followed by effector cell response, could conceivably benefit various solid tumors. More passive immunotherapy approaches such as those represented by herbal supplements are less likely to have direct effects in most cancers. The role of immune activities arguably has more relevance in resistance to community-acquired respiratory viruses, which, it has recently been noted, contribute to many cases of idiopathic pneumonia that affect cancer patients, with commonly fatal consequences.[23] This finding makes the clinical role of immune stimulating herbs, as agents that may potentially aid in resisting the effects of such viral illnesses, one of strong relevance to the health, well-being, and ultimately the survival of these patients.

Echinacea, Ginseng, and Astragalus in Alternative Cancer Treatment

Among the herbal agents thought to function (at least in part) as immunostimulants are echinacea, ginseng, and astragalus (Table 1). Echinacea and astragalus are considered to be immunostimulants, with echinacea extensively studied in the United States and Europe, and research on astragalus coming primarily from China. Ginseng, widely researched in Asia and elsewhere, is considered both an immunostimulant and an adaptogen, although most research to date has focused on the latter characteristic.

All 3 herbs are recommended in alternative and traditional medicine literature for cancer patients. Echinacea is recommended by practitioners of Western alternative medicine methods. For example, taking several capsules of echinacea each day to increase lymph flow is recommended by a naturopathic doctor in one Internet site.[24] Another naturopathic doctor recommends it for prostate cancer, along with several other herbs that are typically characterized as cleansing, or able to rid the body of foreign substances, including pathogenic organisms.[25] A further Internet site recommends echinacea as one of the herbs that can stimulate the immune system to fight cancers, and also notes its cleansing nature.[26] Ginseng and astragalus are associated chiefly with traditional Chinese medicine recommendations. Such recommendations are fairly commonly consulted by cancer patients interested in alternative and integrative medicine. Ginseng and astragalus are both recommended for replenishing of qi (vital energy or the instigator of body functions, a concept closely linked to immunity) in Chinese traditional medicine texts on fu-zheng therapy, or anticancer therapy aimed at increasing the body's resistance to cancer.[27] Other specific functions attributed to these herbs are increasing the numbers of white blood cells and enhancing immunological functions. The first author of this article has observed

Table 1. Three Herbal Immunostimulants

Herb or Extract	*Key Constituents*	*Pharmacolgic Actions*	*Primary Traditional Medicine Uses*
Echinacea purpurea, E. Angustifolia, E. pallida	Polysaccharides, glycoproteins, alkamides, cichoric acid (a derivate of caffeic acid)	Stimulation of cell-mediated immune mechanisms	Used for treatment of upper and lower respiratory infections, pelvic infections
Panax ginseng	Ginsenosides, essential oils, phytosterols	Stimulation of cell-mediated immune mechanisms; effects on cardiovascular and neuroendocrine systems	Used primarily for coping with physical and mental stress; increasingly used as adjunct to cancer therapy
Astragalus membranaceus	Asparagine, calycosin, cycloastragenol, astragalosides, betaine, kumatakenin, glucuronic acid, β-sitosterol, soyasaponin, formononetin astraisoflavan	Stimulation of cell-mediated immune mechanisms; effects on cardiovascular and neuroendocrine systems	Used as an adjunct to cancer therapy and to the treatment of immunodeficiency disorders. Used in treatment of a wide variety of infections

cases in the clinic that appear to support the benefits of these herbs in cases of treatment-induced neutropenia. Both herbs appear in numerous herbal formulas for specific aspects of a variety of cancers, chiefly the formulas that are used to replenish qi and yin and strengthen resistance.[27]

An examination of scientific evidence concerning the immune function of these herbs would help health practitioners in counseling patients interested in their use. This review examines the effect of each of these herbs on immune function in experimental animal models as well as in humans and explores their proposed modes of action. Also addressed are the strengths and limitations of studies that have focused on the potential efficacy of the agents in the treatment of immune-related disorders. The amount and quality of the evidence for the use of herbal agents in cancer, both for affecting the course of malignant disease and for prevention or treatment of infections in late-stage patients, will be discussed. It is hoped that such information will encourage further research in the use of herbal agents and improve our understanding of their potential impact on cancer treatment and management.

Echinacea

Background on Echinacea

The genus *Echinacea* (coneflower, family Asteraceae) is endemic to North America, where it was first used by Native Americans in the Great Plains region and later adopted by White settlers. Echinacea preparations, commonly perceived as herbal immunostimulants or "cold fighters," are among the most widely used dietary supplements in Europe and the United States.[28] Echinacea-containing products have the greatest popularity in Germany, where they are approved for supportive treatment of respiratory and urinary infections and for the external treatment of wounds.[29] More than 800 echinacea-containing products and phytopharmaceuticals (plant-based medicines, including homeopathic preparations) are currently on the market,[30,31] and more than 3 million prescriptions containing echinacea are written by German physicians annually.[32,33] The presence of echinacea products in the German market meant for intravenous administration should be noted; such products are not available in the United States.

Different preparations sold under the common name echinacea can show substantial disparities in composition. These variations are primarily due to different species of echinacea as well as different modes of extraction, though some preparations also include other substances such as goldenseal and ascorbic acid (vitamin C). Three species are commonly used medicinally: *Echinacea purpurea* (L.) Moench, *E. angustifolia* DC., and *E. pallida* (Nutt.) Nutt. Preparations of the root and of the above-ground parts of the 3 echinacea species are all marketed as immune stimulants. It has been suggested that echinacea preparations may be useful in the treatment of URIs (eg, colds and flu),[34,35] infections with *Candida albicans* and *Listeria monocytogenes*,[36] chronic pelvic infections,[27] chronic fatigue syndrome,[37] herpes infections,[38] cancer,[39,40] chronic arthritis,[41] and a variety of skin diseases, wounds, and ulcers.[42] To date, more than 400 papers, mostly in German, have been published on the biochemistry, immunopharmacology, and clinical uses of *E. purpurea*, and to a lesser extent *E. angustifolia* and *E. pallida*.[18,26,31,43-46]

This literature must be regarded with extreme caution, however, due to the excessive chemical variability of echinacea preparations. Numerous phytochemicals in the 3 species have been suggested as possible active components: a recent study quantified cichoric acid and some of the echinacea alkamides, proposed active constituents, in 25

commercial preparations in Germany. The cichoric acid and alkamide levels were found to vary substantially among various commercial echinacea preparations, depending upon the species, plant part, and type of extract. Preparations comparable as to botanical origin were found to vary chemically among different manufacturers.[47] In a further example of the complications of using echinacea preparations, an in vitro study of echinacea herb and root, as well as preparations standardized to phenolic acid or echinacoside contents, found that the unstandardized preparations enhanced murine macrophage cytokine secretion and improved the viability and proliferation of human peripheral blood mononuclear cells; the standardized preparations were immunologically inactive, although they did have antioxidant and anti-inflammatory activities.[48] Lack of agreed understanding of the specific mechanisms of action of echinacea preparations, and of the importance of various alleged active constituents, will continue to limit the accuracy and reproducibility of clinical trials until these problems are resolved.

Preclinical Studies of Echinacea

The reputed immune-enhancing effects of echinacea are thought to be mainly directed toward nonspecific immune mechanisms including phagocytic activity, macrophage activation, and NK cell activity. These effects have been demonstrated in vitro and in animal studies for the expressed juice of the upper plant parts of *E. purpurea* as well as for alcoholic extracts of the roots of *E. purpurea*, *E. angustifolia*, and *E. pallida*.[49,50] Among the constituents of echinacea species reported to have immunologic activities are polysaccharides, glycoproteins, alkamides, and cichoric acid (a derivative of caffeic acid).[50] Purified polysaccharides of *E. purpurea* were found to induce macrophage activation and increase phagocytic activity in vitro and in vivo in mice.[51,52]

Reports of enhancement of immune function have suggested that such effects could be mediated by increased monocyte secretion of several cytokines, including tumor necrosis factor-alpha as well as interleukins 1, 6, and 10.[53] However, another study found no evidence of increased levels of cytokines for echinacea-supplemented cultures of leukocytes from cancer patients.[54] By inducing acute phase reactions and activation of phagocytes, *E. purpurea* polysaccharides were observed to augment the resistance of immune-compromised mice against systemic infections with *Candida albicans* and *Listeria monocytogenes*.[32] In mice given the croton oil ear test (to induce inflammation), *E. angustifolia* inhibited the infiltration of inflammatory leukocytes and reduced edema.[55,56] An *E. purpurea* preparation was found to increase significantly the number of NK cells in leukemic mice and to prolong survival time in treated mice.[57] An arabinogalactan-protein fraction isolated from *E. purpurea* was found to stimulate the classical and alternative pathways of complement activation.[58]

Finally, rats treated with *E. angustifolia* showed an increased production of the specific antibody subclass, immunoglobulin G (IgG), following antigenic challenge.[59] However, another study, which used commercial echinacea preparations and echinacea tinctures marketed by local herbalists, found that antibody formation was suppressed in the female but not the male rats in the study; no evidence was found for altered NK cells or T-cell-mediated delayed-type hypersensitivity.[60] In general, immune stimulators are thought to have no antigenic relationship to specific pathogens, and thus their action is nonspecific (cell-mediated via macrophages, leukocytes, and granulocytes). Responses of other antibody subclasses remain to be investigated. Thus, effects in cell-mediated immunity appear to be the primary immunomodulatory activity of echinacea preparations.

Echinacea extracts and phytochemicals have been observed to display other properties that may be relevant to effects on disease resistance seen in traditional use or clinical testing. These include antiviral[61] and anti-inflammatory[62,63] activities.

Clinical Studies of Echinacea

Homeopathic Preparations

In 5 randomized controlled clinical trials (RCCTs; using a placebo control, and either single-blind or double-blind designs), Melchart et al studied the immunomodulatory activity of various echinacea preparations in healthy males (18-40 years old) who had not taken any immunomodulating drugs in the previous 2 weeks.[64] They reported increased phagocytic activity for men receiving either the oral alcoholic extracts of the *E. purpurea* root or intravenous homeopathic complex preparations containing *E. angustifolia*. The benefit obtained from the homeopathic remedies may seem perplexing given that such preparations assign only extremely small doses: the original base substance must first undergo a series of dilutions in alcohol or water.[65] However, several well-designed controlled trials of homeopathy have demonstrated therapeutic efficacy for a variety of health problems, so it is not possible to rule out effects of homeopathic preparations at this time, despite lack of comprehension of any confirmed mechanism of action.[66-69]

Effects in Healthy Individuals

Some studies have examined the immune effects of echinacea in healthy individuals. A placebo-controlled, double-blind randomized trial in which echinacea extracts were given to healthy females observed a significant 21% increase in complement properdin as well as an improvement in health-related quality of life as measured by the SF-36 form after 4 weeks of administration.[70] In another trial, with a double-blind randomized crossover design, expressed juice of enchinacea had no effect on phagocytic activity of polymorphonuclear leucocytes or of monocytes and did not influence production of TNF-α or IL-1β, even though increases in phagocytic activity have been reported in vitro.[71]

Herbal Extracts: Cancer and Other Diseases

Clinical trials of echinacea preparations have been conducted in a variety of conditions. Lersch et al reported on several uncontrolled trials of "far advanced" cancer patients showing extensive metastases and who had become immunosuppressed following conventional cancer therapy.[39,40,72] In these studies, modest clinical and immunologic improvements were noted in several cases following immunotherapy that included *E. purpurea* and thymostimulin (a thymus-stimulating agent), and low-dose cyclophosphamide, which has been reported to counteract tumor-induced suppressor functions. In one of these studies, the combination of these 3 agents increased the activities of LAK cells by 180% ($p < .05$) among patients with inoperable, far-advanced liver cancer.[40] It is not possible, however, to disentangle the effects of echinacea from those of the other immune modulators in the studies reported by Lersch, nor can one determine to what extent the immunologic changes in these studies influenced the course of disease. Controlled trials using larger groups of patients would be needed to assess the validity of these findings. In a comparative study of healthy individuals and immunocompromised patients (with either AIDS or chronic fatigue syndrome), increased cellular immunity resulted in both groups after in vitro exposure of the patients' NK cells and other peripheral blood monocytes to *E. purpurea*.[37] *E. purpurea* extract did not decrease the frequency or severity of attacks of recurrent genital herpes in a randomized, placebo-controlled crossover trial.[73] A polysaccharide isolated from *E. purpurea* was administered intravenously to 15 patients with advanced gastric cancer, starting 3 days prior to chemotherapy. Outcomes were compared to historical controls. Leukocyte number 2 weeks after chemotherapy was significantly higher in the experimental patients than in the historical controls, but no impact on phagocytic activity or lymphocyte subpopulations was observed.[74]

Herbal Extracts: Upper Respiratory Infections

Fluid extracts of *E. purpurea* are currently most often used for the relief of colds and other URIs. Numerous RCCTs have examined the role of echinacea preparations in the treatment of acute URIs after onset of symptoms. Twelve of these studies demonstrated a significant reduction of the duration and/or severity of URIs following echinacea treatment.[75-86] Two treatment studies showed a trend toward significance,[87,88] and 2 showed no significance.[89,90] In the area of prevention, only 2 out of 6 studies found a significant reduction in the risk of developing URIs with regular use of echinacea.[91,92] Four other risk studies were nonsignificant.[93-96] Giles et al published in 2000 a systematic review of clinical studies including both treatment and prevention designs.[97] The majority of studies (13 of 15) indicated effectiveness in treatment of URIs, but the authors concluded that the results overall were inconclusive due to deficits in study design and use of nonstandardized dosage forms.

A discussion of some of these studies provides some insight into the problems with these clinical trials. Among the treatment studies, Braunig and coworkers studied the efficacy of 2 different doses (450 mg/day and 900 mg/day) of expressed juice of *E. purpurea* roots compared to placebo in 180 volunteers with recent-onset colds and URIs.[77] There were 60 participants in each of the 3 groups—placebo, low-dose, and high-dose—and each of the latter 2 groups received twice daily doses of either 1 dropperful (about 4.5 ml) or 2 dropperfuls (about 9 ml) of echinacea juice. The main parameters for assessing efficacy, as recorded by the investigators, included a sum score of 8 symptoms (cough, sore throat, nasal symptoms, fatigue, headache, tearing, sweats, or chills) and 1 global indicator of severity rated on a 0 to 3 scale as either absent, mild, moderate, or severe. Assessments of efficacy were done after 3 to 4 days and again after 8 to 10 days of follow-up. Whereas the lower dose of echinacea had little impact (not significant), the higher dose of *E. purpurea* root extract significantly improved the sum score of patients' symptoms and clinical findings at both follow-up times. This is the only study to date that has reported a dose-dependency effect of echinacea on URIs.

The same investigators also conducted a placebo-controlled, double-blind study that compared the efficacy of an ethanolic extract of *E. pallida* roots (900 mg/day) and placebo juice for reducing symptoms and infection duration in 160 patients with colds and upper respiratory infections.[76] The investigators treated and observed all participants for 8 to 10 days and categorized colds and URIs as either viral or bacterial infections. For bacterial infections, there was a significantly shorter mean infection duration of 9.8 days

in the echinacea group compared to 13.0 days in the placebo group. For viral infections, the mean duration was 9.1 days in the echinacea group compared to 12.9 days in the placebo group. However, as in their previous study, the investigators did not report details concerning their randomization methods, the drop-out rate for participants, or the adequacy of patients' and physicians' blinding.

Hoheisel et al carried out a double-blind controlled trial of Swedish adults recruited at the first sign of URI, but before a full cold had developed.[80] The 120 participants were randomly assigned to either placebo or echinacea (called either Echinagard or Echinacin, a commercial preparation made from the juice from the above-ground parts of *E. purpurea*) and were followed up until symptoms had resolved. Participants were instructed to take 20 drops every 2 hours for the first day, and 3 times per day thereafter. The investigators reported that 40% of the echinacea group developed a "real cold," compared with 60% of the placebo group. Among those participants who developed a real cold, the median time to resolution was 4 days in the echinacea group and 8 days in the placebo group. Among the main limitations of this study were poorly defined inclusion and exclusion criteria and lack of evidence of indistinguishability between the placebo and echinacea preparations. Also, as noted by Grimm and Muller,[93] one must question the use of retrospectively defined criteria for progression from "first sign of a cold" to "real cold."

In another recent study, Brinkeborn et al treated approximately 119 participants for 8 days with 3 doses of 2 tablets each of Echinaforce, a dried ethanolic extract of *E. purpurea*.[81] An "overall clinical picture" and 10 URI symptoms were assessed by physicians on a severity scale of 0 to 3 on day 1 or day 2 of an acute URI. Based on an intention-to-treat analysis, there was a statistically significant improvement in relief of URI symptoms, with an indexed score declining from 9.0 to 4.1 in the treatment group and from 8.8 to 5.3 in the placebo group ($P = .045$). However, the investigators did not adequately report their inclusion criteria, exclusion criteria, and verification of randomization and blinding procedures. The construction of the index was, moreover, not explained, and the definition of "an overall clinical picture" could be subject to inconsistent or unreliable interpretation.

The problem of heterogeneity of echinacea mixtures (hence lack of comparability between studies) is exemplified in a randomized double-blind trial by Dorn.[83] One hundred participants were recruited within 2 days of URI onset. Each participant received 30 ml of either echinacea or placebo on the first and second day, and 15 ml from the third to the sixth day. The outcomes were scored on a 0- to 3-point scale (none, mild, moderate, severe) and included 7 self-reported symptoms as well as several physician-recorded signs. For echinacea versus placebo, there was a significant reduction in symptoms of sore throat, cough, pharyngitis, and running nose. The echinacea preparation in this study consisted of Resistan, a commercial preparation made primarily from *E. angustifolia* herb and root but also containing extracts from *Eupatorium perfoliatum*, *Baptisia*, and *Arnica*. This study's findings may be comparable to the one other Resistan study[78] but not to the majority of echinacea studies, which focused on *E. purpurea*. The same principle applies to the other commercial preparation, Esberitox, which contains *E. purpea* and *E. pallida* along with *Baptisia* and *Thuja* occidentalis.

Reitz followed 150 URI patients who received Esberitox-N.[88] Outcomes consisting of 8 symptoms, 3 signs, and comprehensive blood work were measured at 7 and 14 days, and monthly thereafter. The majority of symptoms and signs at 7 and 14 days were claimed to be significantly better in the Esberitox group compared to placebo. In the report, however, the author provided little statistical analysis to support this conclusion. Whether echinacea was the active herb in this preparation cannot be determined.

Placebo controls in some studies have sometimes included agents that may protect against colds, or immunologically active ingredients. The studies by Reitz,[88] Vorberg,[87] and Vorberg and Schneider[82] used a placebo containing vitamin C (ascorbic acid). However, in a population-based cross-sectional analysis, Ness et al reported that vitamin C may be protective against URIs throughout the whole normal range of dietary intake and lung function.[98] A number of clinical studies have reported that supplemental vitamin C, either alone or in combination with other micronutrients, may enhance immune function[99-103] and reduce the risk of respiratory infection.[104-108] The use of a vitamin with known immunostimulating properties would seem to undermine the intended purpose of a placebo. Equally problematic is the addition of vitamin C to a number of echinacea preparations, which raises questions of either synergisms or additive effects. The issue of possible interactions between echinacea and other nutrients must also be considered, as nutritional influences on susceptibility to infection or on the ability to combat infection are well-documented.[109,110]

A well-conducted double-blind, randomized placebo-controlled trial conducted by Barrett et al,[90] involving 148 students, also used an unrefined echinacea preparation consisting of *E. purpurea* herb and root and *E. angustifolia* root, in doses of 1 gram of powdered material. The preparation was taken 6 times on the first day of self-reported common colds and 3 times daily

thereafter. No differences between the echinacea and placebo groups on outcomes of severity, and self-reported symptoms were observed. The mean duration of colds was not significantly different. Associated with this trial was the development of a new survey instrument for detecting the severity of cold symptoms; validity testing is planned for this instrument.[111] Availability of a validated symptom assessment questionnaire for studies of this sort should contribute significantly to future research on echinacea.

In contrast with the studies of echinacea's therapeutic efficacy, there is little evidence supporting the prolonged use of echinacea for the *prevention* of URIs. Inadequate sample sizes may have accounted for the null findings of several prevention trials.[91-96] Forth and colleagues estimated a relative risk reduction of 38% for nasal symptoms in echinacea versus placebo groups, but the sample size may have been too small (n = 95).[91] Schmidt and coworkers reported a 15% lower incidence of infection (for echinacea versus placebo, n = 646) that approached but did not reach statistical significance ($P = .08$).[92] A subgroup analysis of those participants judged to be more prone to infection (3 or more colds per year for each of the previous 3 years) showed a statistically significant relative risk reduction in echinacea versus placebo.

Grimm and Muller randomly assigned 109 patients to either *E. purpurea* (4 ml fluid extract) or placebo juice twice a day in a double-blind manner for 2 months.[93] All patients had reported a history of at least 3 colds or other URIs in the preceding year. Each patient's physical and hematologic examinations were performed at baseline, after 4 weeks, and at the final visit 8 weeks after enrollment. Patients were instructed to notify their physician of typical URI signs or symptoms such as tearing eyes, earache, loss of hearing, stuffed or runny nose, sore throat, coughing, headache, or general weakness or tiredness. After 2 months, there was a nonsignificant 12% reduction in the relative risk of developing URIs in the echinacea group. The average number as well as mean duration and severity of URIs indicated protective trends for the echinacea group, but these trends were not statistically significant.

In their report, Grimm and Muller acknowledged that the size of the study sample was not large enough to detect small to moderate differences in the incidence and severity of URIs between the echinacea and placebo groups. Statistical power may have been enhanced by the use of all types of URIs; however, by mixing different types of infections together, it is possible that the intervention had an impact on one outcome, such as colds, that was obscured by a lack of impact on the other URIs. In addition, there were substantial differences in the baseline characteristics of patients, such as more women, more patients with influenza vaccination, and fewer patients who engaged in regular sports activities in the echinacea group. With the relatively small sample size, such differences could have markedly affected the association of the use of echinacea with the risk of URIs. Moreover, in their analysis, the investigators did not adjust for differences in baseline characteristics between the treatment groups.

In the study by Turner et al,[96] 117 patients were treated with 300 mg of an echinacea preparation for 14 days prior to being challenged with infective rhinovirus. Viral infection was documented by viral culture and antibody responses, as well as a measure of cold severity. Rhinovirus infection occurred in 44% of echinacea-treated and 57% of placebo-treated groups ($P = .3$); 50% of the echinacea-treated and 59% of the placebo-treated groups developed colds. Echinacea treatment did not affect symptom scores. Power calculations for the study showed that it had a 75% power to detect a reduction in cold incidence from 59% to 20%, a size of reduction that may be overly optimistic. Phytochemical analysis of the echinacea preparation showed that it contained 0.16% cichoric acid but no echinacosides or alkamides. The methodology of Turner et al is admirable in the precision with which they were able to induce and assess presence of colds: they did not rely on potentially inaccurate passive reporting of colds, which has been the usual pattern of other prevention studies. They point out, also, that none of the prevention studies (and few of the treatment studies) used chemically characterized extracts.

Despite the modest methodologic quality of the majority of echinacea trials, one may conclude that there is evidence for a beneficial effect of echinacea on URIs. It is plausible that echinacea could exert some effects against other forms of infection as well as URIs; however, the current reputation of echinacea as a "cold remedy" has narrowed the research focus and diverted attention from echinacea's potential impact on other types of infection. As Barrett observed in a recent review,[112] preclinical studies have demonstrated immunomodulatory effects of echinacea, including phagocytic leukocyte and NK cell activation, macrophage activation, and changes in number and activity of T- and B B-cell leukocytes. The actual role of these effects in the results observed with URIs, however, has not yet been elucidated.

Safety and Quality Concerns

Safety of echinacea has recently been reviewed.[113] None of the clinical trials of echinacea has reported higher rates of adverse effects in the treatment than in the placebo groups. There is some concern, however, with allergic reactions to echinacea, particularly

among atopic patients. Cases of atopic patients experiencing reactions to echinacea without prior exposure raise the possibility of cross-reactivity.[114] No colchicine was found in validated echinacea samples in a recent phytochemical analysis of 26 samples of ginkgo and echinacea purchased from pharmacies in Chicago,[115] in contrast to a previous report suggesting the presence of colchicine in these products (which would not be expected from chemotaxonomy or previous chemical analysis). Quality of echinacea preparations, however, is far from completely satisfactory. In a recent analysis of commercially obtained echinacea, only half of the samples showed chemical evidence of containing the species listed on the label, whereas 10% had no discernable echinacea content.[116] No evidence of herb-drug interactions was found for echinacea in a recent systematic review.[117]

Ginseng

Background on Ginseng

Ginseng, meaning "man-root," is a slow-growing root herb that has been used medicinally for more than 3000 years by practitioners of traditional Chinese medicine (TCM).[118] Touted by many TCM-trained physicians as the "root of longevity," ginseng is considered to be an adaptogen, a substance thought to enhance the body's ability to resist physical and mental stress.[119,120] Traditional herbalists also consider it to be a "general tonic," a substance that helps protect the body against disease, much as one would expect from an immunostimulant.

Several species are commonly referred to as ginseng. The 3 most commonly used are Asian or Korean ginseng (*Panax ginseng* C.A. Meyer [Araliaceae]), American ginseng (*Panax quinquefolius* L.), and Siberian ginseng, more properly called "eleuthero" (*Eleutherococcus senticosus* Maxim. [Araliaceae]). The *Panax* species are sometimes considered "true" ginseng; eleuthero is not in the same genus but comes from the same family and has effects reputedly similar to those of the *Panax* species. As a result, all 3 forms are typically lumped together as "ginseng" and used interchangeably in Western countries. Other species, quite unrelated to the Araliaceaeous ginsengs, are also called "ginsengs" in commerce and are asserted to have similar effects. All mentions of the term *ginseng* in this article that are not further specified will refer to *Panax ginseng*, the most prominent and best-studied of the ginseng species. American ginseng will refer to *P. quinquefolius*, whereas eleuthero will refer to *E. senticosus*.

The main active components of ginseng are glycosidal saponins (glycosylated steroids) known as ginsenosides. In *P. ginseng*, 36 different ginsenosides and many minor constituents (essential oils, phytosterols, amino acids, peptides, vitamins, and minerals) have been extracted and isolated from the root, stem, and leaves.[119] Cui et al reported that the ginsenoside content of 44 different ginseng products varied by more than 4-fold (from 2% to 9%).[121] In another study, which examined products sold as "ginseng," the contents of ginseng per capsule, when measured by weight, varied by more than 6-fold, and the ginsenoside content per capsule varied by more than 20-fold.[122] However, the latter study may not have distinguished eleuthero from true ginseng products. Eleuthero contains low concentrations of saponins and no ginsenosides.[123] Another recent effort at assessment of the chemical contents of ginseng preparations, the Ginseng Evaluation Program, analyzed multiple lots of 13 standardized ginseng products to determine the extent to which they met label claims as to percent ginsenosides contained in the products. If no claim as to percent ginsenosides was made, the level of 4% ginsenosides was used as a comparison standard.[124] Of the 8 products that made specific claims, 4 contained the claimed levels of ginsenosides in 80% to 100% of the lots analyzed. For those products that did not make specific claims of ginsenoside contents, 4 of 5 met the standard of 4% total ginsenoside content in all lots tested. Substantial variation does, thus, exist even among standardized products in the reliability of product claims. Unstandardized products may be assumed to be even more variable.

Preclinical Studies of Ginseng

In the discussion of preclinical and clinical work on ginseng, we will concentrate on studies of the effects of *P. ginseng* on immune parameters. Based on extensive in vitro and in vivo studies, the main activities of ginseng can be summarized as follows: immunostimulation, increased antitumor activity, improved cardiovascular function (vasodilation and reduced platelet aggregation), antioxidant activity (increased oxygen radical-scavenging and decreased lipid peroxidation), hypoglycemic activity, and stimulation of the pituitary-adrenocortical system (steroidal effect).[125,126] Mitigation of oxidative stress, or excessive free-radical damage, may be especially relevant. Many ginsenosides function as antioxidants that protect the outer membranes of cells, particularly nerve and immune cells.[127] The cell membranes of circulating lymphocytes have a very high phospholipid content, rendering them vulnerable to oxidative damage. High concentrations of reactive oxygen intermediates, such as superoxide and hydrogen peroxide, can suppress NK activity,[128-130]

whereas antioxidant micronutrients have been reported to enhance immune function in laboratory and human studies.[131-134]

Panax ginseng has been examined for its immunomodulatory properties in vitro and in animal studies. In vitro, ginseng activated macrophages to produce reactive nitrogen intermediates and become tumoricidal.[135] Ginseng enhanced the activity of macrophages in mice infected with *Candida albicans*[136] and in mice exposed to the cold-water swim stress, which causes immunosuppression.[137] Ginseng also stimulated basal NK cell activity following subchronic exposure and helped stimulate recovery of NK function in mice that had become immunosuppressed via cyclophosphamide treatment.[138,139] These studies did not find that ginseng enhanced mitogen-induced T-lymphocyte proliferation. Similarly, treatment with ginseng had no effect on cell-mediated immune responses during viral infection[140] and actually suppressed T-cell proliferation in vitro.[141] Mouse macrophages were exposed to ginseng and eleuthero and chemokine and cytokine secretion measured. Significant but probably biologically irrelevant increases in IL-2 expression were observed for ginseng but not eleuthero. No changes in IL-1β, IL-15, TNF-α, or MIP-1α mRNA were observed for either plant.[142] Other studies, however, reported that ginseng stimulated mitogen-induced lymphoproliferation[143] and enhanced the graft-versus-host reaction and expulsion of *Trichinella spiralis* in mice.[144] Ginseng treatment also increased the resistance of athymic rats to *Pseudomonas aeruginosa* pneumonia (a lung infection mimicking cystic fibrosis that is virtually impossible to treat with antibiotics), probably via a cell-mediated mechanism. Observations included changes in IgM, lung IL-4, IFN-γ, and TNF-α.[145-147] Controlled experiments in farm animals indicate that ginseng has adjuvant effects in stimulating antibody responses to immunization against various pathogens in cattle and pigs[148-150] and that subcutaneous ginseng extract injections increased phagocytosis and oxidative burst activity, as well as numbers of monocytes and lymphocytes in injected cows with subclinical mastitis; a trend toward reduced bacteria counts in milk from treated animals was noted.[151]

Multiple immune functions may be simultaneously activated by ginseng,[122] although some studies suggested that the immunologic effects are relatively selective for NK cell activity.[152,153] Such disparities may have arisen from differences in dose levels, exposure duration, or composition of the extract (total ginseng or ginsenoside content) between the studies. One intriguing study by Mizuno et al indicated that immunomodulating effects of wild *Panax ginseng* may be substantially stronger than those of cultured or domesticated *Panax*.[154] Whereas hot-water soluble extracts of wild ginseng resulted in increased lymphocyte proliferation in vitro, extracts from cultured ginseng did not. In mice, the percentages of T-helper and cytotoxic T cells were significantly higher in animals treated with wild versus cultured ginseng. The effects of individual ginsenosides on immune function have also been studied. One ginsenoside (Rg1) enhanced interleukin-2 activity, a stimulator of T-cell proliferation, in cell culture[155] and in aged rats.[156] In vitro studies suggested that ginsenosides Rg1 and Rb1 were able to stimulate the proliferation of human granulocyte-macrophage progenitor cells.[157]

Clinical Studies of Ginseng

More than 300 scientific papers have been published on ginseng and its diverse therapeutic effects, emphasizing enhancement of performance and diminution of fatigue. Based on the findings of 15 controlled trials, Schulz et al conclude that ginseng users show significant improvements in mood, as well as in physical and intellectual performance.[19] Two recent systematic reviews, by Vogler et al and by Bahrke and Morgan, have evaluated these studies.[158,159] They point out numerous problems with the design of the clinical studies and suggest that the performance-enhancing effects of ginseng is not currently supported by the available evidence and that considerable advances in study design and use of standardized preparations will be necessary to validate these effects.

Relatively few clinical studies have focused on the possible immunomodulating properties of ginseng. Liu et al reported that the ginsenoside Rg1 stimulated proliferation of lymphocytes drawn from 10 young and 19 elderly persons; Rg1 also significantly increased the fluidity of lymphocyte membranes of these individuals.[160] Such increased fluidity, possibly attributable to the antioxidant activity of ginsenosides, has been reported to enhance cellular immune function in studies with other natural substances.[161,162] In a double-blind, placebo-controlled trial of 20 healthy adults, Scaglione et al reported that ginseng extracts led to significantly increased phagocytic activity and chemotaxis of peripheral blood mononuclear cells (PBMCs).[163] The stimulatory effect on PBMCs was also demonstrated using the whole ginseng extract in patients with either chronic fatigue syndrome or AIDS (acquired immunodeficiency syndrome).[37] The small size of both studies may have resulted in inadequate statistical power.

In a randomized, placebo-controlled double-blind trial, Scaglione et al followed 227 volunteers over a 3-month period who had been treated with an influenza vaccine plus either placebo or 100 mg of a standard ginseng extract called G115.[164] These participants

received the vaccination during the fourth week of the study, which took place at 3 private medical facilities in Milan. The frequency of URIs (colds and flus) showed a highly significant reduction following ginseng treatment: only 15 cases of influenza or the common cold occurred in the ginseng group, compared to 42 cases in the placebo group. In addition, antibody titers and NK activity were significant at 8 and 12 weeks: NK activity of the experimental group at both follow-up times was twice as high as that of the placebo group. The main adverse effect of the ginseng appeared to be insomnia, which was seen in 4 ginseng participants and in 1 placebo participant; 2 ginseng participants complained of nausea, whereas 1 other reported increased anxiety. This trial is of interest in view of the vaccine adjuvant activities in animals noted above.[148-151]

Cancer patients represent a unique group for the study of these agents because cancer is inherently immunosuppressive due to tumor-derived factors,[165] and standard cancer treatments (notably chemotherapy) are likewise immunosuppressive.[166] Herbal immune stimulants may be used by patients to attempt to overcome immunosuppression or to counteract the infections that are of concern among patients with advanced-stage diseases. It has been hypothesized that ginseng extracts may exert anticancer activity modulated by improvements in the cell-mediated immune system (most notably macrophage and NK cell activity), which is part of the body's anticancer defenses.[167] Lin et al randomized 63 patients with stomach cancer to chemotherapy combined with injections of an herbal combination, Shenmai, which contains ginseng, versus chemotherapy alone.[168] Shenmai treatment resulted in significantly increased T-cell and NK levels; a trend toward increased T-helper/T-suppressor ratios was also reported. In marked contrast, the control group showed decreases in each of these parameters. It should be noted that herbs used as immunostimulants in TCM are typically provided in combination with other herbs; this applies to most ginseng preparations used in TCM.[169,170] In a group of 131 patients receiving radiotherapy for nasopharyngeal carcinoma, 64 were randomly assigned to receive ginseng polysaccharide injections.[171] Clinical remission rates were similar among the treatment and placebo groups, as were overall survival and rate of disease-free and metastasis-free survival. The activities of NK and LAK cells, and T3 and T4 values in peripheral blood, were significantly higher in the treatment group. No toxic effects of ginseng injections were observed. Patients with stage 3 gastric cancer taking red ginseng were observed to have a higher 5-year disease-free survival rate than control patients in a study with 42 participants.[172] Ginseng was also associated with restoration of CD4 levels to initial preoperative values during adjuvant chemotherapy.

No clinical trials on immune effects of *Panax quinquefolius* have been located, although an in vitro study indicates increased production of cytokines in macrophages treated with *P. quinquefolius* extracts.[173] Some clinical trials of eleuthero, however, have been published. In a nonrandomized study, Vereshchagin et al studied the course of infectious disease and host immunocompetence in 258 children suffering from acute dysentery attributed to *Proteus* infection.[174] Treatment with eleuthero in combination with antibiotics was found to reduce the duration of disease when compared to antibiotics alone. In a placebo-controlled study of healthy volunteers, an experimental group received eleuthero extract daily for 4 weeks. Flow cytometric analysis showed a large increase in the number of immunocompetent cells in the experimental group, especially T-helper/inducer cells, and also increases in cytotoxic cells and natural killer cells.[175]

Safety

Safety of ginseng has recently been reviewed elsewhere.[176] The ginsengs are generally considered to have a relatively low level of adverse reactions. Possible contraindications include hypertension and use of warfarin, for which concerns with drug interactions have been noted. Some reports of adverse reactions to ginseng are attributed to adulterated or contaminated preparations. Because of ginseng's antifatigue effect, sleep difficulties may be seen if it is taken in the evening, and excessive doses may result in feelings of overstimulation.

Astragalus

Background on Astragalus

Astragalus root (*Astragalus membranaceus* Moench [Fabaceae]), an adaptogenic herb, holds an important place in traditional Chinese herbal medicine. Physicians in that system use astragalus for cardiovascular disease, and in addition for all diseases caused by "insufficient qi" (life energy) that typically include the following symptoms: feelings of weakness, fatigue, apathy, poor appetite, clammy hands, and vulnerability to infection.[177] For many centuries, the herb has been used by TCM practitioners to correct a condition referred to as "spleen deficiency,"[178] which has been associated with cellular immune dysfunction.[179] Some preliminary confirmation of these adaptogenic properties is seen in reports that it increases the production of white blood cells, notably T cells and macrophages,[180] and that it enhances both adrenal[181] and cardiovascular functioning.[182]

In the TCM system, astragalus is usually prescribed in combination with other Chinese herbs depending on the diagnosis and desired therapeutic impact. A number of Chinese herbs, collectively known as Fuzheng therapy, are used to enhance host defenses against infectious and neoplastic diseases.[183,184] Human and animal studies of astragalus, combined with other herbs in the herbal formula called Juzentaihoto (Ten Significant Tonic Decoction), report immunopotentiating effects that include increased NK activity and production of interleukins.[143] This formula was claimed to potentiate the activity of chemotherapy drugs, prevent recurrences, prolong survival time, and reduce host toxicity due to chemotherapy. However, randomized controlled trials have not been conducted to test these observations.

Major constituents of astragalus include D-β-asparagine, calycosin, cycloastragenol, astragalosides I-VII, choline, betaine, kumatakenin, glucuronic acid, β-sitosterol 1, soyasaponin I, linoleic acid, linolenic acid, and the plant pigments formononetin and astraisoflavan.[185] Certain flavonoids and saponins found in astragalus are thought to have considerable free-radical-scavenging ability.[186]

Preclinical Studies of Astragalus

In vitro and in vivo studies suggest some immune-stimulating effects. Astragalus has shown in vitro antibacterial activity against *Shigella dysenteriae*, *Streptococcus hemolyticus*, *Diplococcus pneumoniae*, and *Staphylococcus aureus*.[182] Yoshida et al reported that astragalus stimulated murine macrophages to produce interleukin-6 and tumor necrosis factor.[187] In mice infected with coxsackie B-3 virus, astragalus blocked viral replication in the myocardial tissue while improving myocardial electric activity.[188-190] In an in vitro study,[191] proliferation of peripheral blood mononuclear cells and production of cytokines and IgM were stimulated by an astragalus extract.

The success of recombinant interleukin-2 (rIL-2) in immunotherapy is limited by toxicity at higher doses. Renal cell carcinoma is a highly immunogenic cancer, which suggests that immunotherapy may have a substantial impact on this particular disease. In a study of murine renal carcinoma cells, astragalus resulted in a 10-fold potentiation in the in vitro antitumor activity of rIL-2-generated LAK cells.[192] In 2 separate studies, Chu and colleagues reported in in vitro studies that astragalus significantly potentiated the LAK cell–inducing activity of rIL-2 against a melanoma cell line: rIL-2 combined with astragalus was more effective than rIL-2 used alone with the interleukin dose increased by 10-fold.[193,194]

Mice implanted with renal cell carcinoma showed a significantly improved cure rate following treatment with astragalus and another TCM herb, *Ligusticum lucidum* Miller (Apiaceae), though the response was halved when tumor size doubled.[195] It has been proposed, based on cell culture studies, that astragalus exerts an antitumor effect via abolition of tumor-associated suppression of macrophage function.[196] Additionally, in vivo studies in mice suggest that astragalus may reverse the suppressed T-cell functions induced by the chemotherapy agents, cyclophosphamide[197,198] or mitomycin C.[199] However, this immune restorative effect was not demonstrated in a subsequent rat study of cyclophosphamide.[200] The polysaccharide astragalan, isolated from astragalus, enhanced the in vitro secretion of tumor necrosis factor in human peripheral mononuclear cells.[201]

Clinical Studies of Astragalus

Sun et al sought to determine whether astragalus root extract was capable of restoring a graft-versus-host (GVH) reaction in cancer patients.[202] The T-lymphocytes isolated from 10 cancer patients showed subnormal GVH reactions in all 10 compared to the 10 healthy controls, all with normal GVH. When the cells from cancer patients were treated with astragalus ex vivo, the GVH reaction was restored in 9 of 10 samples. In some samples, the immune restoration even exceeded that seen in normal controls. In a similar study of GVH reactions in blood samples from 13 cancer patients, Chu et al concluded that treatment of mononuclear cells with extracts and fractions of astragalus corrected the immunosuppression observed in the lymphocytes of these patients.[203]

Hou et al found that 8 grams of astragalus given orally to 14 healthy volunteers for 2 months led to a significantly increased interferon-inducing ability of blood cells as compared to controls.[204] Two months after therapy had halted, the interferon-inducing ability remained significantly higher than that of the controls. In an older article, healthy adults were given astragalus extract for 20 days, and increases in serum IgM, IgE, and CAMP were observed.[205] In another study, 54 consecutive cases of small-cell lung cancer (SCLC) were treated with a combination of conventional treatment, astragalus, and other Chinese herbs. Ten out of 12 SCLC patients, including 4 with extensive disease, survived for between 3 and 17 years when the herbs were included with chemotherapy and radiation.[206] In a randomized study involving 120 patients, an astragalus preparation was administered intravenously along with cancer chemotherapy. The treated group showed a lower incidence of disease progression, smaller chemotherapy impact on white blood cells and platelets, improved CD4/CD8 ratios,

increased IgG and IgM levels, and higher Karnofsky scores relative to the control group.[207] Patients with gastrointestinal cancers were injected with a ginseng and astragalus preparation in a Chinese study. It was observed that patients in the treatment group had a lower degree of suppression of white blood cell count; differences in phagocytic index and percentage of phagocytes were reported as well.[208]

Viral myocarditis patients, when given an oral extract of astragalus, showed improved T3, T4, and T4/T8 cell ratios, indicating an enhancement of the immune response.[209] Natural killer cell activity was reported to be enhanced in myocarditis patients dosed with astragalus extract for 3-4 months.[210] Finally, 28 patients with systemic lupus erythematosus (SLE) had significantly lower natural killer cell activity when compared to normal controls. Preincubation of their peripheral blood mononuclear cells with astragalus stimulated natural killer cell activity in SLE patients and in healthy controls.[211]

Safety

Astragalus membranaceus appears to have a very low toxicity. A report indicates an LD50 in mice of greater than 1 gm/kg.[212] Astragalus is traditionally used for cardiovascular conditions in TCM. Reports from studies in rabbits indicate potential hypotensive activity[213]; patients who are hypotensive or are taking antihypertensive drugs may need to avoid use of large doses of the herb although no clinical observations of adverse effects from this hypotensive activity have been noted. Cardiotonic activity, antiarrhythmic activity, and improvement of myocardial ischemia have also were reported in laboratory studies.[214-216] The antiarrhythmic activity may have been due to antiviral effects, as it was reported from rat myocytes infected with Coxsackie virus; other antiviral effects have also been reported for this herb from in vitro studies.[217]

Discussion

This review indicates that immunomodulating activity of various types has been reported for all 3 herbs, including enhancement of levels or activities of specific cell types associated with disease resistance to infection and cancer. All 3 have demonstrated cytokine-modulating and either macrophage- or NK-cell-activating activity in vitro and in animal studies. All have also had, to a greater or lesser extent, trials in humans that indicate relevance in some immune-related conditions. But the quality of available preclinical evidence is mixed in the 3 herbs, and specific design problems pertain to the clinical studies of the 3 agents. In addition, overarching concerns about the design of clinical trials of herbs used in traditional Chinese medicine and the lack of phytochemical standardization cloud the meaning of existing work. The relevance of these herbal immune modulators in cancer treatment is also still in question.

Echinacea

Echinacea has substantial support from randomized controlled trials, though studies of higher quality are needed, particularly in the area of prevention. Specifically, the clinical efficacy of various preparations of echinacea in the treatment of acute URIs has been demonstrated in more than a dozen well-designed trials. As noted above, however, many of the clinical trials have limitations that cast some doubt on their findings, and it is not certain how immune effects reported in preclinical and human studies relate to effects on URIs; since antiviral and other activities have been reported for echinacea, it is conceivable that these could be responsible for the effects on duration and severity of URIs. In addition to the problems discussed above such as sample size, inclusion of potentially immunologically active materials in placebo preparations, and lack of clarity of inclusion and exclusion criteria in trials, the study of the effects of echinacea on URIs would be greatly clarified by the use of reliable and validated measures of assessment of URI symptoms. A wide variety of physician and patient assessments of URI symptoms have been used in existing echinacea trials, not all of which have been validated, casting into question the basic outcome measures of these studies, and thus the clinical import of their findings. Finally, no testing of the effects of echinacea on URIs in immune-compromised cancer patients has been published.

Ginseng

Preclinical studies on ginseng have indicated a number of immunologically relevant biological activities, including activation of macrophages, increases in NK cell activity and lymphocyte proliferation, increased graft-versus-host reactivity, and antioxidant activity. Substantial clinical work on ginseng has been done in the area of fatigue and enhancement of performance; however, many fewer studies have been reported in the widely available literature on the immunological effects of ginseng in humans. There have been reports of increases in lymphocyte proliferation and phagocytic activity in human trials, and increased response to vaccination. There are few reports on immunological effects of eleuthero in humans. Few trials have been done on the ability of ginseng to affect the course of specific diseases that have strong immunological components, although the Chinese literature contains a large number of reports of treatment of specific diseases with multicomponent herbal preparations that contain ginseng along with other herbs.

Astragalus

Astragalus has been reported to have antibacterial and antiviral activity in vitro, in addition to immunological activities such as potentiation of rIL-2 generation of LAK cell antitumor activity, and rather equivocal results on reversal of T-cell suppression after administration of cyclophosphamide in vivo. Specific extracts and fractions of astragalus have been reported to have immunological activities in ex vivo settings, including increasing activity in graft-versus-host rejection models. Antiviral activity has been noted for the herb. Very little clinical work on astragalus is available, although some human studies do indicate stimulation of activity of immune cells in clinical populations. As is the case with ginseng, the Chinese literature contains many reports of clinical uses of astragalus in multicomponent herbal preparations that are outside the scope of this article.

Clinical Trials on TCM Herbs

The various design deficits noted in the Chinese studies of astragalus and ginseng arise in part from the medical philosophy of TCM, according to which treatment must be highly individualized.[218] There are several inherent difficulties in studies of ginseng and astragalus in the context of the individualized protocols used in traditional Chinese medicine. The classical Chinese herbal prescriptions often include between 5 and 10 botanicals per formula. Although these are typically provided in very specific proportions, there may be hundreds of potentially active ingredients. In a recent detailed comparison of the constituents of some of these herbal formulas, Borchers and colleagues concluded that many of these formulas have similar compositions, often differing by only 1 or 2 components.[219] Astragalus and ginseng, considered to be highly effective tonics or adaptogens, are among the most commonly included components. Borchers et al suggest that mixtures of several crude extracts could have greater beneficial effects compared with a single plant extract because of synergistic interactions as well as interactions that diminish possible adverse side effects of one or more components. Another proposed rationale for herbal combinations is the prevention of the gradual decline in effectiveness observed when single drugs are administered over long periods of time.[220]

Such formulas, however, do not readily lend themselves to the Western model of analyzing a solitary agent for a specific effect. It would certainly be possible to study standard multicomponent agents in randomized trials. However, as individual responses to herbal extracts may vary, it seems reasonable to conclude that such variations would only increase with increasing complexity of the herbal mixtures. This would thus require conducting studies with much larger sample sizes than are typical in Western models outside of expensive multisite trials used late in drug development. Large-scale studies conducted on complex formulas were not included in this article, as they did not conform to the single-agent emphasis favored by the Western scientific model. However, it should be recognized that in studying TCM herbal medicines in isolation, there is a risk that some biological effects, mediated by synergistic activities, may be overlooked qualitatively or quantitatively.

Chemical Standardization

This is perhaps the most worrisome concern with the herbal immune stimulants, since lack of standardization casts doubt on the very identity of the formulas used, in both preclinical and clinical testing. Assessment of the phytochemical composition of the available preparations of these herbs is complicated by the lack of agreement on acceptable standards and consequent confusion as to the clinical relevance of work done on different types of extracts.

For echinacea, several different chemical compounds with evidence of some type of relevant biological activity have been described, and formulas have been made that are standardized on each of these. Preclinical and clinical studies have used a wide variety of extract types, with little attention being paid to whether the biological activities reported for these extracts (such as increases in macrophage activation, increased phagocytic activity, increases in NK cell numbers and increases in cytokine secretion) are in fact directly relevant to treatment of common URIs. If we are to have a scientifically meaningful assessment of the effect of echinacea, the question of whether even standardized echinacea preparations actually are exerting effects on URIs through immune mechanisms needs to be studied with greater seriousness—preferably before more randomized clinical trials on echinacea preparations take place. The possibility that echinacea preparations might act through symptom-relieving, rather than immune, mechanisms should also probably be explored. The methods of bioassay-guided fractionation, commonly used in the discovery of natural-product drugs, can be used to determine which specific components of echinacea or other herbal species are active in specific tests of biological activity. These methods are now being used in the analysis of herbal medicines to produce specific conclusions as to the active compounds and actual biological activities of herbs that can then be used to guide standardization.[221]

In the case of ginseng, standardization on ginsenoside content has been agreed to be the most relevant marker, at least for fatigue and performance-

related studies. There is a minimal amount of evidence that ginsenosides are the immunologically active components in ginseng, in addition to a strong medical tradition indicating that ginseng may be useful to increase bodily resistance. Commercial ginseng preparations reliably standardized on ginsenoside content are widely available and have been used in numerous performance-related clinical studies. Preclinical investigation of ginseng's immune activities should proceed using either ginsenosides or ginsenoside-standardized extracts, to determine whether the ginsenosides are indeed immunologically active, or whether other components of the species—which can be isolated through bioassay-guided fractionation—are the active components. Once this has been determined, clinical studies of ginseng in conditions for which immune system activation would be beneficial can be rationally undertaken. Randomized studies of ginsenoside-standardized extracts before this preclinical step is completed can certainly be done, but if we do not know whether the ginsenosides actually have the biological activity necessary to affect immune modulation, we risk studying the wrong agent. Smaller-scale pilot trials or retrospective studies of ginseng preparations in immunologically related diseases may make some contribution to the study of ginseng in assisting in the determination of the conditions for which ginseng use might be most fruitful, and thus guiding the choice of bioactivities to be studied.

Astragalus, like many herbal medicines, is currently in the status of a traditional medicine remedy for which some evidence of specifically active compounds has been published, and which has a small background of clinical trials with some intriguing results. Like ginseng, there is a strong traditional use justification for the investigation of astragalus as a resistance-enhancing herb. Much further basic research needs to be conducted to determine the constituents of astragalus that affect the immune system, and their relevance to specific diseases. As is the case with ginseng, small-scale pilot trials or retrospective studies of astragalus used as a traditional medicine might give some guidance as to the selection of appropriate immune activities for study. At the present time, there are no reliable standardized extracts of astragalus that could be used in clinical trials.

Herbal Immune Stimulants in Cancer

As reviewed above, all 3 of these herbs have some records of use in cancer and may be of interest to cancer patients who are suffering from immune suppression, or who are searching for additional agents with antitumor activity. Modest clinical and immunologic improvements were reported in patients with hepatocellular carcinoma and colorectal cancer who were given a preparation that included echinacea and a thymus-stimulating agent,[39,40] although another study recorded no increases in cytokine production in cancer patients given echinacea.[54] Tests of echinacea in leukemic mice indicated increases in NK cells.[57]

Reports of enhancement of NK activity and macrophage activity by ginseng suggest usefulness in cancer. Clinical studies of ginseng in cancer are limited to those of herbal combinations in the Chinese literature, such as those reported for the Shenmai combination, which increased T-cell and NK activity during chemotherapy.[168] Ginseng has been reported to stimulate NK cells in healthy adults and in AIDS patients,[37] and in mice.[135,143]

In animal studies, astragalus was reported to reverse the suppression of T-cell function after cyclophosphamide treatment in mice, but not rats.[197,200] It was also reported to increase antitumor activity of LAK cells from cancer patients.[193,194] Astragalus extracts restored the suppressed activities of T-lymphocytes and monocytes from cancer patients in a local graft-versus-host reaction model. Finally, herbal combinations containing astragalus and ginseng are reported to have immune effects in TCM human studies.[204,205,207,209]

Several of these reports indicate stimulation of NK cell activity. NK cells play an integral role in host resistance to tumor growth[222] and in the control of solid tumor metastases.[223,224] NK cells also play important roles in combating viral infections, as these cells can cause the lysis of virus-infected cells.[225] This may have special relevance to cancer patients, since infection is a common cause of death, frequently occurring as a consequence of chronic immune dysfunction and treatment-induced granulocytopenia (notably neutropenia).[226,227] Low NK activity has been correlated with a poor prognosis for cancers of the lung,[228,229] breast,[230] bladder,[231] stomach,[232] and colon.[233,234] The diverse activities of NK cells may become profoundly impaired due to surgery or chemotherapy,[235] as well as marijuana smoking (which may be favored by some cancer patients for relief of nausea and other symptoms),[236] morphine,[237] sleep disturbances (common among stressed cancer patients),[238] xenobiotic exposures,[239,240] and emotional distress[241]; emotional distress accompanied by low NK function has been found to be correlated with breast cancer prognosis.[242,243]

These studies offer intriguing glimpses of potential clinical helpfulness in cancer but no solid evidence of usefulness either in restoring suppressed responses or fighting malignancy. However, because of the lack of effective conventionally tested agents in many cancers, the clinical urgency facing many patients, and the good safety record of the herbal immune stimulants, patients may choose to use these herbs with the

understanding that their efficacy in those with malignant disease is not clearly established and that usefulness to the individual patient will be observed empirically, rather than supported in an evidence-based manner.

Conclusion

This review has focused on 3 representative examples of herbs classically used as immunostimulants: echinacea, ginseng, and astragalus. Although by no means exhaustive, the review demonstrates some preclinical and clinical research indicating beneficial effects of each of these botanical agents on immune function. In particular, the safety profile of echinacea appears favorable, and the use of echinacea products as early treatment for URI seems reasonably supported. A few studies for each herb indicate some relevance for use in restoring the immunosuppression commonly seen in cancer patients; such use, however, would have to be undertaken with the understanding that minimal scientific evidence supports it. One possibility is that herbal agents may be used in conjunction with more conventional forms of immunotherapy, such as vaccines, to further enhance immune responsiveness in the oncologic setting; to our knowledge, such combinations have yet to be investigated. Numerous immunologic mechanisms are likely involved in the various actions of each of these agents, and the mechanisms become complicated by additional synergisms that are introduced when the herbs themselves are combined, as in TCM. Additionally, limited studies with astragalus and ginseng demonstrate some potential for tumoricidal and survival impact. Whether or not the elucidation of these mechanisms will improve our understanding of the efficacy and safety of these herbal immunostimulants, there is a need for well-designed studies of the phytochemical standardization and the potential immune-enhancing value of echinacea, ginseng, and astragalus. With their low toxicity and long history of empirical support, the use of these herbs as immunostimulants may have therapeutic applications in the setting of integrative medicine.

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