Chapter 3
An Evidence-based Review of *Astragalus membranaceus* (Astragalus) for Cancer Patients

K. Simon Yeung, Jyothirmai Gubili and Barrie R. Cassileth

Abstract *Astragalus membranaceus* (astragalus), originally described in the Shennong's Classic of Materia Medica two thousand years ago, is used as a Qi-tonifying herb in traditional Chinese medicine. It is an important ingredient in many herbal formulas used to treat a variety of symptoms and ailments including fatigue and rectal prolapse. The root of astragalus is rich in saponins and polysaccharides. Modern research suggests antioxidant, immunomodulatory, and cytostatic properties. Animal and anecdotal human data show that astragalus reduces immunosuppression, a side effect of chemotherapy and it may also enhance the effects of such treatments. Whereas oral and parenteral preparations have been developed in Asia, products containing astragalus are consumed as dietary supplements in the West. Several formulas containing astragalus have been studied in cancer patients. Data indicate that they are safe to use in conjunction with chemotherapy and reduce treatment associated adverse effects. Based on existing evidence, there is also substantial interest in developing astragalus-based preparations for certain cancers. Although all products studied to date contain astragalus as the main ingredient, the variation across formulas makes it difficult to draw definitive conclusions. Future studies should address this issue. Astragalus is generally considered safe for traditional use, but the potential for herb-drug interactions exists because botanicals contain biologically active compounds. This chapter presents information about the use of astragalus in traditional medicine and summarizes existing scientific evidence of its benefits and limitations as an adjuvant cancer treatment.

3.1 Introduction

Many cancer patients use dietary supplements to enhance the likelihood of cure and to control treatment-related symptoms. They are also used to improve various aspects of quality of life and to prevent cancer recurrence (Correa-Velez et al. 2005;

J. Gubili (✉)
Integrative Medicine Service, Memorial Sloan-Kettering Cancer Center, 1429 First Avenue, New York, NY 10021, USA
e-mail: gubilij@mskcc.org

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Verhoef et al. 2005; Evans et al. 2007). A majority of herbal supplements, including *Astragalus membranaceus* (astragalus) and formulas containing astragalus, are consumed based on their traditional use. Astragalus may benefit cancer patients in various ways. It demonstrates chemo-preventive effects by enhancing immune defenses against cancer and serves as an adjuvant to cancer treatments. The most common application, however, is to relieve the side effects produced by cancer treatments.

Although astragalus has been used for many centuries, there is a paucity of scientific evidence and only limited data on its safety and efficacy. Earlier studies often were limited to *in vitro*, animal studies and case reports. The culture of publishing only positive results (Vickers et al. 1998) and unsophisticated peer review process often in place cast doubt on the credibility of many of these publications. However, traditional herbal medicine has been subjected to modern evidence-based research to examine safety, to validate indications and for drug development, and as a result, several high quality and well-designed studies and meta-analyses were published during the past decade.

3.2 Applications in Traditional Medicine

Astragalus was originally described in Shennong's Classic of Materia Medica more than two thousand years ago. It is considered to have "sweet" and slightly "warm" properties that enter the "Spleen" and "Lung" channels. The indications for as-

Table 3.1 Astragalus in traditional Chinese medicine and modern medicine

Function according to traditional Chinese medicine (Chen and Chen 2004)	Implications in biomedicine
Tonify the "Spleen" and raise Yang	Treat blood loss and anemia (Chang et al. 2009) Treat adverse effects from chemotherapy and radiotherapy (Cho and Chen 2009)
Tonify Wei (defensive) Qi, consolidate the exterior	Strengthen the immune system (Cho and Leung 2007a, b)
Promote the discharge of pus and generate flesh	Promote wound healing after surgery (Gao et al. 2001; Han et al. 2009; Huh et al. 2009)
Regulate water circulation	Reduce edema caused by poor circulation (Zhang et al. 2006a, b, c)
Relieve numbness and pain	Reduce pain and neuropathic symptoms (Chan et al. 2009; Lu et al. 2010)
Reverse Xiao Ke (wasting and thirst syndrome)	Treat diabetes related symptoms (Zhang et al. 2007; Liu et al. 2010)

tragalus use are numerous. They include deficiency of Qi characterized by lack of strength, anorexia and loose stools; sinking of "Spleen" Qi manifested by chronic diarrhea, rectal prolapse, abnormal uterine bleeding, spontaneous sweating due to weakened superficial resistance, edema due to deficiency of Qi, abscesses that are difficult to burst or heal, anemia, wasting-thirst caused by internal heat, albuminuria in chronic nephritis and diabetes (Pharmacopoeia 2005; Cho 2009) (Table 3.1). In traditional use, astragalus is employed as the chief ingredient in herbal formulas that may contain up to twenty different herbs. It is believed that the herbs mutually enhance the actions or counter side effects. Most modern clinical studies often follow this principle: Herbal formulas containing astragalus, rather than astragalus alone, are employed in clinical trials.

3.3 Botany and Phytochemistry

The Chinese pharmacopeia lists two entries on astragalus—*Radix astragali* (Huangqi), the dried root, and *Radix astragali Praeparata cum Melle* (Zhihuangqi), the honey processed root from *Astragalus membranaceus* of the Leguminosae family. The herb is usually cultivated and collected in spring and autumn. Besides macro- and microscopic identification, astragalus can be standardized based on the amount of astragaloside IV, a saponin constituent (Pharmacopoeia 2005). Astragalus root can be obtained from many different sources. For example, researchers of one study collected 43 astragalus root samples from farms located in the north of China and Mongolia (Tanaka et al. 2008). Genetic fingerprinting can be used to identify the origin (Yip and Kwan 2006). While *Astragalus membranaceus* and *A. membranaceus* var. *mongolicus* are two commonly used species, many other species with similar phenotype are mixed in commercial products. The amount of the main constituents between species can vary greatly which in turn affects the quality and medicinal results (Ma et al. 2002).

Traditional methods of preparing astragalus include boiling slices of the whole root in hot water or soaking the herb in wine. Extracts used in previous studies had been processed by hot water, which yields mainly polysaccharides, or by alcohols, yields saponins. Using advanced chromatography techniques, isoflavonoids, including formononetin, calycosin, astragalosides, and α-(1-4)-D-glucans and other constituents were detected in astragalus root samples (Yu et al. 2005; Huang et al. 2009; Li 2009; Auyeung and Ko 2010).

Each constituent is bioactive and can act synergistically with other components. In evidence-based botanical research, it is important to identify and characterize the constituents for the selection of chemical or bioactivity markers and to help understand the biological effects.

Tragacanth, a polysaccharide gum derived from *A. gummifer*, often is employed in the pharmaceutical industry as an emulsifier and thickening agent, rather than used for its medicinal properties.

3.4 Dosage and Toxicity

3.4.1 Dosage

In herbal medicine, the traditional dosage usually is applied as dose escalation trials are rarely conducted. Astragalus has very low toxicity; therefore, very high doses can be tolerated. The dose of raw astragalus root is 9–30 g (Pharmacopoeia 2005), but a daily dose as high as 90 g was used safely in children with acute leukemia (Dong et al. 2005). Since astragalus products are not standardized based on their bioactivity, no equivalent doses have been established. Astragalus often is used as an immunostimulant, and studies with other immunomodulators show that the dose-curve may peak in a non-linear fashion. In some cases, higher dose may be less effective than lower (Hishida et al. 1988; Deng et al. 2009). Future studies are needed to determine optimal dosage prior to use in clinical trials (Vickers 2006).

3.4.2 Toxicity

Generally, astragalus is considered safe. It has been used for many centuries with no reports of major adverse effects. Animal studies conducted to date have not revealed significant toxicity. Up to 40 g/kg given to rats intraperitoneally produced no adverse reactions. This is the equivalent of 70 times the human dose (Yu et al. 2007).

There are concerns that saponins present in astragalus may have hemolytic activities. However, an *in vitro* study showed that saponins are safe in that regard (Yang et al. 2005). Several other species of astragalus, such as *A. lentiginosus* and *A. lusitanicus*, are known to be toxic to livestock, where cases of poisoning have been reported. These species are called locoweed or milkvetch, and are not used in traditional medicine.

3.5 *In Vitro* and Animal Studies

In vitro and animal studies to date indicate that astragalus and its active constituents have immunomodulatory, antioxidant, and anti-inflammatory effects. Astragalus helps reduce the side effects of chemotherapy probably through its hemopoietic activity and its protective effects on vital organs. It may also help improve quality of life by reducing stress and fatigue.

3.5.1 Immunomodulation

The immune system is long known to be associated with cancer development and progression. For example, lymphocytes and interleukins (ILs) play a major role in

immunosurveillance against cancer (Dunn et al. 2004). Many studies have explored the mechanisms responsible for the modulation of immune defenses that help prevent and treat cancer. Astragalus has been shown to function as an immunomodulator. In a study of cultured peripheral blood mononuclear cells from lung cancer patients, it lowered the Th2 cytokine, which is associated with tumor growth (Wei et al. 2003).

A water extract of astragalus root reduced the suppression of cell proliferation induced by methotrexate in mouse spleen cells. It also modulated the expression of *IL-1α* and *IL-12p40* mRNA, which suggests that astragalus may help protect against the immunosuppression caused by chemotherapy (Lee et al. 2003).

In models of murine renal cell carcinoma and murine bladder tumor urological neoplasm, cancer cell survival was shown to be due to suppression of macrophage function, which was reversed by astragalus extract (Rittenhouse et al. 1991). Astragalus extract also increased lymphocyte cytotoxicity by promoting production of IL-2 and γ-IFN (Kurashige et al. 1999).

In another study, astragalus was found to induce lymphokine-activated killer cell activity in patients with cancer and AIDS. It also potentiated the effects of recombinant IL-2 treatment (Chu et al. 1994).

Various fractions of astragalus also were found to enhance immune reaction in mononuclear cells from cancer patients (Chu et al. 1988), to restore immune function in tumor-bearing mice and in mice treated with cyclophosphamide, and restore the lymphocyte blastogenic response (Cho and Leung 2007a, b).

Further, polysaccharides derived from astragalus enhanced the immunomodulatory effects of probiotics in animals by suppressing *E. coli* and by regulating the intestinal flora (Li et al. 2009b). They were shown also to activate mouse B cells membrane Ig in a TLR4-independent manner (Shao et al. 2004), and to stimulate spleen lymphocyte production in rats with stomach cancer (Li et al. 2009a). These mechanisms may help explain the benefits of astragalus in cancer treatment.

Astragalus also has been examined as a candidate for cancer vaccine. Astragalus injection can enhance the anti-metastatic action of mice dendritic cells pre-sensitized by a tumor antigen (Dong and Dong 2005). The ethanol extract of astragalus showed potent activity as an immunologic adjuvant when administered with vaccines of various types (Ragupathi et al. 2008). Further study to identify the components that are responsible for the adjuvant activity found that astragalosides II and IV were the active constituents but the toxicity of these two differed dramatically. Astragaloside IV caused very few side effects in animals and can potentially be used as an immunological adjuvant. Other flavonoids also showed significant adjuvant activity (Hong et al. 2010).

3.5.2 Inflammation

Inflammation can be a sign of an activated immune response, but chronic inflammation of the microenvironment has been associated with tumor development (Mantovani et al. 2010). Some studies demonstrated that astragalus exerts its anti-inflam-

matory effects by suppressing p38 and Erk1/2 through MKP-1 (mitogen-activated protein kinase phosphatase-1) mediation (Ryu et al. 2008). Astragalus also down-regulates the iNOS, P-selectin, and ICAM-1 (inter-cellular adhesion molecule 1) protein expression (Ko et al. 2005).

The regulated expression of adhesion molecules on the surface of endothelial cells is a key process in the pathogenesis of inflammation. Astragaloside IV significantly reduces this adhesion and also inhibits TNF-α in the NF-κB pathway (Zhang et al. 2003).

In a mouse asthma model, astragalus injection reduced inflammatory infiltration and mucus secretion by inhibiting Th2 cytokines (Shen et al. 2008), and reduced chemical induced colonic lesions. Human studies are needed to determine the effectiveness of astragalus in inflammatory conditions.

3.5.3 Antioxidant Effects

Antioxidants are thought to prevent oxidative damage and to exhibit chemo-protective effects although large studies found no benefit of antioxidant supplementation for cancer prevention (Meyer et al. 2008; Lippman et al. 2009). Further research is needed.

Antioxidants may also help protect healthy cells from the side effects of cancer therapies, but evidence is mixed (Lawenda et al. 2008). In a model of oxidative stress-induced endothelial dysfunction, astragalide IV was found to reverse the inhibition of nitric oxide (NO) synthase pathway and to enhance superoxide dismutase activity (Qiu et al. 2010). Of all of its constituents, calycosin showed the most potent antioxidant activity (Yu et al. 2005).

Glutathione is an endogenous antioxidant that helps to reduce free radicals. Astragalus preserves glutathione level (Ko et al. 2005). Danggui Buxue Decoction, a classical formula with astragalus as a major ingredient, was shown to protect cells against oxidant injury by increasing cellular gluthathione level (Chiu et al. 2007). It also affords protection against myocardial ischemia-reperfusion injury in rats in a dose-dependent manner by stimulating myocardial mitochondrial and red blood cell glutathione status (Mak et al. 2006).

3.5.4 Cytostatic and Cytotoxic Effects

In vitro studies indicate that astragalus can halt tumor growth. The active constituent of astragalus, formononetin, was shown to inhibit colon cancer cell growth by facilitating apoptosis through caspase activation and the suppression of Bcl-2 and Bcl-XL proteins (Auyeung and Ko 2010). Similar effects were seen on mesothelial cells as well (Na et al. 2009).

The saponins present in astragalus also show antitumor properties and stimulate apoptosis by up-regulating the *NAG-1* (NSAID-activated gene) (Auyeung et al. 2009), inhibit p21 expression and cyclin-dependent kinase activity that lead to accumulation in S phase and G2/M arrest. They may also promote apoptosis through caspase 3 activation and poly (ADP-ribose) polymerase cleavage (Tin et al. 2007). Astragalus extract induced apoptosis by up-regulating the Apaf-1 (apoptotic protease-activating factor 1), caspase-3, and acetylcholinesterase (Cheng et al. 2004).

Various fractions from astragalus increased cytostatic activity against cancer cells by inducing lymphokine-activated killer-like activity (Cho and Leung 2007a, b). The addition of high doses of astragalus enhanced the activity of 5-fluorouracil against chemically-induced gastric tumors in mice (Zhang et al. 2006a, b, c).

3.5.5 Hematopoiesis

A common adverse effect experienced by cancer patients is anemia due to myelosuppression caused by chemotherapy and radiation therapy. Formulas containing astragalus and *Angelica sinensis* (angelica) are used to improve energy and to enrich the blood in traditional Chinese medicine (TCM) (He et al. 1986). Modern studies indicate that astragalus can increase red blood cell production by stimulating erythroid differentiation (Cheng et al. 2004; Yang et al. 2010).

Danggui Buxue Decoction, when applied to cultured Hep3B human hepatocellular carcinoma cells, induced mRNA expression of erythropoietin in a dose-dependent manner, suggesting a hematopoietic function (Gao et al. 2008). In a mouse model, this combination increased the production of red blood cells and platelets by promoting the growth of megakaryocytes and stromal cells in the bone marrow (Yang et al. 2009).

In another study of rats with cyclophosphamide-induced anemia, a similar formula enhanced blood cell count by increasing erythropoietin mRNA expression (Chang et al. 2009), which suggests that astragalus may play a role in reversing cyclophosphamide-induced anemia.

3.6 Protective Effects on Organs and Tissues

There is evidence that astragalus has protective effects on vital organs such as the liver, kidneys, and heart. Following are a few examples.

3.6.1 Liver

Astragalus has been used to treat liver diseases in TCM, and experimental evidence indicates that its antitumor potential can delay chemically-induced hepatocarcino-

genesis in rats (Cui et al. 2003). When used along with *Schisandrae chinensis*, astragalus protected rat liver from chronic injury *via* antioxidant effects (Yan et al. 2009).

Another study in mice also showed the hepatoprotective effects of a combination of *Paeonia lactiflora* and astragalus against injury caused by bacillus Calmette-Guerin and lipopolysaccharide by inhibiting pro-inflammation mediators, TNF-α and IL-1 (Sun et al. 2008).

When used in carbon tetrachloride-treated rats, a raw astragaloside fraction showed antioxidant effects, reduced TNF-α and TGF-β1 activity, and slowed the progression of liver fibrosis (Gui et al. 2006).

The saponins extracted from the root of astragalus also were found to protect the liver from chemical-induced injury in mice (Zhang et al. 1992).

3.6.2 Kidneys

Alpha glucans isolated from astragalus were found to reduce proteinuria in rats with glomerulonephritis, suggesting renoprotective properties (Li 2009). In another study conducted in rats, a combination of astragalus and angelica enhanced the anti-fibrotic effect of enalapril, an ACE inhibitor, in the kidneys. This formula may have a role in treating ureteral obstruction (Wojcikowski et al. 2010). A case study in humans reported similar findings (Ahmed et al. 2007). Astragalus also protects rats from cyclosporine induced kidney damage (El-Kenawy 2010).

A systematic review of animal studies concluded that astragalus can effectively reduce serum sugar level, urine albumin, and improve glomerular filtration (Zhang et al. 2009).

3.6.3 Heart

Astragalus has been used in TCM formulas for cardiovascular diseases. *In vitro*, astragaloside IV improved post-ischemic heart function and ameliorated perfusion arrhythmias. The cardioprotection afforded by astragaloside IV was accompanied by a significant increase in coronary flow both *in vivo* and *in vitro* probably due to astragaloside IV's antioxidative and NO-inducing properties (Zhang et al. 2006a, b, c).

Astragaloside IV also helps dilate aortic vessels through the endothelium-dependent NO and cGMP pathways in a dose-dependent manner. Further, it may play a role in calcium channel blocking and in the inhibition of angiotensin II (Zhang et al. 2006a, b, c).

Anthracyclines, a class of chemotherapy drugs, are known for their cardiotoxicity, which limits their use. But a recent study found that astragalus can protect heart cells from anthracycline-induced cardiotoxicity by exerting antioxidant effects (Luo et al. 2009).

3.6.4 Nervous System

Nerve damage is a common adverse effect associated with chemotherapy. Symptoms can range from peripheral neuropathy to memory loss. Some studies suggest that astragalus has protective effects on the nervous system. For example, astragaloside IV was shown to protect against nerve degeneration (Chan et al. 2009), and astragalus extract helps regenerate nerve fibers (Lu et al. 2010).

In a rat focal cerebral ischemia/reperfusion model, astragaloside IV was found to protect the brain by reducing blood-brain barrier permeability through the regulation of tight junction proteins, occludin and ZO-1 (zonae occludens-1) (Qu et al. 2009).

Buyang Huanwu Decoction, a TCM formula that contains astragalus as its main ingredient, is used for treating stroke-induced disability. In a study with rats, this formula improved neurologic function and reduced the infarction volume in ischemic brains by stimulating the progenitor cells at the hippocampus and sub-ventricular zone. It also increased the number of VEGF-positive and Flk1-positive cells in this region. These results suggest that this formula can assist the recovery of neurologic deficits (Cai et al. 2007).

3.6.5 Bone

In an *in vitro* study, formononetin affected the process of bone remodeling in normal and osteoarthritic osteoblasts (Huh et al. 2010). Whether this means that astragalus plays a role in affecting bone metastasis remains to be examined in future studies.

3.7 Astragalus for Stress and Glycemic Control

In animal studies, astragalus reduced stress-induced anxiety and improved learning and memory (Park et al. 2009). Animals with artificially induced fatigue also displayed improved immune function after being fed astragalus (Kuo et al. 2009). Human studies are needed.

In traditional medicine, astragalus is used for Xiao Ke, a wasting and thirsting syndrome commonly experienced by patients with diabetes. Many cancer patients also have poor glycemic control and experience similar symptoms. Modern research shows that astragalus can reduce the formation of proinflammatory chemicals produced by normal metabolism that can lead to diabetes (Motomura et al. 2009).

In a diabetic mice model, polysaccharides from astragalus reduced hyperglycemia and insulin resistance by regulating insulin signaling in skeletal muscle, and are recommended for use in the treatment of type 2 diabetes (Liu et al. 2010). They also reduced blood glucose, plasma lipid and microalbuminuria by improving renal

function through the reduction of NF-κB. This suggests that astragalus may help prevent and treat diabetic nephropathy (Zhang et al. 2007).

3.8 Clinical Studies

Several clinical studies have been conducted to determine the beneficial effects of astragalus.

In a study of 43 patients with systemic lupus erythematosus and compromised kidney function, patients receiving standard cyclophosphamide treatment at 0.8 g per month were randomized to trial and control groups. The trial group received 20 ml of astragalus injection (equivalent to 40 g of raw herb) daily for 12 days each month. After 3 months, the trial group had significant reduction in active clinical symptoms ($P<0.05$) and reduced infection rates compared to the control group (4.4% *vs* 25%). Patients also had decreased urine protein and increased red blood cell count (Su et al. 2007). Although the dosage and frequency of cyclophosphamide differ in chemotherapy regimens, this study suggests that astragalus can reduce the toxicity of cyclophosphamide.

A study conducted in patients with leucopenia showed that astragalus can increase white blood cell count in a dose-dependent manner. A pure astragalus preparation when given twice daily at a concentration equivalent to 15 g astragalus was 65% more effective ($P<0.01$) than a lower concentration of 5 g astragalus in increasing white blood cell count after 8 weeks of treatment (Weng 1995).

In another study of patients undergoing hemodialysis, 31 patients were divided into a treatment group with daily 30 ml astragalus injection and a control group with no additional treatment. After 2 months, the treatment group had significant increase in serum IL-2 level (from 3.86–5.38 ng/ml) compared to the control group (3.72–3.85 ng/ml) ($P<0.001$). This demonstrates that astragalus can help enhance immune function patients undergoing hemodialysis (Qun et al. 1999).

Astragalus can also enhance the dendritic cell induction of mononuclear cells. In a study of 44 children with acute leukemia undergoing chemotherapy, 20 children in the treatment group were given large daily doses (up to 90 g) of astragalus while the others received only chemotherapy. After 1 month, the treatment group had significantly higher proportion of dendritic cells 4.4×10^6 per 2.5×10^6 of mononuclear cells *vs* 2.6×10^6 per 2.5×10^6 ($P<0.01$) of mononuclear cells in the control group (Dong et al. 2005).

These results support the traditional theory that astragalus has potent immunostimulant effects and therefore may be used as a biological response modifier (Sun et al. 1983).

Astragalus injection also has benefits in patients with advanced non-small cell lung cancer (NSCLC) when given with chemotherapy. In a study of 60 NSCLC patients (stage IIIb or stage V) randomized to astragalus injection (10 ml equal to the potency of 20 g of raw herb) daily with chemotherapy, or chemotherapy alone, patients in the former group had statistically significant response rate (40.0% *vs* 36.7%), higher survival rate in 1 year (46.7% *vs* 13.3%) ($P<0.05$), and improve-

ment in quality of life compared to the control group 80.4% *vs* 43.3% ($P<0.01$) (Zou and Liu 2003).

The effectiveness of astragalus extract (Injectio Radici Astragali) was also tested by a point injection to reduce adverse effects from chemotherapy. In a study, 78 cancer patients all with stage III or higher lung, breast, liver, GI and other cancers and a leukocyte count lower than 4.0 G/L were randomized to 2 groups. The treatment group was given astragalus injection once a day into the acupoint Zusanli (ST-36) along with chemotherapy. The control group took a TCM preparation Gan Xue Bao orally 3 times a day. After 3 weeks, the treatment had a significant total effective rate defined by restoration of the total and differential leukocyte counts compared to the control group (82.2% *vs* 51.5%, $P=0.01$), Astragalus extract when injected into acupoint is more effective than oral supplements in improving immune function measured by natural killer cell activity (Chen et al. 2005). However, it is unclear whether the effect was due to the astragalus extract or acupuncture or both.

Astragalus is often consumed orally and is rarely used alone in traditional medicine. Herbalists generally customize formulas that contain multiple ingredients based on each patient's pattern presentation. The selection of ingredients is guided by descriptions in classical literature. Similarly, products used in clinical studies generally follow these traditional formulas. Many proprietary products have been developed, some of which claim to have unique activity; they are often patented based on special usage or manufacturing processes to protect commercial interest. Several such formulas have been studied in cancer patients.

A formula called Huangqi Zengmian Powder, consisting of astragalus, *Panax ginseng, Lycium barbarum, Ligustrum lucidum*, and *Cistanche salsa* was tested in esophageal cancer patients for interstitial response following surgery. Thirty-seven patients with stage I to stage IV esophageal cancer were treated with 10 g of this formula given 3 times a day starting 1 week before surgery and continued for 4 more weeks; 14 patients in the control group did not receive any herbal treatment. Results showed that the treatment group had an increase in interstitial mastocytes ($\chi^2=11.14$, $P<0.01$) and improvement in microvessel damage ($\chi^2=7.10$, $P<0.01$). The histological and immunological improvements suggest that this formula can accelerate wound healing and recovery after surgery in patients with esophageal cancer (Gao et al. 2001).

Formulas containing astragalus, have been studied as a treatment for fatigue and as hematopoietic agents.

Myelophil, an extract containing astragalus and *Salvia miltiorrhiza* roots reduced fatigue in a randomized double blind controlled trial. In this study, 36 patients with persistent fatigue for more than 6 months were randomized to low-dose group that consumed 1.5 g extract twice daily; high-dose group that took 3 g extract twice daily; or a placebo control group. Following 4 weeks of treatment, the low-dose group had significantly lower fatigue severity score compared to the controls ($P<0.05$) (Cho et al. 2009). Similarly, Huangqi Jianzhong Decoction, a formula containing astragalus, *Paeonia lactiflora, Zingiber officinale, Zizyphus spinosae, Glycyrrhizae uralensis, Cinnamomi cassiae*, and *Saccharum granorum*, reduced fatigue in athletes by increasing oxygen uptake and systemic utility. In this study, 12 male ath-

letes were randomly divided into experimental and control groups. Athletes in the experimental group took Huangqi Jianzhong Decoction while those in the control group took a placebo made of fried starch. After 8 weeks, the anaerobic threshold, a marker for stamina building and fatigue recovery, was significantly increased in the experimental group ($P = 0.02$) (Chen et al. 2002).

In another randomized, double-blind placebo-controlled study, 103 women with acute menopausal symptoms were enrolled. The patients were given 3 g daily of Danggui Buxue Decoction (a mixture of 5 parts of astragalus and 1 part of angelica) orally, or a placebo. After 6 months, this formula was found to be effective only for mild hot flushes. The number of mild hot flushes per month improved from 18.9 ± 23.5 at baseline to 8.6 ± 17.1 in the treatment group ($P < 0.01$) and 26.0 ± 43.5 to 12.4 ± 17.6 in the placebo group ($P > 0.05$). No overall changes were found in vasomotor symptoms (Haines et al. 2008).

Studies also show that some astragalus products can be used safely with chemotherapy. In a pharmacokinetic study of Jin Fu Kang, an astragalus-based oral herbal formula, researchers found that it did not cause significant interactions with docetaxel when used in NSCLC patients (Cassileth et al. 2009).

In a review of four clinical trials conducted to assess the effectiveness of astragalus compounds on the quality of life, side effects of chemotherapy, and on adverse effects in colorectal cancer patients, astragalus use was found to help reduce nausea and vomiting along with a decrease in the rate of leucopenia and an increase in CD3, CD4, and CD8 subsets of T-lymphocytes compared to those treated with chemotherapy alone. Use of Chinese herbal medicine along with chemotherapy appears promising for patients with colorectal cancer (Taixiang et al. 2005).

A recent meta-analysis of fourteen randomized controlled trials published from 1980–2008 on Aidi, a parenteral formula containing astragalus, found that it has therapeutic effects when used with radiation therapy or with navelbine and platinum compounds. Studies also suggest that Aidi can improve quality of life, immune function, and hematopoiesis. However, the formula did not improve survival (Ma et al. 2009).

Due to its Qi tonifying property, astragalus is used also to treat lung ailments. Platinum-based drugs, like cisplatin and carboplatin, often are used in conjunction with taxanes and vinca alkaloids in chemotherapy regimens for NSCLC. In addition, gemcitabine, premetrexate, and bevacizumab are also used. Several studies have examined the benefits of using both oral and parenteral astragalus-containing formulas along with these chemotherapy drugs. A meta-analysis of 34 randomized studies totaling 2,815 patients found such a combination to improve survival and improve tumor response to treatment (McCulloch et al. 2006). Further, a systemic review of 15 trials of oral astragalus formulas in patients with NSCLC reported quality of life improvement (Chen et al. 2010).

In a meta-analysis of TCM and chemotherapy for hepatocellular carcinoma (HCC), of 26 studies analyzed, 12 used herbal formulas that contained astragalus. Researchers concluded that these products improve survival and tumor response when used along with chemotherapy (Shu et al. 2005).

In another meta-analysis, thirty studies published over the last decade involving patients with HCC treated by transcatheter arterial chemo-embolization and 5-flu-

rouracil based chemotherapy regimens were examined. Patients who used Chinese herbal therapies with standard treatments were found to have improved survival; improved quality of life; and fewer adverse effects. No benefits were seen in liver function tests or in short-term survival (>6-month). Of the 30 studies analyzed, 18 used herbal formulas that contained astragalus as major ingredient (Cho and Chen 2009).

Although all products studied to date contain astragalus as the main ingredient, the variation across formulas makes it difficult to draw definitive conclusions (Firenzuoli et al. 2006). Future studies should address this issue.

3.9 Herb-drug Interactions and Other Concerns

Although astragalus is generally considered safe for traditional use, the potential for herb-drug interactions exists because botanicals contain biologically active compounds (Meijerman et al. 2006; Yeung and Gubili 2007).

For example, saponins from astragalus can induce the hepatic microsomal cytochrome P-450 enzymes, which may account for its hepatoprotective effects but can also alter the metabolism of other herbs or drugs that are substrates of these enzymes (Zhang et al. 1992).

In an early study of a xenogeneic graft-*versus*-host reaction model, an astragalus fraction reversed the immunosuppressive effect of cyclophosphamide on mononuclear cells derived from cancer patients. This led to the use of astragalus as an immunomodulating agent to reduce the adverse effects of chemotherapy (Chu et al. 1988, 1989). However, it may also reverse the effects of immunosuppressants in patients following organ or bone marrow transplants.

A few studies showed that compounds present in astragalus may have estrogenic activities (Zhang et al. 2005; Huh et al. 2010), although it is unclear whether astragalus affects hormonal therapy in cancer patients. Many Western oncologists advise patients with hormone-sensitive cancers to avoid phytoestrogens, while others argue that phytoestrogens may actually provide a protective effect (Virk-Baker et al. 2010).

3.10 Future Research

There has been an increase in basic research and the number of clinical trials over the last two decades to determine the effectiveness of botanicals in the treatment and prevention of cancer. Several studies to date have demonstrated that astragalus plays a positive role in reducing the adverse effects when used with standard chemotherapy. However, the majority of studies used compound astragalus formulas, and the observed benefits may be due to synergistic effects contributed by other components. Whether astragalus alone would provide similar benefits needs to be determined.

Botanicals research involves unique issues ranging from product standardization to study design. From a drug development perspective, future clinical studies should focus on testing purified constituents. Using a single, well defined compound can provide consistent and measureable results for comparison of efficacy.

Astragalus products have not been used in dose escalation studies. It is important to determine an optimal dose in order to design meaningful large clinical trials. Clinical outcome may vary depending on the dose regimen.

Few studies have looked into how genetic variation in humans can affect the utility of astragalus. Given the current understanding of pharmacogenomics and polymorphism, such studies are particularly important in cancer treatment as genetics play a major role in cancer diagnosis and treatment.

Preliminary results also hold promise in developing astragalus as a cancer vaccine adjuvant, but the field of cancer vaccine treatment is still new. We believe that astragalus, with its unique constituents and immunomodulatory properties, is a potential candidate for this role.

3.11 Conclusions

Used in traditional medicine for millennia, astragalus continues to be an important constituent of traditional medicine formulas in Asia, and to a limited extent as a dietary supplement in the West. Its pharmacologic effects have not been fully elucidated but current research supports its use as an immunomodulator. Both classic and modern patented astragalus formulas are used in cancer care although human studies are limited. Use of astragalus products may help reduce adverse effects from chemotherapy. However, before they can be incorporated as standard therapy, products should be well characterized. Large clinical studies using standardized products with known optimal doses should be conducted. Using astragalus extract with a cancer vaccine is an exciting new frontier but this also requires more definitive clinical research. Until then, astragalus products will likely continue to be used by cancer patients in conjunction with standard therapies. Patients and practitioners should be aware of the benefits and risks of adverse effects and of potential astragalus-prescription drug interactions.

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