Astragalus membranaceus

Description

Astragalus membranaceus (Latin*);* membranous milk-vetch root (English), huang qi (Chinese), ogi (Japanese), and hwanggi (Korean) is one of the important "Qi tonifying" adaptogenic herbs from the Chinese materia medica. The Chinese species *A. membranaceus* and the related *A. membranaceus var mongholicus* (synonym: *A. mongholicus*) are defined in the *Pharmacopoeia of the People's Republic of China* as Radix Astragali. It has been prescribed for centuries for general weakness, chronic illnesses, and to increase overall vitality. The genus Astragalus is a very large group of more than 2,000 species distributed worldwide, and is commonly known as milk-vetch root. Currently, much of the pharmacological research on Astragalus is focused on its immune-stimulating polysaccharides and other active ingredients useful in treating immune deficiency conditions. Astragalus has demonstrated a wide range of potential therapeutic applications in immunodeficiency syndromes, as an adjunct cancer therapy, and for its adaptogenic effect on the heart and kidneys. Astragalus root has been used to promote immune function and as a tonic to build stamina. Ancient Chinese texts record the use of Astragalus for tonifying the spleen, blood, and qi.

Traditional Indications

In Traditional Chinese Medicine (TCM), Astragalus is classified as an herb that tonifies the qi and is indicated for symptoms of spleen qi deficiency such as diarrhea, fatigue, and lack of appetite.[1] It also raises the yang qi of the spleen and stomach, thus addressing prolapses of organs such as the uterus, stomach, or anus. In this capacity it can also address uterine bleeding. Astragalus tonifies the lung qi and is used in cases of frequent colds, spontaneous sweating, and shortness of breath.[1] Other traditional indications include wasting disorders, night sweats,[2] chronic ulcerations and sores,[1] numbness and paralysis of the limbs, and edema (from deficiency).[1] Its properties are sweet and slightly warm. Astragalus is typically prescribed as a dried root, powdered, or in a decoction. Classically, it is prescribed in combination with other Chinese medicinal herbs, depending on the desired therapeutic effect and the specific TCM diagnosis.

Active Constituents

The main constituents of *Astragalus membranaceus* include polysaccharides, saponins, flavonoids, amino acids, and trace elements.[3]

Polysaccharides

The polysaccharides found in Astragalus have received a great deal of attention, especially the polysaccharide fraction F3. They have been shown to play a role in immunomodulatory actions. Polysaccharides A, B, and C have been identified as glucans, and polysaccharide D as a heteropolysaccharide.[4]

Triterpenoid Saponins (Astragalosides)

Astragalus root contains a series of cycloartane triterpene glycosides denoted astragalosides I-VII (saponins), that are based on the aglycone cycloastragenol and contain from one to three sugars attached at the 3-, 6-, and 25-positions.[5-8] In the predominant astragalosides I-III, the 3-glucose is acetylated. Several saponins have also been reported that are based on the oleanene skeleton.[9]

Flavonoids

Using high performance liquid chromatography-electrospray ionization mass spectrometry to analyze the flavonoids in the roots of *Astragalus membranaceus* and *Astragalus mongholicus*, eight flavonoids were identified, including calycosin-7-O-beta-D-glucoside, calycosin-7-O-beta-D-glucoside-6'-O-malonate (2), ononin, (6aR,11aR)-3-hydroxy-9,10-dimethoxypterocarpan-3-O-beta-D-glucoside, calycosin, (3R)-7,2'-dihydroxy-3',4'-dimethoxyisoflavan-7-O-beta-D-glucoside, formononetin-7-O-beta-D-glucoside-6'-O-malonate, and formononetin.[10]

Other Constituents

Phytosterols, a volatile oil, and amino acids, including gamma-aminobutyric acid (GABA) and L-canavanine, have been isolated from the root.[11] Zinc, iron, copper, magnesium, manganese, calcium, potassium, sodium, cobalt, rubidium, molybdenum, chromium, vanadium, tin, and silver have also been found in the root of Astragalus, as well as traces of tantalum, hafnium, europium, and thorium. Organic compounds identified in the roots include choline, betaine, gluconic acid, and β-sitosterols, as well as aromatic compounds, essential oil, linoleic acid, α-aminobutyric acid, bitter compounds, and asparagine.[4]

Mechanisms of Action

Research shows Astragalus root stimulates the immune system in many ways. It increases the number of stem cells in bone marrow and lymph tissue and encourages their development into active immune cells. It appears to help trigger immune cells from a "resting" state into heightened activity. One study showed Astragalus root helps promote and maintain respiratory health. It also enhances the body's production of immunoglobulin and stimulates macrophages. Astragalus can help activate T-cells and natural killer (NK) cells.[12]

Several studies also show Astragalus proffers heart-protecting effects, including protection against oxidative damage. Additionally, the flavonoids, saponins, and polysaccharides found in Astragalus root help minimize free radical damage to membranes.[13-15]

The flavonoids and saponins in Astragalus can significantly inhibit membrane lipid peroxidation generated by superoxide (O_2-), hydrogen peroxide (H_2O_2), and ultraviolet rays, while the polysaccharides of Astragalus possess weaker protective activity.[14]

Astragalus has been shown to have inhibitory effects on lipid peroxidation and protein oxidative modification by copper. The results of a study showed the free radical scavenging effects were similar to, and stronger than, those of mannitol and superoxide dismutase, respectively, demonstrating inhibitory effects on oxidative stress induced by copper.[13]

Clinical Indications

Current Western applications of Astragalus are primarily for restoring and strengthening the immune response, enhancing cardiovascular function, and increasing vitality. Indications supported by clinical trials include impaired immunity, adjunctive cancer treatment, and viral infections, including the common cold and cervical erosion associated with *Herpes simplex*. Western preparations include dried root for decoction, liquid extract, tablets, and powdered root.

Immune Modulation

In mice, oral doses of Astragalus enhanced several aspects of immunity, including superoxide anion production by peritoneal macrophages,

potentiation of phagocytic function, increased thymus weight, and proliferation of splenocytes.[11] Astragalus stimulated NK-cell activity of human peripheral blood lymphocytes and restored steroid-inhibited NK-cell activity.[11]

In other studies, Astragalus polysaccharides were shown to potentiate the immune-mediated antitumor activity of interleukin-2 (IL-2) and the activity of monocytes, improve the responses of lymphocytes from normal subjects and cancer patients,[16] and enhance NK-cell activity of normal subjects and patients with systemic lupus erythematosis (SLE).[17]

The polysaccharide fraction F3 potentiated the lymphokine-activated killer (LAK) cell-inducing activity of IL-2 in cancer and AIDS patients.[18]

To investigate the immune regulation of the flavonoids of *Astragalus membranaceus*, monoclonal antibody assays of changes in total T-cell count and subsets were taken before and after treatment in immunosuppressed mice. The LAK cell-inducing activity was also tested simultaneously by isotope technique. Results showed the flavonoids could promote the proliferation of lymphocytes, raise the T-cell count, regulate the T-cell subsets, and elevate LAK cell-inducing activity induced by IL-2.[12]

In an open, randomized clinical trial, 115 patients with leukopenia received a high dose of a concentrated Astragalus preparation (equivalent to 30 g Astragalus daily) or a low dose (equivalent to 10 g Astragalus daily) over a period of eight weeks. In both groups there was a significant increase in average white blood cell counts after treatment ($p<0.05$). On the basis of these findings, the author suggests Astragalus is an effective treatment for leukopenia.[19]

Astragalus has also been shown to possess *in vitro* antibacterial activity against *Shigella dysenteriae, Streptococcus hemolyticus, Diplococcus pneumonia,* and *Staphylococcus aureus*.[2]

Antiviral Activity

In viral myocarditis patients given an oral Astragalus extract, enhanced T_3, T_4 and T_4/T_8 cell ratios were demonstrated, suggesting improved immune response.[20]

Patients with SLE have significantly decreased NK-cell activity when compared to normal controls. Pre-incubation of peripheral blood mononuclear cells with Astragalus stimulated NK-cell cytotoxicity in both SLE patients and healthy controls.[17]

In a study by Yuan et al, Astragalus demonstrated significant protective effects in cultured rat heart cells against coxsackie B-2 virus when given in the early period of infection. According to the authors, the results suggest Astragalus should be valuable in preventing and treating acute myocarditis caused by coxsackie-B virus.[21]

In another study by Yang et al, intramuscular injections of Astragalus for 3-4 months in patients with coxsackie-B viral myocarditis resulted in a significant increase in NK-cell activity. Their general condition and symptoms also improved and, compared with pretreatment levels, alpha- and gamma-interferon levels markedly improved. Patients treated with conventional therapy demonstrated no improvement.[22]

In a double-blind clinical trial by Qian et al, 235 patients with chronic cervicitis associated with human papillomavirus type 16 (HPV-16), *Herpes simplex* virus type 2 (HSV-2), and cytomegalovirus (CMV) infections were divided into four groups receiving the following substances applied locally by gauze: (1) recombinant interferon-1 interferon (5 μg); (2) recombinant interferon-1 interferon (10 μg); (3) both interferon (5 μg) and Astragalus extract (0.5 mL of a 1:1 extract); or (4) Astragalus alone (0.5 mL of a 1:1 extract). Application of the substances was made twice weekly for three weeks. The Astragalus-plus-interferon group demonstrated results similar to the high-dose interferon group, with approximately 60 percent of patients showing striking improvement or complete resolution of the cervicitis. In the group of patients receiving Astragalus alone, only eight percent had marked improvement, and none were completely cured. The authors conclude the Astragalus acted synergistically with the interferon therapy.[23]

Prior to the aforementioned study, a double-blind trial showed a similar result for 164 patients with cervical erosion associated with *Herpes simplex* virus infection. Antiviral activity

is most likely due to increased immunity and possibly enhanced interferon production.[11]

Adjunct Cancer Therapy

Astragalus has been shown to increase resistance to the immunosuppressive effects of chemotherapy drugs, while stimulating macrophages to produce interleukin-6 and tumor necrosis factor (TNF).[24] The use of recombinant interleukin-2 (rIL-2) in immunotherapy is limited by the toxicity associated with higher doses. Astragalus and 100 U/mL of rIL-2 were compared with 1,000 U/mL of rIL-2 alone in an *in vitro* study on murine renal carcinoma cells. The Astragalus/rIL-2 group had a tumor cell lysis rate of 88 percent, versus 86 percent in the group with 1,000 U/mL rIL-2 alone. This suggests a 10-fold potentiation of the *in vitro* antitumor activity of rIL-2-generated LAK cells.[25] The authors also suggest that by reducing the dosage required in treating cancer patients, the severe side effects of rIL-2 therapy (e.g., acute renal failure, capillary leakage syndrome, myocardial infarction, and fluid retention) might be reduced. These results were confirmed in another study where Astragalus potentiated the LAK cell-inducing activity of rIL-2 against an Hs294T melanoma cell line.[18]

More than 100 Chinese herbal formulas were screened and evaluated for their ability to ameliorate the toxic side effects of anticancer agents. A formula including both Astragalus and Ligusticum – Shi-Quan-Da-Bu-Tang – was selected as most effective in stimulating hemopoietic factors and interleukin production. It was also shown to potentiate the activity of chemotherapeutic agents, inhibit recurrence of malignancies, prolong survival, and reduce the adverse toxicities of radiotherapy and antineoplastic agents such as mitomycin, cisplatin, cyclophosphamide, and 5-fluorouracil.[26]

Lau et al showed a combination of a water extract of *Astragalus membranaceus* with *Ligustrum lucidum* (500 μg each i.p.) significantly inhibited the growth of renal cell carcinoma in mice. The herbal extract combination restored depressed oxidative burst activity of splenic macrophages from tumor-bearing mice and improved the generation of LAK cells of splenocytes when exposed to IL-2 *in vitro*.[27]

Cardiovascular Disease

The saponins contained in Astragalus were found to have a positive effect on heart function by inhibiting the formation of lipid peroxides in the myocardium and decreasing blood coagulation.[28]

In another study, Astragalus was shown to strengthen left ventricular function and had an antioxidant effect in 43 patients suffering from acute myocardial infarction. After administration of Astragalus, the ratio of pre-ejection period/left ventricular ejection time was decreased, the superoxide dismutase activity of red blood cells was increased, and the lipid peroxidation content of plasma was reduced. Additionally, there was a significant difference between the Astragalus group and the control group in the aforementioned parameters. The authors suggest the antioxidant effect of Astragalus is one of the mechanisms of its cardiotonic action.[15]

Astragaloside IV was isolated from *Astragalus membranaceus* and injected intravenously in 19 patients with congestive heart failure daily for two weeks. After two weeks, symptoms of chest pain and dyspnea were alleviated in 15 of 19 patients. Additionally, radionuclide ventriculography showed with statistical significance that left ventricular modeling improved, left ventricular end-systolic and end-diastolic volumes diminished, and heart rate slowed from 88 beats/minute to 65 beats/minute. The authors conclude two continuous weeks of injections with Astragaloside could improve left ventricular modeling and ejection function in patients with congestive heart failure.[29]

In 92 patients with ischemic heart disease treated with Astragalus, significant relief from angina was achieved, and the effective rate of electrocardiogram improvement was 82.6 percent.[30] In another study of 20 patients with angina pectoris given Astragalus for two weeks, cardiac output was significantly increased and, unlike digitalis, adenosine triphosphatase activity was not inhibited.[31]

Genitourinary and Renal Disorders

Nephritis

Human studies indicate *Astragalus membranaceus* has a moderate diuretic action.[1]

In an uncontrolled study Astragalus and *Angelica sinensis* root, coupled with a high-protein diet, improved protein imbalance and serum protein in nephritic patients.[11]

Male Infertility

Water extracts of 18 major Chinese medicinal plants were tested for sperm motility-enhancing activity *in vitro*. Only *Astragalus membranaceus* demonstrated a significant stimulatory effect on the sperm of healthy donors. Using a solution of 10 mg/mL, sperm motility was increased to 146.6 ± 22.6 percent of control.[32]

Drug-Botanical Interactions

Recombinant interleukin-2 can be potentiated 10-fold by Astragalus extract.[24]

Recombinant interferon-1 can be therapeutically enhanced by Astragalus, thus improving the outcome in chronic viral cervicitis.[23]

There is speculation Astragalus could theoretically offset or minimize the immunosuppressive effects of corticosteroids and cyclosporine, based on its T-cell stimulating activity.[33]

Dosage and Toxicity

Astragalus is safe; doses as high as 100 g/kg of raw herb have been given by lavage to rats with no adverse effects.[1] Astragalus can be given in tincture form at 2-4 mL three times daily. The LD_{50} of Astragalus in mice was determined to be approximately 40 g/kg when administered by intraperitoneal injection.[34]

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