Review paper

Immunotropic and anti-tumor effects of plant adaptogens. III. *Astragalus* (*Fabaceae*)

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Abstract

Astragalus (Fabaceae) has been used in traditional Chinese medicine, usually in combination with other herbs, as an adaptogen and an immune system enhancer. This paper presents a brief review of the scientific publications on immunotropic and anti-tumor activity of this plant and its historical and present medical use.

Key words: *adaptogens, Astragalus, immunity, tumors.*

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Introduction

Astragalus membranaceus (*Fabaceae*) is one of the important traditional herbs used for thousands of years in China and East Asia. It has been prescribed for centuries for general chronic illnesses, weakness and to increase overall vitality. Traditional Chinese Medicine classified *Astragalus* as an herb that reinforced "Qi" and helps protect the body against various stresses, including physical, mental, or emotional stress. It is also still used in China for chronic hepatitis treatment, as an adjunctive therapy in cancer and for its immunostimulating properties [1].

Today animal and modern clinical experiments have shown that *Astragalus* may be useful in protecting the body from many diseases (cardiovascular, neoplastic, infective), in ameliorating chemotherapy side effects, and treatment of diabetic nephropathy. *Astragalus* demonstrates also hepatoprotective and renal protective effects. It exerts diuretic action. The saponins from *Astragalus* demonstrate positive effect on heart function. Some compounds get from *Astragalus* have antioxidant properties, inhibit the formation of lipid peroxides in the myocardium, and decrease blood coagulation. In the study of Bian and Li total flavanoids fraction of *Astragalus mongholicus* expressed stronger antioxidant activity than total saponins and total polysaccharides [2-8].

Wojcikowski *et al*. [9] reported beneficial effect of *Astragalus* extract combined with extract of *Angelica sinensis* and ACE inhibitor Enalapril on tubulointerstitial kidney fibrosis in rats suffering of obstructive uropathy. This combination of drugs was significantly more effective than Enalapril alone in reducing tumor necrosis factor α (TNF-α) and transforming growth factor β1 (TGF-β1) levels, fibroblast activation, collagen accumulation and tubular cell apoptosis. It was also reported by Chen *et al.* that *Astragalus* polysaccharides (APS) could inhibit diabetic cardiomyopathy in hamsters [10].

Astragalus and immunity

Astragalus has antibacterial and anti-inflammatory properties. It works by stimulating several factors of the immune system. In bone marrow and lymph tissue the polysaccharides from *Astragalus* increase the number of stem cells and encourages their development into active immune cells. It stimulates the immune antitumor activity of interleukin 2 (IL-2) *in vitro*. It helps to trigger immune cells from a "resting" state into heightened activity. It corrects the responses of lymphocytes from normal subjects and cancer patients, potentiates effort of the natural killer cell activity and the activity of monocytes. The component isolated from *Astragalus* roots, phytoestrogen formononetin, reduces arachidonic acid release and production of nitric oxide in lipopolysaccharide activated macrophages, and accelerates wound repair.

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Radix *Astragali* (RA) is traditionally prepared from the dried roots of *Astragalus membranaceus* (MJHQ) and *Astragalus mongholicus* (MGHQ) and is used to support and protect the immune system. The main immunomodulatory constituents isolated from *Astragalus* sp. are polysaccharides, triterpenoid saponins (cycloastragenol, astragaloside I to VIII, and cyclocanthoside), cycloartane triterpene and isoflavonoids. From the *Astragalus* roots phytosterols, a volatile oil, aminoacids, including γ-aminobutyric acid and L-canavanine, have been isolated also. The polysaccharides found in *Astragalus* have received a great deal of attention, especially the polysaccharide fraction F3. Polysaccharides A, B, and C have been identified as glucans, and polysaccharide D as a heteropolysaccharide. The component isolated from *Astragalus* roots, phytoestrogen formononetin, reduces arachidonic acid release and production of nitric oxide in lipopolysaccharide activated macrophages, and was described as a blood enhancer. Formononetin accelerates fracture healing and wound repair by the regulation of early growth response factor-1 (Egr-1) transcription factor, and through stimulating angiogenesis by up-regulating vascular endothelial growth factor (VEGF) receptor. Water extract of *Astragalus membranaceus* promotes peripheral nerve regeneration in rats [11-14].

From the wide spectrum of chemical compounds present in plants belonging to *Astragalus* species, polysaccharides are ones of the most active. They display activities in many biological systems, such as immunotropic and anti-inflammatory activity, protection of vessels, and erythroid differentiation. Jiang et al reported the effects of *Astragalus* polysaccharides on immunologic function of erythrocyte in chickens infected with infectious bursa disease virus. In infected chickens blood various types of immune complex and C(3b)rosettes were measured. The results suggested that infection suppressed function of chicken erythrocytes, and the treatment with *Astragalus* polysaccharides have recovered it.

Astragalus polysaccharides combined with alkaloid oxymatrine of *Sophora flavescens* Ait. (SF) has long been used in a variety of Chinese herbal formulations to treat patients with cancer. Chen et al reported that this combination can synergistically improve the immune efficacy of Newcastle disease vaccine in chicken.

Dang *et al.* evaluated the anti-viral effect of *Astragalus* polysaccharide combined with emodin in hepatitis B virus (HBV) transgenic mice. In this study APS and emodin had a weak, but persistent inhibitory effect on HBV replication *in vivo.*

In many study *Astragalus* expressed antiviral activity, it demostrated protective effect to cells against *coxsackie B-2* virus, synergistically acted with the interferon therapy to human *papillomavirus* type 16 (HPV-16), *Herpes simplex* virus type 2 (HSV-2), and *cytomegalovirus* (CMV). *Astragalus* stimulates production of TNF-α when is used in high concentrations *in vitro.* Perhaps it is regulating TNF, that effects phagocytosis. The saponins from *Astragalus* acivate NK cells and restore steroid-inhibited activity of NK cells *in vitro.* The flavonoids from *Astragalus* 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. Many researches in the United States carried *Astragalus* as a possibile treatment for patients whose immune answer have been compromised by radiotherapy or chemotherapy. *Astragalus* stimulate macrophages to produce interleukin-6 and TNF so it has been used to increase resistance to the immunosuppressive effects of chemotherapy drugs [1, 3, 4, 15-24].

The antibacterial activity of *Astragalus* to *Shigella dysenteriae*, *Streptococcus hemolyticus*, *Diplococcus pneumonia*, and *Staphylococcus aureus* was described *in vitro.*

In vivo, *Astragalus* radix enhanced immune response of fish *Cyprinus carpio* and exerted protection against *Aeromonas hydrophila* infection. Synergy of *Astragalus* polysaccharides and probiotics on immunity and intestinal microbiota in chicks was also reported. *Astragalus* polysaccharides enhance innate immune response of bladder epithelial cells through upregulation of TLR4 expression during mucosal bacterial infection of urinary tract. It was also described, that *Astragalus* can correct the immunologic dysfunction of children with Henoch-Schonlein purpura through increasing the IL-12, and decreasing the IL-10 and IL-18 secretions of peripheral blood mononuclear cells.

Astragalus polysaccharides induced the activation and differentiation of dendritic cells and a dose-dependent relationship was observed between *Astragalus* stimulation and IL-12 production. Yang *et al.* have investigated the possible adjuvant effect of aqueous extracts obtained from *Astragalus membranaceus* and *Scutellaria baicailensis* on the immune response to *Toxoplasma gondii*, and obtained positive results. Other Chinese authors described adjuvant activities of saponins from traditional Chinese medicinal herbs, among them, from *Astragalus* [19, 25-29].

Astragalus and endothelial cells

Astragalus membranaceous extract is a widely used herbal remedy for the treatment of cardiovascular diseases in China. Experimental studies performed in rats, on *in vitro* and *in vivo* models provided evidence of significant stimulatory effect of this remedy on proliferation, migration and tube formation of endothelial cells and angiogenesis *in vivo.*

In rat model of ischemic injury *Astragalus* extract inhibited cardiac fibrosis, reduced infarct size, and increased expression of VEGF and capillary and arteriole densities.

This remedy and one of its saponins, astragaloside IV, in *in vitro* experiments performed with rat aortal rings or human umbilical vein endothelial cells, exerted protective effects on free fatty acid – or homocysteine – induced endothelial cell dysfunction, due to oxidative stress.

Astragaloside IV content is main criterion of quality control of *Astragalus membranaceus* in the Pharmacopoeia of the People's Republic of China. There is experimental evidence of its ability to eliminate reactive oxygen species (ROS), due to which it protects cardiomyocytes from oxidative stress – mediated injury, and protects *coxsackievirus* B3 – induced murine myocarditis [30-32].

Astragalus and tumors

Experimental studies performed in mice showed that *Astragalus membranaceus* could exhibit both *in vitro* and *in vivo*, anti- tumor effect. Directly, macrophage-like and myeloid tumors were more sensitive to its cytostatic activity than fibroblast-like tumors and Ehrlich ascites carcinoma. Indirectly, *Astragalus* strongly exerted anti-tumor effects through activating anti-tumor immune response of the host.

Astragalus was shown to delay chemical-induced hepatocarcinogenesis in rats.

In vitro, *Astragalus* extracts inhibit proliferation, induce apoptosis, and interrupt caryocinesia at G0-G1 phase or S phase in hormone-sensitive (MCF-7) breast cancer cells line. Astragalosides combined with salvianolic acids exert anti-hepatoma (HepG2) cell invasion effect by modulating TGF-beta/Smad signaling. Recently, cytotoxic effect of cycloartane-type triterpen glycoside, cyclocephalogenin, isolated from *Astragalus aureus* Willd, against human breast cancer (MCF7) was described.

Most of the clinical trials on *Astragalus* were conducted in China. Anecdotal and preliminary human data show that *Astragalus* reduce immuosuppression due to chemotherapy, may also enhance the effects of platinum-based chemotherapy in advanced non-small cell lung cancer, and appears promising for patients with colorectal cancer. Conclusions from a meta-analysis suggest some beneficial effects for hepato-cellular cancers.

The phase II study from Korea conducted to assess the effect of *Astragali* radix decoction in patients with anorexia in advanced cancer, revealed the beneficial effect of such therapy. Appetite and body weight were improved with this herbal decoction, administered 30 min after meals, three times a day, for 3 weeks [5, 33-39].

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