Pharmacological effects of Astragaloside IV: a literature review

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OBJECTIVE: To review the pharmacological effects and mechanisms of action of Astragaloside IV in Huangqi (Radix Astragali Mongolici).

METHODS: Articles focusing on Astragaloside IV in English and Chinese in databases were collected and reviewed in order to summarize the latest extraction separation, pharmacokinetics, and the pharmacological effects of astragaloside IV.

RESULTS: Protective effects of Astragaloside IV on the cardiovascular system, immune, digestive, nervous system were identified, and the action mechanisms were associated with regulation of the calcium balance, anti-oxidant, antiapoptosis, antivirus, and so on.

CONCLUSION: Astragaloside IV has broad application prospects, especially in cardiovascular diseases, digestive diseases, cancer and other modern high incidence, high-risk diseases, and could be developed as a medicine.

Key words: Astragaloside IV; Extraction; Pharmacokinetics; Pharmacology

INTRODUCTION

In the Chinese Pharmacopoeia, Huangqi (Radix Astragali Mongolici) is described as the dried root of leguminous plants Mongolia Astragalus [Astragalus membranaceus (Fisch.) Bge.). It was first described in the Chinese book Shen Nong Ben Cao Jing in 200 AD with a wide range of treatment effects and no toxicity. It nourishes Qi and blood, and is used for the treatment of cardiovascular disorders, hepatitis, kidney disease, and skin diseases.

According to some reports, the constituents of Huangqi (Radix Astragali Mongolici) include saponins, polysaccharides and flavonoids. More than 40 constituents in Astragalus saponins have been identified from the astragalus root, of which Astragaloside IV is the main compound. Astragaloside IV has various pharmacological activities and is used as a quality-control marker component of Huangqi (Radix Astragali Mongolici) in the Chinese Pharmacopoeia (2005 version). In recent decades, the molecular analyses, pharmacokinetics and pharmacological actions of Astragaloside IV have been studied extensively, which could enable its clinical use.

STRUCTURE, EXTRACTION AND PHARMACOKINETICS OF ASTRAGALOSIDE IV

Astragalus saponin IV (also known as Astragaloside IV and As IV) is 3-O-beta-D-xylopyranosyl-6-O-beta-D-glucopyranosyl-cycloastragenol, is a lanolin alcohol-shaped tetracyclic triterpenoid saponin with high polarity, and its molecular formula is C31H46O14. Its molecular structure is shown in Figure 1.

Some extraction and separation methods of Astragaloside IV (e.g., ultrafiltration, high-speed centrifugation,
reduce collagen synthesis and apoptosis of myocardial myocarditis, inhibit the replication of CVB, as well as increase the prevalence of survival of mice suffering from myocardial injury. It has been shown that, after peritoneal injection of viral myocarditis by peritoneal injection, intragastric administration of Astragaloside IV inhibits the calcium overload caused by calcium. This is related to its high molecular weight, low solubility in fat, and low transmittance in the intestinal tract. Its rate of intravenous combination with plasma protein A is ≈90%. Oral absorption (by passive diffusion in the intestinal tract) has low bioavailability (7.4%) which is related to its high molecular weight, low solubility in fat, and low transmittance in the small intestine. Hence, the selection of pharmaceutical forms is particularly important to improve the oral bioavailability of Astragaloside IV.

**PHARMACOLOGICAL ACTIVITIES OF ASTRAGALOSIDE IV**

**Effect of astragaloside IV on cardiac function**

Lack of a blood supply or oxygen in the myocardium can weaken cardiac function and jeopardize health. Hu et al. reported that Astragaloside IV can protect the myocardial cells of rats from damage caused by lack of oxygen, and increase the content and activity of superoxide dismutase (SOD) in the cytoplasm. Astragaloside IV can improve the cardiac function of the ischemic myocardium and myocardial infarction in rats.7 The mechanism of action would be related to the calcium antagonistic effects of Astragaloside IV. That is, Astragaloside IV inhibits the calcium overload caused by ischemia and hypoxia, thereby restoring the balance between free calcium and total calcium, improving the activity of calcium pumps in erythrocyte membranes, and reducing the secondary injury caused by calcium.7 Coxsackie virus B (CVB) is the main pathogenic factor of viral myocarditis. It has been shown that, after the modeling of viral myocarditis by peritoneal injection to Balb/C mice with CVB, intragastric administration with 9% Astragaloside IV for 7 days can increase the prevalence of survival of mice suffering from myocarditis, inhibit the replication of CVB, as well as reduce collagen synthesis and apoptosis of myocardial cells.9 Li et al. confirmed that Astragaloside IV can suppress myocardial oxidative injury as well as the apoptosis of myocardial cells induced by adriamycin. These findings showed that the mechanisms of action of Astragaloside IV against myocardial damage may be related to regulation of calcium homeostasis, anti-apoptosis and anti-oxidation.

**Effect of Astragaloside IV on the endothelium and functions of blood vessels in newborns**

Vascular endothelial cells are not only the place where blood and tissue fluid complete metabolism and gas exchange but also important endocrine glands that produce and secrete biologically active substances. Vascular endothelial cells play important parts in the maintenance of vascular tension, regulation of blood pressure and anti-thrombosis, and have important effects in the pathogenesis of hypertension, cardiovascular disease and cerebrovascular disease in vitro experiments demonstrated that Astragaloside IV can promote the proliferation of human umbilical vein endothelial cells and the formation of tube-like structures. Astragaloside IV can also promote angiogenesis and keep blood vessels from reducing in vivo in zebrafish. The promotion of angiogenesis can be closely associated with increases in the expression of vascular endothelial cell growth factor and its receptor, thereby activating the pathway of protein kinase B and phosphoinositide 3-kinase as well as regulation of the expression of hypoxia inducible factor protein.11,12 With regard to protection of endothelial function, Ji showed that Astragaloside IV can resist lipoprotein- or acute hyperglycemia-induced injury to endothelial cells, increase the content of malondialdehyde (MDA) and SOD, and inhibit the decrease in endothelial resistance and increase in the permeability of single-layer endothelial cells. The mechanism of action may be associated with regulation of the translocation and activation of high glucose-induced protein kinase C (PKC)α and PKCβ2 in endothelial cells, downregulation of expression of PKC protein and improving the cytoskeleton of endothelial cells, especially those related to F-actin reconfiguration.13 The pathogenesis of the effect of Astragaloside IV on vascular endothelia needs to be clarified, but it protects the endothelium, has antioxidation effects, and promotes the growth of blood vessels. Hence, it could cure diseases caused by abnormal vascular function.

**Effect of Astragaloside IV on metabolism of collagen**

With respect to regulation of the decomposition and synthesis of collagen, Astragaloside IV has a dual effect. Astragaloside IV has protective effects on ultraviolet A-induced photoaging in human fibroblasts, promotes the proliferation of human fibroblasts, and prevents collagen degradation (which is related to reducing matrix metallopeptidase-1 expression and increasing expression of tissue inhibitor of metalloproteinases expression).15,16 Conversely, *in vivo* and *in vitro* experiments...
have shown that Astragaloside IV can resist collagen deposition, and treat the development of organic fibrosis such as in the heart, liver, lungs, and kidneys. For example, Meng et al.\(^7\) reported that Astragaloside IV synergizes with ferulic acid and can inhibit renal tubulointerstitial fibrosis in rats and can also inhibit expression of alpha smooth muscle actin and transforming growth factor (TGF)-\( \beta \) in NRK-49F and HK-2 cells in vitro. Porcine serum-induced hepatic fibrosis in rats and CVB3-induced cardiac-muscle fibrosis in mice can be inhibited by Astragaloside IV,\(^{19,20} \) and is manifested as downregulation of TGF-\( \beta \) expression, and time-dependent increases in MMP13/14 expression with dose.

**Protective effect of Astragaloside IV on the liver**

Cheng et al.\(^21\) noted that pretreatment with Astragaloside IV can protect against ischemia-reperfusion injury after liver transplantation in rats, and participate in up-regulation of the expression of the glucocorticoid receptor and inhibition of nuclear factor-kappa B transcriptional activity. Astragaloside IV acted on HepG2 cells transfected with hepatitis-B virus, and secretion of hepatitis-B surface antigen, hepatitis-Be antigen as well as serum HBV DNA levels were reduced.\(^22\) These results pointed to the anti-inflammatory and antiviral activities of Astragaloside IV.

**Effect of Astragaloside IV on the endocrine system**

The metabolic syndrome is the main risk factor for cardiovascular diseases and glycuresis. Wang et al.\(^23\) found that treatment with Astragaloside IV could improve fructopyranose-induced metabolic syndrome in rats by increasing levels of nitric metabolite and cyclic guanosine monophosphate, which manifested as reduction in blood pressure and improvement in insulin resistance. In the treatment of mice with type-2 diabetes with Astragaloside IV, the level of glycogen phosphatases and glucose-6-phosphatases in the liver was reduced, leading to relief of insulin resistance and reductions in the level of blood sugar and triglycerides.\(^24\)

**Effect of Astragaloside IV on nervous system**

The protective effects of Astragaloside IV against ischemic-reperfusion injury in the brain has been identified in a murine model of transient focal ischemia related to antioxidation, and it is hoped that Astragaloside IV can become a medicine to cure apoplexy.\(^25\,26\) Astragaloside IV can relieve the decrease in the levels of dopamines in 6-Hydroxydopamine-induced substantia neu- rons,\(^27\) so it could be used for curing Parkinson’s disease. Cheng et al.\(^28\) found that different concentrations of total Astragalus saponins had dual effects on reviving the peripheral nervous system.

**Effect of Astragaloside IV on the hematopoietic system**

Astragaloside IV can protect the hematopoietic system from injury due to \( \gamma \)-rays in rats.\(^29\) It can prolong survival, increase three series of blood cells, promote the proliferation of bone-marrow stem cells, and reduce the ratio of G0/G1 cells.\(^30\) It can also increase the expression of stem cell growth factor.\(^31\)

**Effect of Astragaloside IV on the organic immune system**

As an immune-enhancement agent, Astragaloside IV could be used for curing cancer, and it does not have obvious side effects.\(^32\) Whether used alone or with \( \beta \)-elemene, Astragaloside IV can enhance the expression of major histocompatibility complex molecules and immune co-stimulus factors on the surface of dendritic cells (DCs) as well as improve the secretion of interleukin 2 and interleukin 6 to develop antigen presentation and induce T-cell responses.\(^33\) These actions provide the immunological basis for curing gastrointestinal cancers in Traditional Chinese Medicine by tonifying Qi and activating the blood circulation. In a murine model of asthma, Astragaloside IV was shown to increase the level of interferon-\( \gamma \) and improve hypersensitivity in the airways, and decrease the expression of TGF-\( \beta \) and thymic stromal lymphopoietin at the protein level.\(^34,35\) Astragaloside IV against the proliferation of HepG2 cells was associated with a reduction in the expression of oncogenes such as Vav 3.1, and was dose- and time-dependent.\(^36\) It can also reverse multidrug resistance in HepG2/glucosyleramide synthase (GCS) cells, which may be related to reducing expression of the GCS gene in cells.\(^37\) Furthermore, it had effects on resistance of the proliferation of the human breast carcinoma cell line MDA-MB-231 by reducing Akt phosphorylation.\(^38\)

**CONCLUSION**

In the last decade, several studies have focused on the extraction separation, pharmacokinetik and pharmacological activities of Astragaloside IV, but further investigation is needed. For example, Astragaloside IV is considered to be a marker component of total Astragalosides, what have different effects to Astragaloside IV. Many researchers focused on the single pharmacological action of Astragaloside IV; whether a combination of Astragaloside IV with other medicines can be used to cure diseases merits further study. Astragaloside IV has a wide range of pharmacological actions reported from several studies, so the prospect of clinical application is quite good.

**REFERENCES**

Ren S et al. / Review