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Review Article

Pharmacological Review on *Astragalus membranaceus*: Chinese Traditional Herb

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ABSTRACT

Astragalus membranaceus is a Chinese medicinal plant belonging to the family Leguminosae. This plant is actively used in traditional Chinese medicine for its diverse therapeutic application. The plant contains various active phytochemicals that produce various pharmacological activities. From the literature review, the essential pharmacological activities of *Astragalus membranaceus* are reduce oxidative stress, neuroprotective, antiviral, anti-cancer, immunomodulatory, vascular protective, and antimicrobial activities. In this review, we summarize the pharmacological activities of *Astragalus membranaceus* with the proper mechanism of action.

Keywords: Phytoconstituents, Neuroprotective, Antiviral, Anti-neoplastic, Immunodulatory agent, Alzheimer, Cardioprotective.

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INTRODUCTION

Nowadays, traditional Chinese medicine is an important complementary or alternative drug delivery system. Traditional Chinese medicine treatments are based on a holistic approach.[1] *Astragalus membranaceus* (Fisch.) Bunge is a traditional Chinese medicinal herb belonging to the family Leguminosae. The plant is 50–150 cm high, with a straight, long, cylindrical root, measuring 20–50 cm. It consists of an erect type of stem.[2] The root of *Astragalus membranaceus* is known as Huangqi in the Chinese language. The herb is well-known for its various pharmacological activities like neuroprotective, antiviral, anti-cancer, immunomodulatory, vascular protective, and antimicrobial actions.[3] It is also used as a vital-energy tonifying agent. Several herbal formulations are prepared to use the different parts of this Chinese herb. The literature has revealed that the polysaccharide fractions of *Astragalus membranaceus* modulation of immune functions of the human body. The native of *Astragalus membranaceus* is Northern China and the elevated regions, including the provinces of Inner Mongolia, Shanxi, Gansu, and Heilungkiang.[4]

The essential medicinal parts of *Astragalus membranaceus* is four-to seven-year-old dried root. Worldwide more than 2000 species of Astragalus -are available. *Astragalus membranaceus* (Fisch.) Bunge is mostly used as a Chinese traditional medicine.[3] *Astragalus membranaceus* consist of a complex chemical profile. Identified major active phytochemicals are triterpene saponins, flavonoids, and polysaccharides. Other phytoconstituents are triterpene saponins, flavonoids, and polysaccharides. Other components found in the herb include phytosterols, L-canavanine, sterols, betaine, choline, (+)-lariciresinol, (-)-syringaresinol, lupenone, 3-hydroxy-2- methylpyridine, amino acids, bifendatatum, and coumarin. Identified essential minerals are zinc, iron, copper, magnesium, manganese, calcium, sodium, and potassium.[5] The aim of this review is a summarization of pharmacological activities of *Astragalus membranaceus*.

Pharmacological properties of *Astragalus membranaceus*

Oxidative stress reduction

The dried root extract of *Astragalus membranaceus* was found to inhibit the oxidative stress via the up-regulation of antioxidant factors i.e., keeping up the action of superoxide dismutase, reducing the formation of malondialdehyde and free radicals as well as diminishing cell apoptosis.[6] Extracts of *Astragalus membranaceus* can inhibit the mechanism of oxidative stress *via* upregulating the antioxidant factors. In myocardial ischemic rat model, aqueous extract of *Astragalus membranaceus* reduced the myocardial infarction size and ameliorate the cardiac function via maintaining the level of superoxide dismutase, decreased the levels of lipid peroxidation and free radical generation, and reducing programmed cell death i.e apoptosis.[7] In

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rat model of cerebral ischemia, treatment with *Astragalus membranaceus* can profoundly decreased the levels of malondialdehyde and reactive oxygen species via upregulating the expression of superoxide dismutase, glutathione peroxidase, catalase and nuclear factor erythroid 2-related factor 2.[8] High cholesterol feeding in atherosclerotic rabbit model, treatment with *Astragalus flavonoids* reduced the plasma levels of low-density lipoprotein-cholesterol and total cholesterol, increased the high density lipoproyein-cholesterol levels and reduced the aortic fatty streak area.[9] In PC12 cell lines models, isoflavanoids derived from *Astragalus membranaceus* including calycosin, formononetin shown neuronal protection *via* scavenging free radicals' generation in a dose dependent manner.[10] *Astragalus* polysaccharide from *Astragalus membranaceus* shows protective antioxidant properties under *in-vitro* and *in-vivo* conditions.[11,12] *Astragalus* polysaccharide increasing the levels of glutathione, superoxide dismutase, catalase, inhibit the formation of malondialdehyde.[13] In mitochondria of mouse brain and liver, it was shown that treatment with *Astragalus* polysaccharide protects mitochondria from oxidative dysfunction, increased the activities of antioxidase enzymes.[14]

Neuroprotective effect

The aqueous extract of dried roots of *Astragalus membranaceus* shown neuroprotective effect via reversing neurodegeneration and memory impairment. In a rat model, it can increase the number of muscarinic-cholinergic receptor in the cortex and hippocampus region.[15] Additionally, treatment with aqueous extract of *Astragalus membranaceus* prevent the loss of synapses and axon in the hippocampus, and cortex and improved memory impairment.[16] Astragalosides are cycloartone triterpenoid saponins derived from *Astragalus membranaceus* showed improved learning and memory in the Alzheimer's disease model via downregulating the expression of amyloid β (1-40), amyloid precursor protein, and β secretase in hippocampus regions of rats.[17] Moreover, in cerebral ischemia rat model treatment with astragalosides improved the learning and memory abilities by improving the expression of p-ERK and p-Akt, decreasing the expression of p-JNK.[18] An isoflavanoid derived from *Astragalus membranaceus*, formononetin protects the neurons and reduced the apoptotic cells activities by increasing the levels of procaspase-3 and Bcl-2 and decreasing the levels of caspase-3 and Bax.[19] In the Parkinson's disease model induced by 6-hydroxydopamine, administration of astragalosides-IV prevents the loss and degeneration of dopaminergic neurons, increased the nitric oxide synthase levels of dopaminergic neurons and increased the number of tyrosine hydrolase immunopositive neurons.[20]

Antiviral effects

The *Astragalus* polysaccharides could inhibit the reproductive capacity of herpes virus at a concentration of 30μg/mL which leads to a reduction in the occurrences of tumor.[21] It has also been reported that the efficacy of foot and mouth disease virus (FMDV) vaccine can be significantly enhanced by utilizing 0.5mg of APS.[21] APS have the potential to protect our body from viruses by inducing the production of interferons which further leads to the inhibition of viral reproduction.[21] *In-vitro* study revealed that by reducing the levels of oxidative markers and activation of the necrosis factor-κB signaling pathway, *Astragalus* polysaccharide inhibits the replication of porcine circovirus type 2.[22] At a concentration of 30 μg/mL, *Astragalus* polysaccharide significantly inhibits the expression of transcription activator and zipper transcription factor.[23] Similarly, under *in-vitro* conditions *Astragalus* polysaccharide inhibits the replication of infectious bronchitis virus. After treatment with *Astragalus* polysaccharide, the levels of proinflammatory cytokines decrease, these results revealed that *Astragalus* polysaccharide had some activity against bronchitis virus.[24]

Anticancer activity

It has been proven in various clinical studies that a traditional Chinese medicine formulation which comprised of *Astragalus*, significantly improved the therapeutic efficacy of chemotherapy.[25] The stimulation of hematopoietic components as well as production of interleukins was found to be the most effective pathway for this formulation.[25] It was also observed that the formulation comprising of *Astragalus* prevented the occurrence of malignancy thus, prolonging survival.[25] This formulation is also capable of expanding the resistance to immunosuppresion brought about by radiotherapy and antineoplastic medications through the stimulation of macrophages for formation of IL-6 as well as tumor necrosis factor.[25] The extract of *Astragalus membranaceus* combined with anticancer drug, shown positive effect on the treatment of cancer.[26] The hepatocellular carcinoma cell line HepG2, combination of aqueous extract of *Astragalus membranaceus* with *Salvia miltiorrhiza* could inhibit the invasion of tumor cells by modulating the expression of TGF-beta/Smad signaling.[27] Another research work shown that in the hepatocellular carcinoma cell rat model induced by diethylnitrosamine, combination of aqueous extract of *Astragalus membranaceus* with *Salvia miltiorrhiza* could inhibit fibrosis and the transcription of plasminogen activator inhibitor-1 *via* reducing the incidence and multiplicity of hepatocellular carcinoma cell development in a dose dependent manner.[28,29] In a time and dose dependent manner, aqueous extract of *Astragalus membranaceus* can inhibit the growth of human gastric cell lines AGS and KATO-III.[30]

Astragalus membranaceus saponins can inhibit the spread of colon cancer and induce apoptosis. In colon cancer cells HCT116 and HT-29, *Astragalus membranaceus* saponins shown antineoplastic activity *via* modulating the expression of Akt/p13k/mTOR and ERK signaling pathway.[31,32] Similarly, *Astragalus membranaceus* saponins hindered the cell cycle process at the G2/M phase through regulating p21, cmyc and cyclin B1 in human gastric adenocarcinoma cells.[33] In a lung cancer mice model induced by indoleamine 2,3 dioxygenase, administration with astragalosides-IV inhibit the growth of tumor, interfered with T-cell immunity by decreasing Tregs.[34] In breast cancer cell line MDA-MB-231, treatment with astragalosides-IV suppressed the cell viability and invasions of tumor cells, downregulated the expression of Vav3, MMP-2, and MMP-9 through suppressing the activation of ERK1/2 and JNK.[35] In the hepatic cancer rat model induced by N-diethylnitrosamine, rhamnocitrin 4-β-d-galactopyranoside isolated from *Astragalus membranaceus* protects hepatocellular carcinogenesis by increasing the levels of antioxidant enzymes *viz* superoxide dismutase, glutathione peroxidase, glutathione-S-transferase, catalase and decreasing the level of lipid peroxidation.[36,37] In HepG2 cell line, *Astragalus* polysaccharide inhibit the proliferation, arrest cell cycle in the G1 phase and induce apoptosis.[38,39] In tumor bearing mice, treatment with *Astragalus* polysaccharide ameliorate proliferation and activity of intestinal intraepithelial γδT cells by increasing the levels of FasL, GrB and IFN-γ in γδT cells.[40] In Kunming mice with Ehrlich's ascites carcinoma, *Astragalus* polysaccharide can inhibit the growth of tumor cells, decreasing the levels of CDK4 and Bcl-2, increased the percentage of CD^{3+} and CD^{4+} T-lymphocytes, the ratio of CD^{4+}/ CD^{8+} T-cells and the expression of IL-2/IL-2R in spleen and Bax in tumor tissue.[41]

Immunomodulatory effect

A study was conducted to observe the effects of total flavonoids in *Astragalus* on the macrophage-phagocytic index by utilizing the carbon clearance method.[42] This study revealed that total flavonoids in concentrations of 25, 50 and 100mg/kg led to a significant increment in the phagocytosis of macrophages leading to commencement of mononuclear phagocytic framework of immune response against the

unfamiliar materials in our body.[42] Lymphocyte proliferation plays a very crucial role in cellular and humoral resistance thus resulting in activation of a cascade of responses.[43] Thus, the researchers conducted a study to evaluate the immunomodulatory activity of *Astragalus* polysaccharide-iron (III) complex by utilizing the lymphocyte proliferation method.[43] The results of this study indicated that when the concentration of astragalus polysaccharide -iron (III) complex was 50μg/mL the lymphocyte proliferation expanded by 35.7% in contrast to that observed with *Astragalus* polysaccharide.[43] The aqueous extract of *Astragalus membranaceus* also has significant role to promote immune function. In peripheral blood region of mononuclear cells, aqueous extract of *Astragalus membranaceus* induced migration and monocyte maturation.[44]

In the macrophage cell line ANA-1 induced by advanced glycation end products, aqueous extract of *Astragalus membranaceus* inhibits the production of cytokine *via* arresting p38 MAPK and necrosis factor-κB signaling pathway.[40,45] It was shown that the aqueous extract of *Astragalus membranaceus* activated CD^{4+} and CD^{8+} T-cells of humans without influencing proliferation.[46,47] In the mouse macrophage cell line RAW264.7, *Astragalus* saponins can inhibits lipopolysaccharide induced inducible nitric oxide synthase and TNF-α expression via arresting p38MAPK/NF-κB signaling pathway.[48] In mice primary splenocytes and T-cells, it was shown that astragalosides increased the phosphatase activity of CD45.[49] Additionally, proliferation of T and B lymphocytes, and antibody production was increased by astragalosides-IV but suppressed the production of IL-1 and TNF-α from peritoneal macrophages.[50] In HIV-infected patients, astragalosides-IV combined with cycloastragenol may upregulated the activity of telomerase, improved the proliferation and immune function of CD^{8+} T lymphocytes *via* activating Src/MEK/ERK pathway in a dose and time dependent manner.[51] Also, astragalosides-IV profoundly inhibits the lipopolysaccharide and TNF-α induced expression of E-selectin and VCAM-1 *via* arresting the NF-κB pathway.[52] In lipopolysaccharide stimulated RAW264.7 cells, it was revealed that formononetin, an isoflavanoids progressively inhibits the production of nitric oxide and the expression of inducible nitric oxide synthase and cyclooxygenase-2.[53,54]

Vascular protective activity

It has been found that the *Astragalus* saponins are the chief bioactive constituents present in the roots of *Astragalus membranaceus*.[55] The ability of *Astragalus* saponins to enhance the removal of free radicals and to significantly minimize lipid peroxidation is of utmost importance as the *Astragalus* saponins were found to have a protective effect against ischemia repurfusion injury.[55] In the rat myocardial infarction model, treatment with astragalosides promotes angiogenesis via increasing the expression of VEGF and basic fibroblast growth factor.[56] In acute myocardial infarction rat model, treatment with astragalosides-IV protects the cardiac function, reduced the infarct size and inhibit the left ventricular fibrosis.[57] In neonatal rat primary cardiomyocytes, astragalosides-IV reduced the levels of malondialdehyde and reactive oxygen species by upregulating the glutathione peroxidase and superoxide dismutase activity.[58,59] Moreover, astragalosides-IV can reduce the levels of inflammatory cytokines by downregulating the TLR4/necrosis factor-κB signaling pathway, upregulating sonic hedgehog pathway and the expression of TGF-β.[60,61] In the human cardiac microvascular endothelial cells induced by $Na_2S_2O_4$, astragalus polysaccharide inhibits the cell apoptosis process via improving the levels of superoxide dismutase, Bcl-2, p13k/Akt, decreasing the levels of malondialdehyde, reactive oxygen species, and Bax and inhibiting the caspase-3 activity.[62] In the high fat diet mouse, administration of astragalus polysaccharide reduces the levels of plasma cholesterol by upregulating the expression of low-density lipoprotein-receptor and cholesterol-7α-hydroxylase, increasing neutral sterol excretion and fecal bile acid, and inhibits the intestinal cholesterol absorption.[63] In hind limb ischemia rat models, intramuscularly administration of astragalus polysaccharide significantly increase the expression of VEGF, VEGFR-1, VEGFR-2, Ang-1, and Tie-2.[64]

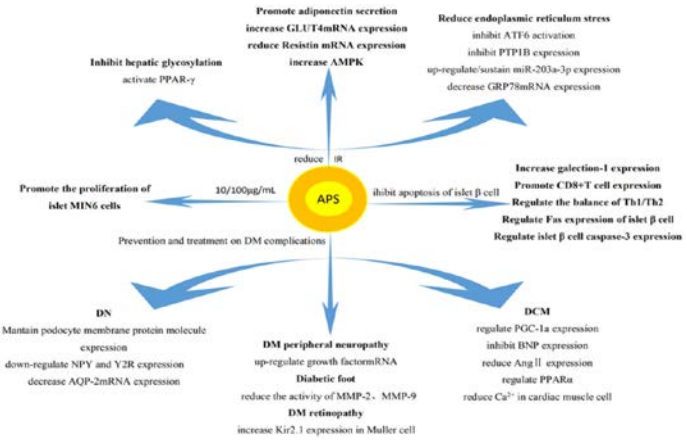

Figure 1: Regulation of blood glucose levels by *Astragalus* polysaccharides.

Antimicrobial activity

The *Astragalus* polysaccharides produced a dose-dependent bacteriostatic effect against pathogenic bacteria like *Streptococcus, Escherichia coli* and *Staphylococcus aureus*.[65] It was also observed that the *Astragalus* polysaccharides could significantly inhibit the strains of *Staphylococcus aureus, Escherichia coli* and *Salmonella* when used in the concentrations of 20mg/L and 40mg/L.[65] Silver nanoparticles were formed by utilizing the water-soluble part of polysaccharides obtained from the roots of *Astragalus membranaceus*.[65] Further studies on the silver nanoparticles revealed that they were resistant to multi-drug resistant bacteria and thus have great potential for their removal from the body.[65]

Antidiabetic activity

Recent studies conducted on the *Astragalus* polysaccharides (APS) have indicated that it significantly lessens the blood glucose, improves any conditions of insulin resistance and also helps in building up the sensitivity to insulin Figure 1.[65] It was also observed to retard the apoptosis of β-cells of islet and thus, plays a crucial role in the remedy of diabetes mellitus.[60,65] In non-obese diabetic mice, it was shown that *Astragalus* polysaccharides reduced the onset and incidence of type1 diabetes mellitus, reduced the inflammation of islet cells, and protects the structure of β cells.[66] Similarly, administration of *Astragalus* polysaccharides (10 and 100 μg/mL) also stimulated the proliferation activity of MIN6 islet cells and decreased the apoptosis of cells. Therefore, improving the production of insulin and lowers the blood glucose levels.[67] In type2 diabetes mellitus, it was shown that *Astragalus* polysaccharides can reduce the levels of blood glucose by reducing endoplasmic reticulum stress in patients, thereby increasing insulin sensitivity.[68] Similarly, *Astragalus* polysaccharides can bind with and activate peroxisome proliferator-activated receptor γ, progressively inhibit hepatic glycosylation, and increased the nonoxidative metabolism of glucose in skeletal muscle.[69] *Astragalus* polysaccharides also promotes cell differentiation, increased the expression of glucose transporter-4 mRNA in adipose tissue and adenosine monophosphate-activated protein kinase in liver tissue of type2 diabetes mellitus, decreased the expression of resistin mRNA and downregulates adipose tissue resistance protein in type2 diabetes rats.[68,70]

CONCLUSION

The antioxidant property is due to the presence of *Astragalus* polysaccharide resulting in augmentation of the action of superoxide

dismutase causing decline of the apoptosis of cell because of declining generation of malondialdehyde and free radicals. Due to this property of antioxidant, utilization in myocardial infarction is greatly exploited. One of the prominent phytoconstituent called *Astragalus flavonoids* decreases the level of low-density lipoprotein-cholesterol in plasma reducing the risk of fatty plug accumulation in artery. This plant has shown excellent result in preventing degeneration of neurons because of the Astragalosides which are cycloartone triterpenoid saponins. Another phytoconstituent called formononetin which is a isoflavanoid which acts safeguarding in neurons. Astragalosides-IV which is a cycloartane-type triterpene glycoside acts in mitigating Parkinson's disease. *Astragalus* polysaccharides which is found in this plant acts as potent antiviral agent curbs the activation of transcription activator and zipper transcription factor. Traditional medicinal use of this plant is also involved in treatment of various types of carcinomas along with combating against immunosuppression after the patient undergoes radiotherapy and anticancer drugs because of presence of astragalosides-IV along with *Astragalus* polysaccharide. The former two phytoconstituents also plays an important role in modulating immune system of the body by upregulating and downregulating various biochemical constituents in our body. The *Astragalus* polysaccharides produced a dose-dependent bacteriostatic effect against pathogenic bacteria like *Streptococcus, Escherichia coli* and *Staphylococcus aureus*. It also possesses antihyperglycemic effect by lowering blood glucose levels.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

APS: Astragalus polysaccharides; **DN:** Diabetic nephropathy; **DCM:** Dilated cardiomyopathy.

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