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Review

Progress in Mechanism of *Astragalus membranaceus* and Its Chemical Constituents on Multiple Sclerosis*

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ABSTRACT The primary chemical components of *Astragalus membranaceus* include polysaccharides, saponins, flavonoids, and amino acids. Recent studies have shown that *Astragalus membranaceus* has multiple functions, including improving immune function and exerting antioxidative, anti-radiation, anti-tumor, antibacterial, antiviral, and hormone-like effects. *Astragalus membranaceus* and its extracts are widely used in clinical practice because they have obvious therapeutic effects against various autoimmune diseases and relatively less adverse reaction. Multiple sclerosis (MS) is an autoimmune disease of central nervous system (CNS), which mainly caused by immune disorder that leads to inflammatory demyelination, inflammatory cell infiltration, and axonal degeneration in the CNS. In this review, the authors analyzed the clinical manifestations of MS and experimental autoimmune encephalomyelitis (EAE) and focused on the efficacy of *Astragalus membranaceus* and its chemical components in the treatment of MS/EAE.

KEYWORDS *Astragalus membranaceus*, chemical components, multiple sclerosis, experimental autoimmune encephalomyelitis, immunoregulation

Multiple sclerosis (MS) is a common demyelinating disease of central nervous system (CNS), with a high incidence in individuals aged 20–30 years.[1] The clinical manifestations of MS include limb weakness, numbness, painful spasms, ataxia, and visual impairments. Moreover, patients with MS need to take medicine for the rest of their lifetime after being diagnosed with MS, and these patients usually have severe disabilities.[2] The primary etiology of MS is immune regulatory dysfunction due to environmental factors and genetic susceptibility.[3] Although great progress has been made in the modern medical for MS treatment in recent years, there is not yet a cure for MS, and current therapeutic drugs have a relatively large number of adverse reaction, especially secondary infections caused by extensive immunosuppression.[4,5] Western medicine (WM) treatment mainly focuses on acute relapse prevention, disease-modifying therapies, and symptom alleviation.[6] The magnitude of MS treatment with WM, such as β-interferon, glatiramer acetate, mitoxantrone, teriflunamide, dimethyl fumarate, fingolimod, alemtuzumab, and natalizumab, has increased.[7,8] However, some serious adverse reactions, such as progressive multifocal leukoencephalopathy (PML) and viral and fungal infections may be induced,[9,10] due to universal immunosuppression.[11-14]

Chinese medicine (CM) includes Chinese herbal medicine (CHM), acupuncture, and other non-medication therapies. The current national medical system in China uses a synergistic combination of CM and WM, producing satisfactory clinical results.[15,16] The 2010 edition of Chinese Pharmacopoeia lists *Astragalus membranaceus* as a leguminous family plant. Pharmacological effects of *Astragalus membranaceus* and its chemical components include immune regulation and antioxidative, anti-radiation, and anti-tumor effects, etc. *Astragalus membranaceus* is used in the clinical treatment of various systemic diseases, particularly autoimmune diseases. An increasing number of research has focused on *Astragalus membranaceus* and its chemical components for

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treating MS.[16-21] In this paper, we summarizes the action mechanism of *Astragalus membranaceus* and its chemical components in the treatment of MS and experimental autoimmune encephalomyelitis (EAE).

Literature Research

Four databases, including ScienceDirect, China Knowledge Resource Integrated Database (CNKI), PubMed, and Scopus, were searched for relevant papers. Keywords "astragalus", "chemical components", "multiple sclerosis", "experimental autoimmune encephalomyelitis" were used to search for *Astragalus membranaceus* and its chemical constituents in treatment of MS and animal models of EAE. All original articles from North America, Europe, Asia, and China, written in English or Chinese, from 1998 to December 2021 were included. The reviews, review-type articles, and case reports were excluded.

Chemical Compositions of *Astragalus membranaceus*

Medicinal astragalus species mainly include perennial herb *Astragalus membranaceus* (Fisch.) Bungeand *A. mongholicus*. The primary function of *Astragalus membranaceus* is to tonify Pi (Spleen) for nourishing qi. The main chemical constituents of *Astragalus membranaceus* are polysaccharides, saponins, flavonoids, alkaloids, and amino acids.[22]

Astragalus Polysaccharide

Astragalus polysaccharide (APS) is mainly composed of dextran and heteropolysaccharides. Dextran mainly consists of α-1,4/1,6-soluble dextran and α-1,4-water-insoluble dextran. Heteropolysaccharides are primarily composed of water-soluble acid heteropolysaccharides, uronic acid-containing polysaccharides, glucose, and arabinose. Water-soluble acid heteropolysaccharides mainly include glucose, rhamnose, arabinose, and galactose, whereas uronic acid-containing polysaccharides include galacturonic acid and glucuronic acid.[19]

Astragalus glycoprotein (HQGP) is a type of binding protein formed by astragalus polysaccharides and polypeptides or proteins in *Astragalus membranaceus* via covalent bonds. Almost all cell types can synthesize glycoproteins. Study has shown that the monosaccharide constituents of HQGP mainly include glucose and arabinose; astragalus polypeptides or proteins are mainly composed of 16 amino acids, with glutamate, arginine, aspartic acid, and lysine being present in the highest proportion.[23]

Saponins

Currently, there are more than 161 types of saponins in *Astragalus membranaceus*, 142 of which are cyclic aromatic saponins and 19 are oleanane saponins. Astragalus saponins are mainly composed of astragalus glycosides Ⅰ–Ⅷ, isoastragalosides Ⅰ, Ⅱ, and Ⅳ, and soybean saponin Ⅰ.[24] Tian, et al[25] used various chromatography-based methods and modern spectral technology to identify 2 triterpenoid saponins in astragalus saponin Ⅱ, a different astragalus saponin Ⅱ, in Mongolian *Astragalus*.

Flavonoids

Flavonoids are divided into 2 classes, including flavonols and isoflavones. Flavonols include kaolin, quercetin, rhamnocitrin, isoquercitrin, and astragalin. Isoflavones include hydroxyisoflavone, calycosin-O-β-D-glucopyranoside, calycosin, ononin, and formononetin.[26] Hydroxyisoflavone and calycosin-O-β-D-glucopyranoside are the main isoflavone components. Tian, et al[25] used various chromatography-based methods and modern spectral technology to identify 6 classes of flavonoid aglycones, namely calycosin, calycosin-7-O-β-D-glucoside, (6aR and 11aR)-9,10-dimethoxy red sandalwood-3-O-β-D-glucoside, and adenine ribonucleoside, in Mongolian *Astragalus*.

Alkaloids

Six alkaloids, viz. astragalus A–F, have been extracted from Mongolian *Astragalus*.[27]

Amino Acids

Twenty-five amino acids, including γ-aminobutyric acid, methionine, threonine, aspartic acid, lysine, glutamic acid, alanine, serine, glycine, proline, alanine cystine, isoleucine, asparagine, leucine, and arginine, have been isolated from *Astragalus membranaceus*.[19]

Other Chemical Compositions

Astragalus membranaceus also contains a variety of other compounds, such as trace elements, cane sugar, phlegmatic, folic acid, bitter principle, amylase, sweet bean extract, niacin, beta sitosterol, vitamin D, riboflavin, vanillic acid, ferulic acid, chlorogenic acid, linolenic acid, caffeic acid, niacin, starch E, carotene, betaine, niacinamide, linoleic acid, lupine alcohol, coumarin, and palmitic acid.[22]

Action Mechanism of *Astragalus membranaceus* and Its Chemical Constituents

Immune Regulation and Anti-Inflammatory Effects

Immune dysfunction is the main pathogenesis of MS.[28] T cells play a key role in the pathogenesis of MS.[29] After a viral infection occurs, T cells are activated, and these activated T cells secrete Th1 and Th2 cytokines. In acute phase of MS, Th1 cytokines are dominant and Th1/Th2 imbalance plays an important role in the pathogenesis of MS.[30] Th17 cells are a highly pro-inflammatory Th cell subtype that has been implicated in various aspects of MS/EAE neuropathogenesis.[31] The breakdown of blood-brain barrier (BBB) causes Th17 cells to accumulate in the cerebrospinal fluid, leading to the formation of MS lesions and promoting the progression of MS/EAE.[32,33]

Wang, et al[17] found that APS reduced serum interleukin (IL)-4 and IL-17 levels in asthmatic rats by regulating Th1/Th2 and Th17/Treg cell balance. In addition, Zhou, et al[18] showed that *Astragalus membranaceus* can effectively reduce the expression of Th17-related factors, such as IL-17, and improve the ratio of $CD4^+/CD8^+$T cells in the peripheral blood of mice with lung cancer. They also demonstrated that HQGP delays the onset of EAE and reduces the severity of EAE, and the therapeutic effect of HQGP on EAE might be mediated by enhanced BBB integrity and its anti-inflammatory effects. Cui,[20] reported that the clinical trial on patients with acute viral myocarditis (AVMC) with a combination of trimetazidine and Astragalus Injection (黄芪注射液). The results found that Astragalus Injection exerted immune regulation and anti-inflammatory effect by reducing C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and IL-6 levels. Study on the treatment of diabetic rats with *Astragalus membranaceus* combined with pueraria has shown that *Astragalus membranaceus* can inhibit the inflammatory response by inhibiting the 5-adenosine monophosphate (AMP) activated protein kinase (AMPK) signaling pathway and expression levels of p38 and mitogen-activated protein kinase (MAPK).[21]

Regulation of Apoptosis-Related Proteins

The apoptosis of tissue cells is closely related to the cysteine protease (caspase) and B-cell B-lymphocytoma-2 (Bcl-2) families.[34] The activation of toll-like receptor 4 (TLR4), nuclear factor-kappa-β (NF-κB) and NOD-like receptor protein 3 (NLRP 3) in astrocytes and microglia can lead to neuronal injury due to neuroinflammation.[35]

Astragaloside Ⅳ, which activates the mammalian target of rapamycin (mTOR) signaling pathways, can reduce caspase-3 and caspase-9 levels and increases livin, microtubule-associatedprotein-1-lightchain3 (LC3-Ⅱ), beclin 1, autophagy-related 5 (Atg5), and lysosome-associated membrane protein-2 (LAMP2) levels, thereby protecting the neurons against apoptosis.[36] Astragaloside Ⅳ plays a neuroprotective role in the oxygen deprivation reoxygenation (OGD/R) model of pheochromocytoma 12 (PC12) cells, and its protective mechanism may be related to activation of phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) signaling pathway and inhibition of apoptosis.[37] Huang, et al[38] studied the effects of astragaloside Ⅳ and pseudo-ginseng in a cerebral ischemia reperfusion mouse model. The results showed that astragaloside Ⅳ can inhibit neuronal cell apoptosis by inhibiting JNK signaling pathway and caspase-12 expression level.

Repair of Axon Demyelination Lesions

Oligodendrocytes in CNS are the primary components of myelin sheath;[39] which can accelerate nerve transmission and provide insulation and nutrition. Myelin loss induced by oligodendrocyte disintegration and death is closely related to the pathogenesis of MS.[40]

Astragalus proteoglycan is effective for the treatment of EAE; its neuroprotective mechanism involves significant reduction in secretion of TNF-α and IL-6 in EAE mice by inhibiting the inflammatory response. Astragalus proteoglycan promotes the secretion of IL-10 and interferon-γ (IFN-γ), regulates the expression of immune cells, reduces the number of $CD68^+$ macrophages and $CD11b^+$ cells in the mouse spinal cord, inhibits the expression of inducible nitric oxide synthase (iNOS) and chemokine chemotactic chemokine ligand 5 (CCL-5) in the spinal cord, and increases the expression levels of microtubule-associated protein 2 (MAP-2) and neuronal nuclear antigen (Neu N).[41] APS also exerted neuroprotective effects in a dicyclohexone oxalodicylhydrazone (CPZ) mouse model mainly by inhibiting Cu^{2+} activity, alliviating myelin loss, increasing the expression of myelin basic protein (MBP), and inhibiting microglia cell aggregation in brain.[42]

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Protection of Nerve Cells and Recovery of Cellular Function

The clinical manifestations of MS mainly include limb weakness, paresthesia, visual loss, diplopia, ataxia, and bladder or rectal dysfunction. The purpose of clinical treatment is to reduce or eliminate these clinical manifestations and recovery nerve cell function.[43]

Wang, et al[44] studied a rat model of sciatic nerve defects transplanted with adipogenic stem cells and showed that astragaloside Ⅳ significantly improves the conduction velocity and amplitude of injured sciatic nerve, shortens the incubation period, and promotes nerve regeneration and motor function recovery. Li, et al[45] demonstrated the effect of Huangqi Chifeng Decoction (黄芪赤风汤) and Dihuang Decoction(地黄汤) for the recovery of impaired nerve function in patients with ischemic stroke. *Astragalus membranaceus* can repair damaged nerve cell function and improve the activities' ability of daily life in rats with sciatic nerve defect, however, its specific mechanism of action has not been clarified. Other study has shown that astragaloside Ⅳ can reduce TNF-α and iNOS expression in ischemia-reperfusion injured neurons in rats with middle cerebral artery occlusion.[46] Astragaloside Ⅳ can also improve the mRNA expression of nerve growth factor (NGF) and promote the proliferation and differentiation of hippocampal neural stem cells. Furthermore, it can increase the expression of NGF and tropomyosin receptor kinase A (Trk A), as well as NF-κB transcription, and promote optic nerve repair and nerve regeneration.[36,46]

Oxygen-Free Radical Scavenging and Antioxidant Acticities

Reactive oxygen species (ROS) are information transmitters. When excessive ROS are present in the body, they can inhibit the functions of related proteins, induce cellular macromolecular oxidative stress, and accelerate cell death.[47] An oxidative stress reaction, which is mainly caused by reactive oxygen radicals, occurs in MS. The most important antioxidant stress defense system is glutathione antioxidant system, which comprises reduced glutathione (GSH) and glutathione peroxidase (GSH-PX).[48]

Astragalus membranaceus can inhibit oxidative stress by increasing the levels of antioxidant factors. The role is related to the antioxidant effect of superoxide dismutase (SOD), which reduces the levels of malondialdehyde (MDA) and free radicals and alleviates cell apoptosis.[49] Zhang, et al[50] intraperitoneallly administrated with 40 mg/(kg·d) Astragalus Injection in mice with spinal cord injury from day 0 to day 3 or day 7. The water content of spinal cord in mice, accumulation of ROS in spinal cord, number of apoptotic cells in area near the damaged spinal cord, and expression levels of TNF-α and IL-10 were measured during the experiment. The results showed that *Astragalus membranaceus* had a neuroprotective effect in mice with spinal cord injury. It has shown that astragaloside Ⅳ can downregulate MDA and ROS levels in brain tissues of stressed rats, increase the total antioxidant capacity (TAC), GSH, SOD, and catalase (CAT) levels, and reduce the brain damage and neuroinflammation caused by oxidative stress.[51] Lu, et al[52] found that astragaloside Ⅳ can significantly increase the contents of SOD, GSH-PX, and CAT, and reduce the content of MDA in brain tissue. Relevant study has shown that *Astragalus membranaceus* can not only effectively eliminate oxygen free radicals and reduce the damage caused by oxidative stress, but also protect cells by protecting the mitochondria.[53] In summary, *Astragalus membranaceus* and its chemical components have beneficial effects on free radical scavenging and antioxidant activities.

Antiviral Effect

Various studies have suggested that demyelination in MS may caused by viral infection.[37,54-56] The virus related to MS included Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), herpes simplex virus type Ⅰ (HSV-1), herpes simplex virus type Ⅱ (HSV-2), MS-related retroviruses, measles virus, mumps virus, human polyoma virus, rubella virus, poliovirus, hepatitis B virus, and Coxsackie virus[16,31,33,57,58] Possible mechanisms of action included molecular simulation, immune regulation dysfunction after viral infection, epitope expansion, bypass activation, superantigen (sAg) activation, and direct cell injury (hit-hit hypothesis). Jiang, et al[55] studied the action mechanism of *Astragalus membranaceus* extract in mice infected with respiratory syncytic virus. The results showed that astragalus extract can reduce the release of IL-23, IL-17, and IL-6 in T cells by regulating the immune response, reduce the levels of nitric oxide (NO) and MDA via antioxidant mechanisms, and reduce airway

inflammation. Calycosin in *Astragalus membranaceus* also has antiviral effects. Zhang, et al[56] showed that calycosin can protect cells against viruses by reducing myosin light chain (MLC) phosphorylation, inhibiting F-actin remodeling, and reducing cell permeability. Yang, et al[55] used astragaloside Ⅳ to treat myocardial cells of suckled mice infected with Coxsackie virus B3 (CVB3), indicating that astragaloside Ⅳ could reduce the levels of lactate dehydrogenase (LDH) and creatine phosphokinase in cells and protect the myocardial cells from viral infection. The above-mentioned experimental studies showed that *Astragalus membranaceus* and its chemical components have strong antiviral effects.

Clinical Applications of *Astragalus membranaceus* and Its Chemical Components in Treatment of MS

Astragalus membranaceus and Its Chemical Components in Treatment of MS

Mi, et al[59] demonstrated the action mechanism of *Astragalus membranaceus* on MS including immunoregulatory effects, protection of BBB, and improvement in the function of cell adhesion molecules and chemokines through Rho kinase pathway. Several studies on HQGP have shown that *Astragalus membranaceus* and its chemical constituents display a certain efficacy in the treatment of autoimmune diseases, revealing a new approach for clinical treatment of MS.[23,59] Yang, et al[60] found that astragalus saponins can be used for the treatment of MS owing to their immune-regulation, anti-inflammatory, antioxidative, antiapoptotic, and nerve-protecting effects. These results suggested that *Astragalus membranaceus* and its chemical components might be a good choice for MS treatment.

Use of *Astragalus membranaceus* and Its Constituent Glucocorticoids in Treatment of MS

Zhang, et al[61] reported Atastragalus Injection combined with prednisolone treatment had better clinical efficacy for MS than prednisolone treatment alone. The total effective rates of prednisolone group and the group treated with Astragalus Injection combined with prednisolone were 74.36% and 92.31%, respectively. Astragalus injection combined with prednisolone treatment can reduce serum IL-23 and IL-17 levels and inhibit peripheral white blood cell proliferation.

Conclusions

Pharmacological action of *Astragalus membranaceus* in treating MS and their animal models is summarized in Appendix 1. In general, *Astragalus membranaceus* may regulate the immune and promote anti-inflammatory, antioxidant, and antiviral effects, enhance nerve repair, and improve nerve function, scavenge free radicals, and produce other effects, especially exert immunomodulatory and anti-inflammatory effects after viral infection, which is consistent with the current view on the pathogenesis of MS. There has been considerable progress in the research on *Astragalus membranaceus* as a treatment for MS, providing a more modern theoretical basis for its clinical application in MS treatment.

Conflict of Interest

The authors have no conflicts of interests to declare.

Author Contributions

Peng Y received funding support and developed the research hypotheses. Peng Y, Deng X, Yang SS, Nie W and Tang YD wrote the manuscript. The final manuscript is the end product of the joint writing efforts of all the authors.

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