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REVIEW

Research Progress on the Treatment of Related Diseases With *Astragalus*

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Abstract: *Astragalus mongholicus Bunge [Fabaceae; Astragali radix]* is an herb widely used in traditional Chinese medicine. It has diuretic, anti-aging, antihypertensive, immune-boosting, liver-protective, anti-stress and other extensive pharmacological effects. In recent years, *Astragalus* and its extract have been used to treat lung and stomach qi deficiency as well as general qi deficiency. This paper summarizes the mode of action and mechanisms of *Astragalus* in treating various diseases, and provides valuable insights for the future application, development, and improvement of *Astragalus*. In this paper, literature on the use of *Astragalus* in treating related diseases over the past five years was collected from PubMed and CNKI databases, and the pathogenic mechanisms of *Astragalus* and its extracts were reviewed. Its mechanism of action is primarily involved in antioxidant protection, anti-inflammatory effects, and anti-apoptotic properties. This provides a new research direction for future studies and clinical treatments using *Astragalus*.

Keywords: *Astragalus*, active ingredient, *Astragalus* extract, traditional Chinese medicine

Astragalus

Astragalus *mongholicus Bunge [Fabaceae; Astragali radix]* is an herb widely used in traditional Chinese medicine TCM) that has historically been used to treat Alzheimer's disease AD).[1] Revered as a sacred remedy for energy, *Astragalus* is renowned for its ability to boost energy levels, improve vitality, and enhance overall well-being.[2] It is commonly used to treat qi deficiency and to support lung and stomach qi.

Astragalus belongs to the leguminous plants, and the main active substances in *Astragalus* are *Astragalus polysaccharides* APS), astragaloside IV AS-IV), cycloastragenol CAG), calycosin-7-O-β-D-glucoside CG), calycosin, and so on.[3] In addition, *Astragalus* also contains saponins, flavonoids, amino acids and alkaloids among other chemicals. Dextran, along with heteropolysaccharides, is categorized into two forms: water-soluble and water-insoluble.[4,5] Heteropolysaccharides are mainly water-soluble acidic heteropolysaccharides, with a small portion consisting of small molecular weight glucuronic acids. APS are the most abundant and active compounds in *Astragalus*, and are recognized for their various biological activities, such as improving immunity, offering antioxidant protection of the heart, anti-inflammatory effects, intestinal flora regulation, anti-tumor activity[4] and treatment of ulcerative colitis.[6] According to studies, AS-IV and APS in *Astragalus* have protective effects on the heart, lungs, kidneys and nervous system, and they can inhibit and kill tumor cells.[7] CAG, a natural compound in *Astragalus*, has been found to stimulate Farnesoid X receptor FXR) transcriptional activity and reduce liver steatosis in mice with nonalcoholic steatohepatitis NASH) induced by a methionine-and choline-deficient L-amino acid diet MCD).[8] CG has a protective effect on vascular cell injury,[9] reduces oxidative stress and nerve cell apoptosis,[10] and improves lipid accumulation in hepatocytes through

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AMPK activation.[11] Calycosin exhibits an inhibitory effect on cancer cells[12] and significantly reduces kidney inflammation caused by diabetes by inhibiting the NF-κB dependent signal transduction pathway in vivo and in vitro.[13] Calycosin is involved in oxidative stress, synaptic function and PI3K/Akt/GSK-3β pathway. It plays a beneficial role in improving, preventing and treating diabetes-related cognitive impairment.[14] Therefore, *Astragalus* is a Chinese herbal medicine with therapeutic value.

Up to now, there have been several review articles on *Astragalus* extract, most of which focus on its cultivation,[15] the extraction of active compounds[16] and its therapeutic applications in certain diseases, mainly viral myocarditis[17] and diabetic nephropathy.[18] According to relevant data, *Astragalus* is recognized as being widely used to treat many diseases. We conducted research and analysis on relevant data to understand the distinct characteristics and properties of *Astragalus*, as well as its ability to treat related diseases, ultimately identifying its potential as a therapeutic agent.

Methods

Search Strategy

From September 2019 to November 2023, studies on *Astragalus* and its associated illnesses were gathered through the CNKI and PubMed databases. Medical subject headings MeSH) terms such as "tumor", "lung disease", "kidney disease", or "diabetes" with keywords such as "astragalus", "astragalus polysaccharides", "cancer", "qi deficiency syndrome", "liver and lung", "heart", "virus", "extract" to search for related articles. To identify relevant studies, all retrieved articles from both databases were carefully reviewed, and duplicate entries were eliminated.

Criteria for Selecting Studies

The inclusion criteria are as follows:

1) Articles reporting the efficacy of *Astragalus* whole herb extract in any dosage form extract, injection, tablet, pill, etc).;
2) Perform experiments in vitro, in vivo, or ex vivo;
3) original research articles;
4) articles published between September 2019 and February 2023;

The exclusion criteria are:

1) Review articles;
2) Articles on diseases other than cancer, diabetic nephropathy, liver and lung injury, and viral myocarditis.

Data Extraction

The information extracted included the publication year, the primary author's name, the disease studied, the extraction method, the type of cell line or animal model used, the dosage and duration of extract administration, the effectiveness of the treatment, and the reported mechanism of action.

Cancer

Cancer is the leading cause of premature death worldwide[19] and has become a very common disease globally. In the treatment of cancer, powerful chemotherapy drugs are used to control the disease. However, these drugs, including doxorubicin DOX), have significant side effects for patients.[20] Therefore, the exploration of natural plant-derived products is crucial for future advances in cancer treatment.[21] According to the global cancer statistics report, gender differences exist in cancer incidence and mortality. Women have lower rates of both than men. Lung cancer is the primary reason of male mortality, whereas breast cancer is the leading cause of death among females.[22] In China, 23.7% of new cancer cases and 30.2% of cancer related deaths worldwide occur, ranking the country first in both categories. The cancer burden in China cannot be ignored.[23] Currently, there are four main treatments for cancer: surgery, chemotherapy, radiotherapy, and immunotherapy.[24] The primary goal of cancer treatment is to cure tumors by targeting them directly, allowing patients to live normal, pain-free lives. Today, many traditional and advanced cancer treatments, such as hormone therapy, radiation therapy, surgery, immunotherapy, targeted therapy, stem cell therapy, or

chemotherapy, are used to combat this devastating disease. Chemotherapy remains one of the most recommended conventional cancer treatment strategies.[25] Since its discovery, DOX has become well-known as a potent antitumor agent and is widely used to treat various malignancies. However, its clinical use has been limited by serious side effects, mainly due to their toxicity to healthy tissues and organs, particularly the kidneys. Studies suggest that plant-derived therapeutic agents may provide renal protection by alleviating induced nephrotoxicity and maintaining normal renal function and structure.[26] Radiation therapy is another key cancer treatment, along with surgery and chemotherapy. The balance between anti-inflammatory and pro-inflammatory mediators may fluctuate for some time after radiation exposure.[27] Conventional treatments, however, have serious side effects. New chemotherapy drugs like bleomycin, vinblastine and cisplatin are also associated with adverse effects, such as severe vomiting.[28] Although Apatinib can inhibit tumor neovascularization and is classified as a small molecule anti-angiogenesis inhibitor,[29] it can cause adverse reactions in the blood system drug adverse reactions such as thrombocytopenia and coagulation disorders.[30] As a result, there is significant interest in developing new drugs that mitigate or prevent the side effects of radiation therapy. Cancer patients benefit most when their treatment is provided in a multidisciplinary format, with surgical care being a key pillar. Surgery contributes to all stages of the cancer treatment pathway, from prevention, screening, and diagnosis to treatment, reconstruction, rehabilitation, and palliative care. It is not only cost-effective but also provides durable results for many malignancies.[31] Cancer immunotherapy, a method of enabling the immune system to recognize and eliminate cancer, has emerged as a unique pillar of cancer treatment. Among the most promising approaches are therapeutic vaccines, immune checkpoint blockade, bi-specific T-cell engagers BiTEs), and adoptive cell therapy.[32]

Cancer and Astragalus

Astragalus has been used for thousands of years in mixed decoctions to treat cancer.[33,34] It is known to have several effects, including inhibiting tumor growth, regulating the immune system, alleviating adverse reactions of cytotoxic drugs and providing chemoprophylaxis.[35] Several studies on *Astragalus* and cancer have been reported Table 1 and Figure 1), showing that the treatment of cancer patients with *Astragalus* injection can reduce the number of acute exacerbations, improve clinical efficiency, enhance lung function, and lower mMRC scores, IL-8 and TNF-α levels, thereby improving patients' quality of life and exercise ability.[36] AS-IV, considered the main active ingredient of *Astragalus*, has a variety of pharmacological effects, such as anti-inflammatory, hypoglycemic, anti-fibrotic and anticancer activities. It participates in cell cycle arrest, induces apoptosis and autophagy, and inhibits cancer cell proliferation,

Table 1 Mechanism of Action of Astragalus in the Treatment of Cancer

Disease	Administration and Dose	Experimental Models	Efficacy	Mechanism	Reference
Colon cancer	100 mg/kg of APS for 14 days	AOM/DSS induced CAC mouse model	Inhibits epithelial-mesenchymal transition EMT) in human colon cancer cells	E-cadherin↑ LoVo, HCT116, NF-kB A. Cadherin, TLR4/NF-kB↓	[45]
Lung cancer	Astragalus polysaccharide PG2) 16 mg/mL for 48 h	Monocyte-derived macrophages MDMs) were co-cultured with lung cancer cell lines; Mice were inoculated with LLC1 cells or H1437 cells and THP-1 cells	Inhibition of xenograft tumor growth, cisplatin-associated cachexia, and weight loss are significantly inhibited	DC, LPS/IFN-γ NSCLC) H441 and H1299↑	[40]

(*Continued*)

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Table 1 (Continued).

Disease	Administration and Dose	Experimental Models	Efficacy	Mechanism	Reference
Tumor	Astragalus injection 50~200 μg/mL for 24 h	BALB/c mice Macrophages	It significantly enhances the proliferation of spleen lymphocytes, increases the phagocytic ability of abdominal macrophages, and improves the anti-tumor effect	Peripheral blood IL-2, TNF-α and IFN-γ↑ 5-FU's suppression of the immune system↓	[46]
Gastric cancer	APS 50–200 μg/mL was given for 24–72 h with or without adriamycin 0.1 μg/mL	GC cells	APS can independently induce apoptosis in gastric cancer cells and enhance the pro-apoptotic effect of doxorubicin on gastric cancer cells, suggesting that APS may be a chemosensitizer	p-AMPK, SEMA3F, P21WAF1/CIP1, FBXW7↑	[38]
Ovarian cancer	APS 0~2 mg/mL for 24 h	Human OC cell line OV-90; SKOV-3 and HEK293T cells	APS can inhibit the proliferation of OC cells and induce apoptosis of OC cells	miR-27a↓ FBXW7, OV-90↑	[41]
Endometrial carcinoma	Astragalus membranaceus 40 and 80 μM for 24 h	Human endometrial cancer cell lines Ishikawa, HEC-1A and HEC-251)	Elucidating the mechanism of action of Astragalus in the treatment of endometrial cancer provides a scientific basis	Up-regulated expression of ERβ and p53↑	[47]
Esophageal cancer	APS 1.0, 1.5, 2.0 mg/mL for 24 h	Esophageal cancer Eca-109 cells	APS can change the morphology and destroy the surface structure of Eca-109 cells, and can inhibit the proliferation, migration and invasion of Eca-109 cells and promote the apoptosis of Eca-109 cells	ECA-109 cell autophagy↑	[42]

Abbreviations: QLQ-C30, Quality of Life Core Questionnaire; APS, Astragalus Polysaccharides; GC, Gastric Cancer; SEMA3F, P21WAF1/CIP1, FBXW7, Tumor Suppressor Genes; OC, Ovarian Cancer; OV-90, Human Ovarian Cells; SKOV-3, Human Ovarian Cancer Cells; HEK293T, Human Embryonic Kidney Cells; ERβ and p53, Human Tumor Suppressor Genes; NSCLC) H441 and H1299, Non-Small Cell Carcinoma.

invasion, and metastasis.[33] One study found that APS can inhibit the growth and movement of colon cancer cells and HCT116, playing a role in preventing colitis-associated cancer CAC) by blocking gram-negative pathogens and inhibiting the TLR4/NF-κB signaling pathway.[37] Administration of 50 to 200 μg/mL APS can reduce the viability of gastric cancer cells.[38] Additionally, astragaloside II has been shown to affect the Wnt/β-catenin signaling pathway, impeding EMT in renal cancer cells and thus hindering the migration and invasion of clear cell renal cell carcinoma.[39] Therefore, *Astragalus* could potentially inhibit the growth and movement of cells, which could be beneficial in cancer treatment. Simultaneously, PG2 suppresses tumor growth and spread in genetically similar C57BL/6 mice by controlling inflammation-linked macrophage behavior and blood vessel formation, while also enhancing cisplatin's cancer-fighting capabilities within the body.[40] APS has the potential to boost the immune system's response to suppress the proliferation of cancer cells. After treatment with APS, ovarian cancer cells OCs) show inhibited proliferation and induced apoptosis.[41] APS has also been found to alter the morphology of Eca-109 cells, destroying their surface structure, inhibiting the proliferation, migration and invasion, and promoting apoptosis and autophagy.[42] These results highlight the therapeutic potential of APS in the treatment of OC. At the same time, a systematic review and meta-analysis of *Astragalus* herbal medicine combined with chemotherapy for cervical cancer found that *Astragalus* improves the efficacy

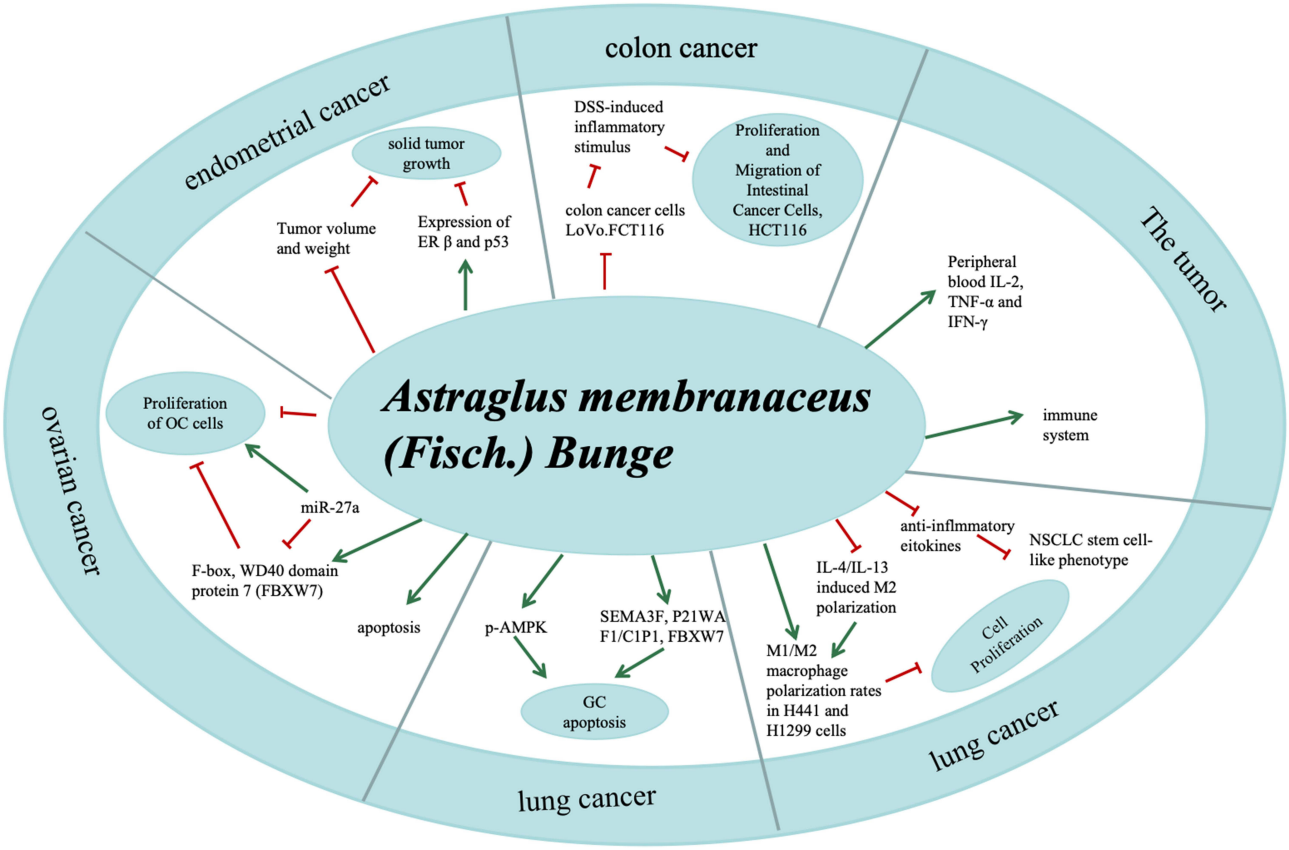

Figure 1 Mechanism of action of Astragalus on cancer.

of treatment and reduces chemotherapy´s toxicity.[43] Cheng et al also conducted a systematic review and meta-analysis on the combination of *Astragalus* in the treatment of advanced gastric cancer and found that combining *Astragalus* with chemotherapy results in better efficacy and fewer side effects in the treatment of advanced gastric cancer.[44] Therefore, *Astragalus* may be a viable option for treating cancer.

Astragalus Exhibits Anticancer Activity by Inducing Apoptosis in Cancer Cells

Astragalus was found to trigger cancer cell death through apoptosis in the studies discussed in our earlier analysis, primarily focusing on the following factors. The immune system is modulated by *Astragalus* extract, which also promotes cancer cell death via apoptosis. The study by Bamodu et al showed that PG2 has the ability to suppress tumor growth and spread in mice by regulating the activity of macrophages involved in inflammation and angiogenesis.[40] Li et al found that *Astragalus* injection could effectively inhibit the proliferation of human non-small cell lung cancer A549 cells in a time- and concentration-dependent manner, which was related to the drug-regulated apoptosis-related gene and protein expression.[48] Liu Leilei et al[45] discovered that the appropriate concentration of APS could inhibit the proliferation and migration of colon cancer cells LoVo) and HCT116 cell line. Relevant studies have shown that miR-29c can directly target and bind to B7-H3, facilitating its role, while AS-IV can inhibit the expression of B7-H3 by increasing miR-29c expression levels, thus inhibiting the growth of CRC cells.[49]

Astragalus extract also inhibits cancer cells growth through non-coding RNA, enhancing drug sensitivity. According to the relevant literature, DOX is a chemotherapy drug with a broad antitumor spectrum, and it has a significant killing effect on tumor cells.[50,51] According to Song et al,[38] APS independently induced apoptosis, enhanced the pro-apoptotic effect of DOX on gastric cancer cells, and regulated the tumor microenvironment. Gou et al discovered that microRNA miRNA) patterns in cells exposed to APS showed that increased levels of miR-27a counteracted the growth-inhibiting and pro-cell death effects of APS on ovarian cancer cells. Additionally, miR-27a directly targeted and suppressed the

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translation of F-box and WD-40 domain protein 7 FBXW7), a well-known tumor suppressor in OC Ovarian Cancer) cells. Furthermore, APS demonstrated the ability to impede the growth of OC cells.[41]

Diabetic Nephropathy

Diabetes mellitus DM) is a chronic metabolic disease characterized by elevated blood sugar levels hyperglycemia) and disorders of carbohydrate, lipid, and protein metabolism.[52] Complications of diabetes include cataracts, neuropathy, retinopathy, nephropathy, and others.[53] During hyperglycemia, the glucose flux through the polyol pathway is thought to be a key event leading to long-term diabetic complications such as retinopathy, kidney disease, and neuropathy.[54] Diabetic nephropathy DN), also called diabetic glomerulosclerosis, is a frequent complication of diabetes that affects small blood vessels and is a primary cause of end-stage kidney disease.[55] According to statistics, more than 463 million people worldwide are affected by diabetes.[56] DN is a prevalent chronic microvascular complication of diabetes.[57] The etiology and pathogenesis of DN are extremely complex, and many influencing factors have yet to be fully elucidated.[58] The overproduction of aldose reductase AKR1B1, AR, EC number 1.1.1.2) 1 and sorbitol dehydrogenase on the polyol pathway, along with the depletion of reduced $NADP^+$ and oxidized NAD^+, are cofactors in this process, leading to various metabolic process disorders such as kidney disease, retinopathy, cataracts, and neuropathy. The metabolic abnormalities are the primary target of diabetic complications in tissues involved in insulin-independent glucose uptake, resulting in early tissue damage in organs.[59] At the same time, the residual risk of DN processing to end-stage renal disease remains high, and once end-stage renal disease is reached, the only effective treatment is renal replacement therapy.[60] Both traditional Chinese medicine and Western medicine have been used to treat DN in recent years. However, currents drugs such as GLP-1 analogs,[61] SGLT2 inhibitors,[62] DPP-4 inhibitors,[63] and SGLT-2i inhibitors[64] are mainly used for treating diabetic nephropathy. Despite this, basic medicine still lags behind, and these treatments have not been fully effective.[65] Research has found that the polysaccharides in *Astragalus* can treat DN, improve kidney function in patients, and correct the balance of Th1 and Th2 in the body, thereby acting as an effective therapeutic agent.[66] Several results suggest that *Astragalus* extract is a promising choice for treating diabetic kidney disease.

Diabetic Nephropathy and Astragalus

Diabetes is the third leading non-communicable disease, after cardiovascular disease and cancer. There are two types of diabetes: type 1 diabetes mellitus T1DM) and type 2 diabetes mellitus T2DM). Chinese medicine has a long history of treating diabetes, and *Astragalus* is a commonly used Chinese herb for this purpose. APS, the main active component of *Astragalus* polysaccharides, has anti-oxidative stress, immunomodulatory, and anti-apoptotic activities[67]. APS has significant pharmacological value and clinical potential in treating diabetic complications, including diabetic retinopathy, nephropathy, cardiomyopathy, cognitive dysfunction, wound healing, and more.[68] Several studies on *Astragalus* for treating diabetic nephropathy have been reported Table 2 and Figure 2). In a study where 100 patients were treated with conventional medicine and a mixture of APS injections, levels of BUN, Cr, Th1, Th2, NLR and the Th1/Th2 ratio decreased in both groups compared to pre-treatment levels $p<0.05$). Additionally, the observed group showed lower levels of the indexes compared to the control group $p<0.05$).[66] After treatment with *Astragalus membranaceus* extract, glomerular filtration rate GFR) increased and urinary protein levels decreased, significantly improving diabetic nephropathy.[55,69] Administering *Astragalus* to patients with DN can enhance treatment outcomes by lowering blood sugar levels, decreasing MCP-1 and TNF-α in the blood, preventing proteinuria, and ultimately improving kidney function.[70] After treating patients with *Astragalus* injection, a comparison of renal function monitoring indicators, total effective rates, and adverse reactions before and after treatment showed that the conventional regimen combined with *Astragalus* injection had a significant effect on treating diabetic nephropathy, improving renal function and therapeutic outcomes with high safety and no serious adverse reactions. This combination treatment regimen is worthy of clinical application.[71] After 8 weeks of treatment with Astragaloside IV, it was found that AS-IV may improve pyroptosis and alleviate the progression of DN by down-regulating the expression of cell death regulator protein GSDMD) and caspase-1 in kidney tissue of DN rats.[72] Rats treated with *Astragalus* injection for 6 weeks showed significant reductions in proteinuria and improvements in kidney pathology in DN rats, which is associated with the inhibition of endoplasmic reticulum stress in kidney tissue by *Astragalus*.[73] In a study using male diabetic db/db mice

Table 2 Summary of the Therapeutic Mechanism of Astragalus in Diabetic Nephropathy

Disease	Administration and Dose	Experimental Models	Efficacy	Mechanism	Reference
Diabetic nephropathy, DN	Astragalus polysaccharide 0.5 mg/mL for 14 d	Patients with diabetic disease	Treat DN and improve the patient's kidney function	BUN, Cr, Th1, Th2 level and NLR, Th1/Th2↓	[66]
	Astragalus 30g/d, 1 month	50 patients with diabetic nephropathy	Improve the therapeutic effect and avoid the exudation of urine protein, thereby improving the patient's renal function	MCP-1 and TNF-α level; UAER↓	[70]
	Astragalus granules 12 mg/kg/d for one week	Normal control Model) diabetic nephropathy Model) astragalus treatment group AS-M) and phenylbutyric acid group PBA), 6 animals in each group	Significantly reduce proteinuria in diabetic nephropathy rats and improve renal pathological changes in diabetic rats	Phosphorylation levels of GRP78 and ORP150 in KI, UAER, renal tissues, eIF2α, PERK and JNK, and gene expression↑	[73]
	AS-IV 40 mg/mL for 8 weeks	Diabetic nephropathy group DN group) Astragaloside IV intervention group AS-IV group) Resveratrol group	Improve pyroptosis and delay the progression of DN	GSDMD;Caspase-1↓	[72]
	Huangqi astragalus) decoction extract of 7 kinds of herbs) for 14 weeks	Male diabetic db/db mice with spontaneous diabetic nephropathyNon-diabetic db/m control mice	Prevents the development of diabetes mellitus and improves kidney function, regulates the IRS1-PI3K-GLUT signaling pathway	Serum creatinine, blood urea nitrogen, urine albumin water↓ phospho-IRY1361, phospho-IRS1Y896, phospho-PI3K↑	[55]
	APS 200 mg/kg/d solution for 12 weeks	DN rat model was induced by a high-fat diet combined with streptozotocin Healthy rats	Activates autophagy and inhibits oxidative stress, improves glycolipid metabolism and alleviates kidney injury in DN rats	Relative mRNA expressions of AMPK, SIRT1 and FOXO1 in kidney tissue↑ p-AMPKα/AMPKα, SIRT1, FOXO1 and LC3B Proteins↑ Acetyl-FOXO1/FOXO1 and P62 relative expression of protein↓	[74]

Abbreviations: BUN, Urea nitrogen; Cr, creatinine; NLR, Th1, Th2 and Th1/Th2 values, blood indicators; MCP-1, Serum monocyte chemokine-1; TNF-α, Tumor necrosis factor-α; UAER, Urinary albumin excretion rate; HD, Huangqi astragalus) decoction.

that naturally developed DN and non-diabetic db/m control mice, results after 14 weeks of treatments with HD Huangqi) *Astragalus*) decoction showed that HD prevented the decline of the glomerular capillary basement membrane, mesangial matrix, and tubular lumen in db/db mice. Additionally, HD prevented the onset of diabetes and enhanced kidney function in db/db mice. Furthermore, HD adjusted the IRS1-PI3K-GLUT signaling pathway, notably ameliorated diabetic nephropathy.[55] Mice treated with *Astragalus* were studied in a control experiment, and the results showed that APS activated autophagy and inhibited oxidative stress by regulating the AMPK/SIRT1/FOXO1 signaling pathway in kidney tissue of DN rats, improving glucose and lipid metabolism and alleviating kidney injury in DN rats.[74] Therefore, *Astragalus* can be an effective treatment for diabetic nephropathy.

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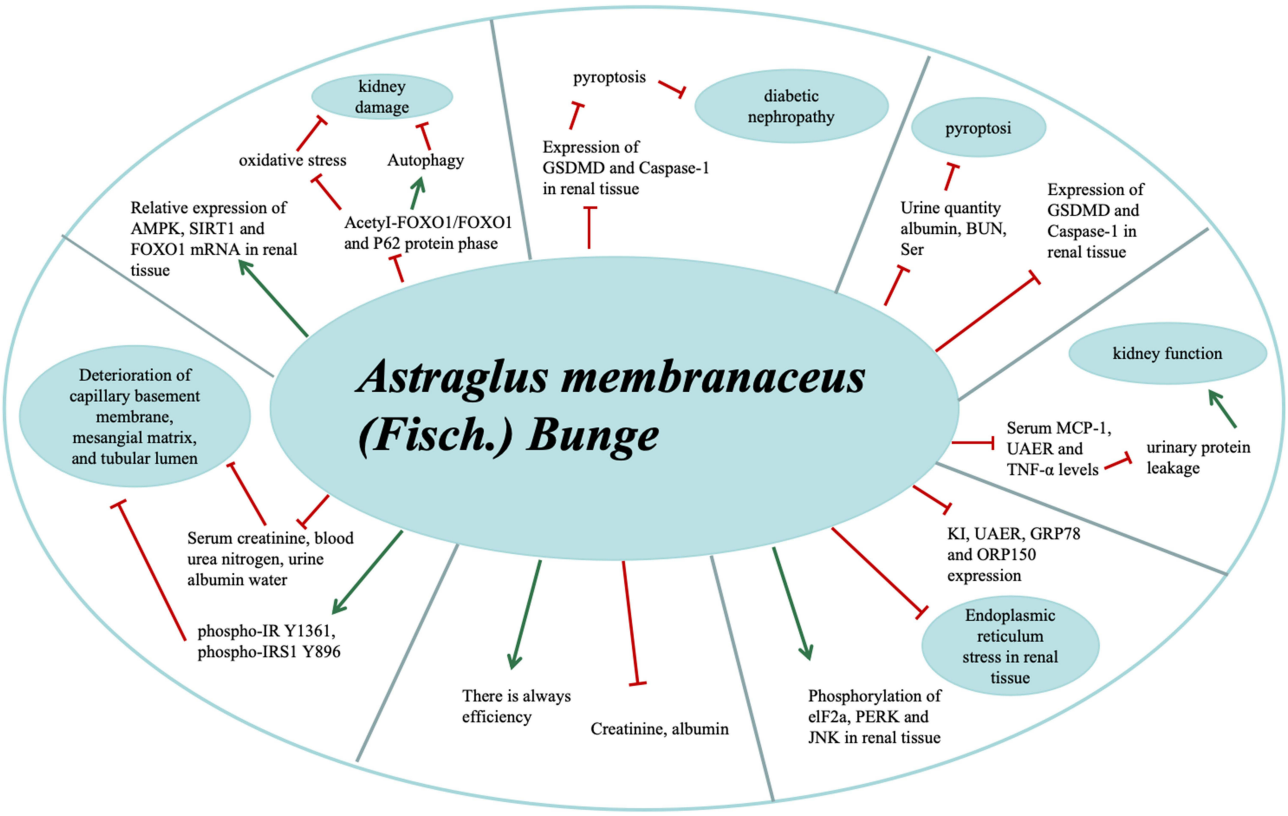

Figure 2 Mechanism of action of Astragalus on diabetic nephropathy.

Astragalus Has Shown the Effect of Improving Kidney Tissue by Regulating Anti-Inflammatory Signaling Pathways

Diabetes is defined as hyperglycemia, protein abnormalities and lipid metabolism disorders. Diabetic complications associated with hyperglycemia typically occur in conditions like diabetic retinopathy, cancer, neuropathy, emotional disorders, kidney disease, and more.[75] In some clinical studies, complications in diabetic patients have been linked to high blood sugar levels.[76] DN is a common microvascular complication in individuals with diabetes, a metabolic disorder in which prolonged high blood sugar levels lead to dysfunctions in kidney cells, ultimately causing gradual kidney failure.[77] Modern medicine believes that the onset of DN is related to glomerular hemodynamic changes, oxidative stress and inflammatory reactions, with symptomatic treatment typically focused on improving symptoms through dietary adjustments, blood pressure control, blood sugar regulation, and lipid management.[78] Hu Yaling et al found that high glucose intervention could inhibit the autophagic activity of renal tubular epithelial cells, induces the expression of pro-inflammatory factors and epithelial-mesenchymal transition indicators. The mechanism was linked to the inhibiting of SIRT1 expression, regulation of the SIRT1/NF-κB signaling pathway, and modulation of autophagy and inflammation.[79] According to our review, it is likely that *Astragalus* plays a role by targeting cells to regulate signaling pathways.[80] Enhancing the IRS1-PI3K-GLUT signaling pathway through HD modulation has the potential to greatly improve the treatment of diabetic nephropathy.[55] As mentioned in the review, *Astragalus* extract likely alleviates DN by improving kidney function and inhibiting endoplasmic reticulum stress in kidney tissue.[70,73]

Liver and Lung Damage

There are many classifications of liver injury, and *Astragalus* has therapeutic effects on certain types of liver injury Table 3 and Figure 3). Drug-induced liver injury DILI) results from liver damage caused by drugs or their metabolites during use. The frequency of DILI is rising annually in our country, making it a significant contributor to cases of sudden liver malfunction.[81] However, the exact cause of DILI remains unclear, with notable variations among individuals. There

is no effective treatment for advanced DILI, except liver transplantation, so early diagnosis and precise treatment are particularly important.[82] Additionally, approximately 90% of hepatocellular carcinoma HCC) cases develop from chronic fibrous liver lesions. Hepatic stellate cells HSCs), which are activated by cytokines such as TGF-β, transdifferentiate into myofibroblast-like cells, eventually leading to liver fibrosis.[83] Acute lung injury ALI) is lung damage caused by various pathogenic factors, which can lead to acute respiratory distress syndrome ARDS). ARDS is a common clinical acute and critical illness of the respiratory system, with a complex pathogenesis and a high mortality rate. Even if the patient survives, his lung function is severely impaired. Currently, available treatments for ALI are relatively limited.[84] Therefore, *Astragalus* may be an option for the treatment of acute lung injury. At the same time, studies have shown that *Astragalus* injection can alleviate hepatocyte apoptosis and has a hepatoprotective effect.[85]

Table 3 The Role of Astragalus in Alleviating Liver and Lung Injury

Disease	Administration and Dose	Experimental Models	Efficacy	Mechanism	Reference
Drug-induced liver injury	Mongolian astragalus polysaccharide 100 mg/kg for 14 d	Drug-induced liver injury induced by overdose of APAP intraperitoneal injection	Mongolian Astragalus polysaccharides can alleviate APAP-induced drug-induced liver injury	Nrf-2 and LC3Nrf-2, Keap-1 and their downstream target genes↑ MAPK, TNF-α, IL-6 and IL-1β↓	[37]
Liver damage	Astragalus injection 2 g/mL for 7 d	Adult healthy male Wistar rats	Relieves hepatocyte apoptosis and has a hepatoprotective effect	Bcl-2, Bcl-2/Bax↑	[85]
Liver damage	AS-IV 20 and 40 mg/kg for 1 week	ICR clean-grade mice treated with AS-IV	AS-IV can significantly reduce the expression of inflammatory factors in mice with paracetamol-induced liver injury, and can play a certain therapeutic role in liver injury	TNF-α, IL-1β, IL-6↓	[86]
Liver damage	AS-IV 80 mg/kg for 8 weeks	With AS-IV 80 mg/kg) and Metformin, Met; 120 mg/kg) separately treated in T2DMSD rats	AS-IV has a certain protective effect on liver injury in T2DM	Liver index, serum HOMA-IR, serum TNF-α, IL-6 levels↓ AMPK/mTOR pathway↑	[87]
Oxidative damage to hepatic stellate cells	100 and 200 μmol/L AS-IV for 36 h	Hepatic stellate cells	Astragaloside pretreatment attenuates oxidative damage to rat hepatic stellate cells	Cell viability↑ Apoptotic cells, intracellular Caspase-3 and Caspase-9 expression levels, ROS levels↓	[88]
Acute liver injury	Astragalus extract 350 mg/kg for 12 h	Normal mice were treated with Astragalus extract and modeled 3 days after prophylactic administration of Astragalus extract	Astragalus extract has anti-APAP acute liver injury effects	Apoptosis-related genes MAPK14, CAT, ALT, AST↓	[89]
Liver fibrosis and liver injury	Astragalus wt> 99.5%) Compound soft-shelled turtle soft liver tablets, 9 weeks	Healthy mice were injected subcutaneously with corn oil solution containing 20% CCl4 at a dose of 6 mL/kg twice a week to establish a rat model of liver fibrosis injury	Astragalus has an effective protective effect on liver injury in experimental liver fibrosis rats through the p38MAPK signaling pathway	The expression of ALT, AST and TBIL, p38MAPK, MKK3 and ATF-2 proteins in serum↓	[90]

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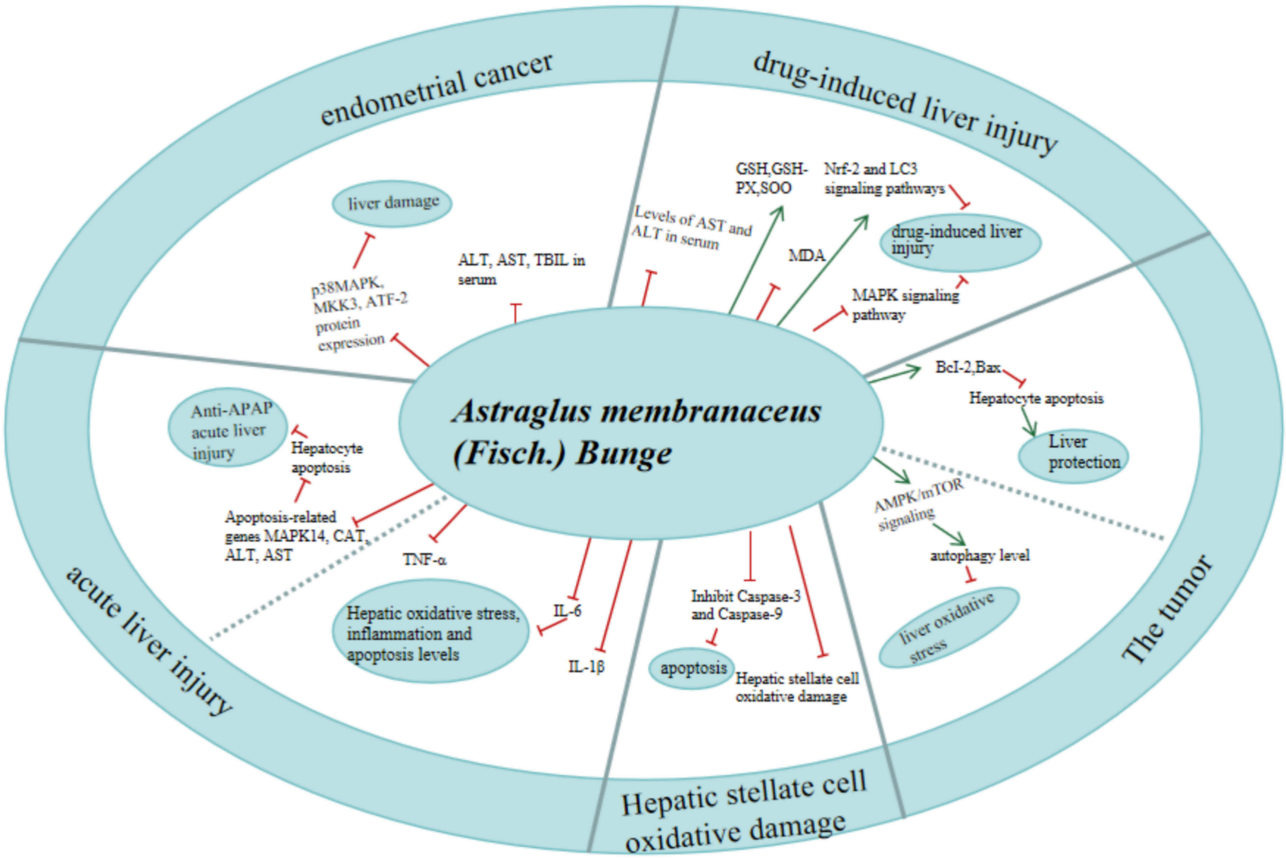

Figure 3 Mechanism of action of Astragalus on liver injury.

Liver and Lung Damage and Astragalus

The findings indicated that the polysaccharides from Mongolian *Astragalus* have the ability to block the MAPK signaling pathway, trigger the Nrf-2 and LC3 signaling pathways, and demonstrate pharmacological effects, including anti-inflammatory, antioxidant, and autophagy properties. These effects help alleviate APAP-induced drug-induced liver injury.[37] APS can reduce AST and ALT levels and protect against liver injury.[91] Both *Astragalus gummifer F. Fabaceae)* and *Astragalus root extract* showed significant anti-inflammatory $p<0.001$). *Astragalus* root extract demonstrated more significant liver-protective activity $p<0.001$) compared to *Astragalus F. Fabaceae)* $p<0.05$), as evidenced by decreased serum levels of Aspartate aminotransferase AST), Alanine aminotransferase ALT), γ-glutamyl transpeptidase GGT), alkaline phosphatase ALP) and total bilirubin.[92] After comparing the sham operation group, the *Astragalus* group, and the model group of mice, it was concluded that intestinal ischemia and reperfusion liver injury IIR) could lead to liver damage in rats. The expression levels of Bcl-2 and Bax increased, and the mechanism of action of *Astragalus* injection may lie in regulating the expression of the two proteins, thereby alleviating hepatocyte apoptosis and protecting the liver.[85] Wang et al found that AS-IV pretreatment could alleviate oxidative damage in rat liver stellate cells, and its mechanism of action may be related to inhibiting the expression of caspase-3 and caspase-9, thereby inhibiting apoptosis.[88] AS-IV's impact on liver injury induced by paracetamol in mice demonstrated a notable decrease in the expression of inflammatory factors, suggesting a potential therapeutic effect on liver injury.[86] Zhu Yunfeng et al concluded through experiments that AS-IV has a certain protective effect on T2DM liver injury, with the mechanism potentially involving the restoration of autophagy levels in the liver of T2DM rats by activating the AMPK/mTOR signaling pathway, thereby improving insulin resistance and dyslipidemia, inhibiting liver oxidative stress, inflammation, and apoptosis.[87] Acetaminophen was used to induce acute liver injury in mice, and *Astragalus* extract was used for in vivo validation. Experiments conducted both in living organisms and in laboratory settings verified that *Astragalus* extract can counteract acute liver injury caused by APAP. This is achieved by regulating the

expression of genes associated with apoptosis, such as MAPK14, TRPM2, SOD1, FOS, CAT, STAT1, and GADD45a, among others, and preventing hepatocyte apoptosis.[89] The study also found that *Astragalus* extract could improve hepatocyte viability, reduce TRPM2 expression in hepatocytes, and provide a good protective effect against APAP-induced acute DILI.[93] After treating mice with liver fibrosis, it was concluded that *Astragalus* has an effective protective effect on liver injury in experimental rats with liver fibrosis through the p38MAPK signaling pathway.[90] These findings suggest that *Astragalus* may alleviate liver damage by inhibiting hepatocyte apoptosis and inflammation levels.

Astragalus Acts on Multiple Signaling Pathways and Exerts Anti-Inflammatory Effects to Improve Liver and Lung Damage

Liver injury mainly includes drug-induced liver injury, alcohol-induced liver injury, and other causes. Studies have found that the covalent binding of NAPQI to glutathione can activate the body's innate immune system, leading to the release of cytokines and the formation of an inflammatory response, which maintains the state of drug-induced liver injury.[94] According to our review, Li Xinyi et al have shown that APS can exert pharmacological activities, including anti-inflammatory, antioxidant and autophagy activation, by inhibiting the MAPK signaling pathway and activating Nrf-2 and LC3 signaling pathways.[37] Zhu Yunfeng et al experimentally concluded that AS-IV restored the inhibited level of autophagy in rat liver by activating the AMPK/mTOR signaling pathway, thereby inhibiting the level of oxidative stress, inflammation and apoptosis in the liver.[87] Sun Kecheng et al found that AS-IV significantly reduced the expression of inflammatory factors in mice with paracetamol-induced liver injury and demonstrated a potential therapeutic role in liver injury.[86] In terms of lung injury, the fermentation products of *Astragalus* can counteract the increase of PM2.5-induced inflammatory factors in the lungs to a certain extent, and reduce the inflammatory response induced by PM2.5 by inhibiting the TLR4-Src-NFκB-ICAM-1 pathway.[95] Therefore, *Astragalus* may mainly exert anti-inflammatory effects to alleviate the corresponding liver and lung damage.

Viral Myocarditis

The incidence of viral myocarditis is between 10 and 22 per 100,000 people. While myocarditis affects all age groups, ethnicities, and both men and women, it is primarily a disease of young adults and middle-aged adults, with a median age of 42 years at diagnosis.[96] The prevalence of viral myocarditis is currently on the rise.[97] A significant challenge in clinical practice is the lack of specific treatment for viral myocarditis patients, due to the rapid disease progression and complex pathogenesis, which includes acute myocardial injury and persistent inflammatory response.[98] Some patients will develop chronic inflammatory and dilated cardiomyopathy, even after receiving currents treatments. The disease progression involves both direct damage to the heart muscle by the virus and an immune reaction targeting specific areas of the heart.[99] In modern medicine, symptomatic measures, such as anti-virus treatments,[100] myocardial nourishment, and immune enhancement, are often given to patients with viral myocarditis. These treatments can effectively kill the virus, reduce myocardial damage, and improve cardiac function. However, the overall efficacy of these supportive treatment still needs improvement.[101] Therefore, discovering appropriate treatment options and techniques is crucial. Research has shown that using *Astragalus* granules to treat viral myocarditis in children can significantly enhance the treatment effectiveness, as well as improve immune and cardiac function, with no reported serious side effects.[102] The clinical efficacy is significant, and its use is safe. Numerous experiments suggest that *Astragalus* is a promising therapeutic option Table 4 and Figure 4).

Viral Myocarditis and Astragalus

In a clinical study, compared with the control group, *Astragalus* significantly decreased serum myocardial enzyme levels and myocardial troponin I in patients with viral myocarditis, and improved the clinical treatment efficiency $p<0.05$). There was no significant difference in the incidence of adverse reactions $p>0.05$).[108] *Astragalus* injection treatment in viral myocarditis patients improved the Th17 and Treg cell subset imbalance in peripheral blood, suppressed downstream inflammatory responses, and alleviated myocardial damage.[103] When comparing clinical efficacy, T cell subset levels CD3+, CD4+, CD8+), cardiac enzyme profiles CK, LDH), and adverse reaction rates between the two groups, it was found that

Table 4 Mechanism of Action of Astragalus in the Treatment of Viral Myocarditis

Disease	Administration and dose	Experimental models	Efficacy	Mechanism	Reference
Viral myocarditis	Astragalus injection 20 mL/d for 2 weeks	Patients with viral myocarditis	It can improve the inhibition of downstream inflammatory response activation and reduce myocardial damage in patients with viral myocarditis	Treg cell↑ Th17 cells and Th17/Treg, markers of myocardial damage CKMB, cTnI, MYO)↓	[103]
	Astragalus injection 20 mL/d for 2 weeks	Patients with viral myocarditis were divided into control group n=35) and observation group n=35) by random number table	Astragalus injection combined with sodium phosphocreatine in the treatment of patients with viral myocarditis can improve the total effective rate of treatment	CD3+, CD4+, CD8+↑ CK, LDH↓	[104]
	Astragalus injection 20 mL/d for 2 weeks	A total of 160 patients with viral myocarditis were divided into Astragalus injection treatment group observation group) and conventional treatment group control group) according to the random number table method	Astragalus injection can be used to treat patients with viral myocarditis, thereby improving clinical efficacy	Peripheral blood NLRP3mRNA, Caspase-1 mRNA, IL-1β and IL-18, serum CKMB and cTnI↓	[104]
	AS-IV 100 mg/kg for 2 weeks	Sixty male C57BL/6 mice were infected with 0.1 mL PBS intraperitoneally with 103TCID50CVB3	AS-IV treatment improves CVB3-induced viral myocarditis	FAS, FASL, cleaved caspase-8 and cleaved caspase-3↑ serum creatine kinase-mb CK-MB) and lactate dehydrogenase LDH), cvb3↓	[105]
	Astragalus saponin injection solution 40, 80 and 160 mg/kg/d for 15 d	Adrenal medullary hyperplasia in a rat model	SA can inhibit the activation of PI3K/AKT/mTOR signaling pathway, reduce the levels of serum cardiac enzymes and inflammatory factors, inhibit CVB3 gene replication, improve myocardial injury, enhance cardiac function, and inhibit cardiomyocyte apoptosis	CVB3 virus expression, serum levels of creatine kinase CK), creatine kinase isoenzyme CK-MB) and troponin I cTnI); Tumor necrosis factor TNF-α), interferon γ IFN-γ), interleukin-7 IL-7), and interleukin-6 IL-6) levels↓	[106]
	Astragalus extract 10 and 40 mg/kg/d for 2 weeks	SD rat model of viral myocarditis	Astragalus extract can inhibit cardiomyocyte damage and improve oxidative stress level in rats infected with viral myocarditis, and its mechanism of action may be related to Nrf2 and HO-1 pathways	LVEF, SOD, Nrf2, HO-1↑ Pathological score, LVESD, LVEDD, IL-6, TNF-α, IL-10, MDA↓	[107]
	40, 80 and 160 mg/kg/d for 15 days	SD rat model of viral myocarditis	SA can inhibit the activation of PI3K/AKT/mTOR signaling pathway, reduce the levels of serum cardiac enzymes and inflammatory factors, inhibit CVB3 gene replication, improve myocardial injury, enhance cardiac function, and inhibit cardiomyocyte apoptosis	CVB3 virus expression, creatine kinase isoenzyme CK-MB) and troponin I cTnI), tumor necrosis factor TNF-α), interferon γ IFN-γ), interleukin-7 IL-7), interleukin-6 IL-6)↓	[106]

Notes: Creatine kinase (CK), lactate dehydrogenase (LDH), T cell subsets: CD3+, CD4+, CD8+; FAS, FASL, cleaved caspase-8 and cleaved caspase-3: pro-apoptotic genes.

treating viral myocarditis patients with *Astragalus* injection and sodium phosphocreatine improved the overall treatment effectiveness and T cell subset levels pre- and post-treatment, while also lowering cardiac enzyme levels.[104] After the administration of *Astragalus* injection, a reduction in the levels of NLRP3, caspase-1 mRNA, IL-1β, and IL-18 was observed in the peripheral blood of the experimental group $p<0.05$). Additionally, following therapy, the levels of CKMB and cTnI in both groups decreased compared to pre-treatment levels, with a more significant decrease in the observation group $p<0.05$). This suggests that *Astragalus* injection may lower NLRP3 inflammasome expression in the peripheral blood of patients with viral myocarditis, leading to improved clinical outcomes.[109] In an experiment on rats with viral myocarditis

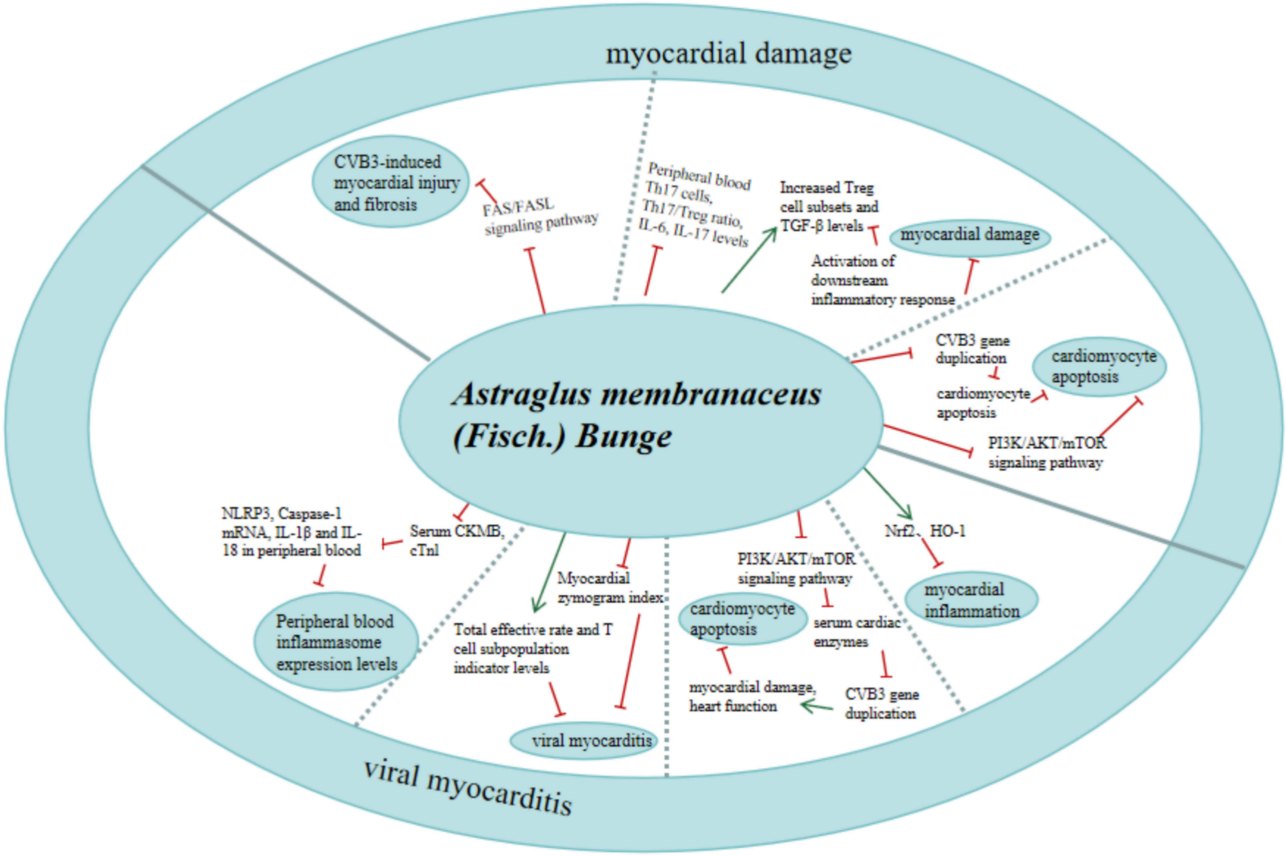

Figure 4 Mechanism of action of Astragalus on viral myocarditis.

VMC), after 15 days of uninterrupted treatment, it was determined that Astragalosides could block the activation of the PI3K/AKT/mTOR signaling pathway, reduce cardiac enzyme and inflammatory marker levels in the blood, suppress the replication of the CVB3 gene, enhance myocardial healing, improve heart function, and prevent cardiomyocyte apoptosis.[106] Research indicates that AS-IV can block cell death in various disease conditions, both in living organisms and controlled environments. AS-IV has been shown to protect against heart muscle damage and scarring caused by CVB3, possibly by preventing activation of the FAS/FASL signaling pathway.[105] After two weeks of *Astragalus* extract administration to model mice, a reduction in cardiomyocyte damage and an improvement in oxidative stress levels were observed in rats with viral myocarditis.[107] In a 15-day study on rats with viral myocarditis, *Astragalus* saponin treatment was found to suppress the PI3K/AKT/mTOR signaling pathway, lower serum cardiac enzymes and inflammatory markers, inhibit CVB3 gene replication, alleviate myocardial damage, improve heart function, and prevent cardiomyocyte apoptosis.[106] This study suggests that *Astragalus* extract could inhibit cardiomyocyte damage and improve oxidative stress levels in rats infected with viral myocarditis, making it a viable option for managing the condition.

Astragalus Acts on Peripheral Blood to Exert Anti-Inflammatory Effects to Alleviate Viral Myocarditis

Viral myocarditis refers to inflammatory lesions in the myocardium induced by related viruses, and its incidence has been gradually increasing in recent years.[110] The clinical symptoms of the disease are often subtle, and when the infection causes heart block, it can seriously threaten the life of the patient.[111] According to Luo Suhong et al, the imbalance between Th17 and Treg cells may be a key factor in the development of viral myocarditis.[112] Yang et al found that *Astragalus* injection could improve the imbalance between Th17 and Treg cell subsets in the peripheral blood of patients with viral myocarditis, inhibit the activation of downstream inflammatory responses, and reduce myocardial damage.[103]

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At the same time, *Astragalus* injection can lower the expression level of the NLRP3 inflammasome in the peripheral blood of patients with viral myocarditis, thereby enhancing clinical outcomes.[109] Wei et al discovered that peripheral blood NLRP3 inflammasomes are closely associated with the occurrence and progression of viral myocarditis, and they hold potential for predicting the severity of the disease.[113] Moreover, combining *Astragalus* injection with trimetazidine significantly reduced NLRP3 inflammasome levels in the peripheral blood of elderly patients with viral myocarditis, exerting anti-inflammatory and antioxidative stress effects and decreasing myocardial damage.[114] According to the literature, *Astragalus* extract may alleviate myocardial damage by inhibiting the PI3K/AKT/mTOR signaling pathway, reducing the levels of serum cardiac enzymes and inflammatory factors.[104,106]

Discussion

Astragalus membranaceus Fisch). Bge, formerly known as *Astragalus membranaceus Fisch)*., boasts a wide range of pharmacological effects, including diuretic,[115] anti-aging,[116] antihypertensive,[117] immune-enhancing,[118] liver-protective, and anti-stress properties.[119] It has been used to treat conditions such as cancer, liver and lung injury, and viral myocarditis. However, few studies have explored its potential for multi-disease treatment. Zhang Di et al reviewed the chemical components of *Astragalus* in the context of single-disease applications.[120] In contrast, our goal was to gather data on the therapeutic effects of *Astragalus* whole grass extract across multiple diseases, providing insight into how *Astragalus* extract exerts its therapeutic role in various conditions.

Due to the time constraints of this review, we primarily relied on CNKI as the literature source, with a 5-year time frame and a focus on well-recognized disease group studies. We acknowledge that differences between experiments may influence the interpretation of results. For instance, variations in dosage and form of *Astragalus* used across studies could impact outcomes. Standardizing doses is an important aspect for future *Astragalus* research to ensure comparability between studies. Moreover, we observed that the dosage varies depending on the disease, which also warrants further investigation. Although Astragalus has a long history of clinical use in traditional Chinese medicine, its long-term safety and potential side effects need to be further validated by increasing the sample size and conducting multi-center clinical trials in the future. Additionally, the interaction between *Astragalus* and other drugs, as well as its therapeutic effects in specific diseases, need further exploration. These studies will help deepen our understanding of *Astragalus*' pharmacological actions and clinical applications. The relationship between *Astragalus* dosage and efficacy also requires more thorough investigation. Despite these limitations, this review provides a summary of the therapeutic potential of *Astragalus* extract in various diseases. It serves as a useful resource for understanding the multifaceted benefits of *Astragalus* and can guide further research in this area.

Conclusion

This article reviews recent experimental research on the use of *Astragalus* in the treatment of cancer, diabetic nephropathy, liver and lung injury, and viral myocarditis. Studies have demonstrated that *Astragalus* extract exerts anti-inflammatory, pro-apoptotic, antioxidant effects, and activates specific neural pathways in the treatment of these conditions. While this review highlights the therapeutic mechanisms of *Astragalus*, fully elucidating its multifaceted therapeutic potential remains a significant challenge.

Abbreviations

TCM, Traditional Chinese medicine; AD, Alzheimer's disease; AS-IV, astragaloside IV; APS, *Astragalus* polysaccharides; CAC, colitis-associated carcinoma; GC, gastric cancer; NSCLC, non-small cell carcinoma ; OCs, ovarian cancer cells; DN, Diabetic nephropathy; HD, Huangqi *astragalus* decoction; IIR, intestinal ischemia and reperfusion liver injury; VMC, viral myocarditis; OC, Ovarian Cancer.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there is no conflict of interest in this work.

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