

Astragaloside IV: An Effective Drug for the Treatment of Cardiovascular Diseases

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

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Abstract: Cardiovascular disease (CVD), the number one cause of death worldwide, has always been the focus of clinical and scientific research. Due to the high number of deaths each year, it is essential to find alternative therapies that are safe and effective with minimal side effects. Traditional Chinese medicine (TCM) has a long history of significant impact on the treatment of CVDs. The mode of action of natural active ingredients of drugs and the development of new drugs are currently hot topics in research on TCM. *Astragalus membranaceus* is a commonly used Chinese medicinal herb. Previous studies have shown that *Astragalus membranaceus* has anti-tumor properties and can regulate metabolism, enhance immunity, and strengthen the heart. Astragaloside IV (AS-IV) is the active ingredient of *Astragalus membranaceus*, which has a prominent role in cardiovascular diseases. AS-IV can protect against ischemic and hypoxic myocardial cell injury, inhibit myocardial hypertrophy and myocardial fibrosis, enhance myocardial contractility, improve diastolic dysfunction, alleviate vascular endothelial dysfunction, and promote angiogenesis. It can also regulate blood glucose and blood lipid levels and reduce the risk of cardiovascular diseases. In this paper, the mechanism of AS-IV intervention in cardiovascular diseases in recent years is reviewed in order to provide a reference for future research and new drug development.

Keywords: *Astragalus membranaceus*, astragaloside IV, traditional Chinese medicine, cardiovascular diseases, cardiomyocytes

Introduction

Cardiovascular diseases (CVDs) are disorders of the heart and blood vessels.¹ As the number one cause of death, CVDs pose multiple threats to health, overburdening the global economic system. An estimated 17.9 million people died from CVDs in 2016, accounting for 31% of all deaths worldwide. More than three quarters of CVD deaths occur in low- and middle-income countries.¹ Given present trends, the annual number of deaths from CVD will increase to 22.2 million by 2030. One-third of deaths occur in people under the age of 70.² However, a large number of people fail to recognize the risks of CVD. Individuals at risk for CVD may present weight issues, high blood pressure, and altered glucose or lipid levels. Studies on the pathogenesis and pharmacological mechanisms of CVD have made great progress, but the morbidity and mortality associated with CVD remains high. Drugs with better therapeutic efficacy and minimal side effects are urgently needed to prevent and treat these diseases.

Therefore, therapeutic strategies for intervening in chronic diseases such as CVDs are important for prolonging healthy aging, and various approaches are being used to develop effective drugs for the treatment or prevention of CVDs.

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Natural products may have advantages over traditional compound-based drugs, such as fewer side effects, decreased long-term toxicity, and variable bioavailability.³ Bioactive natural products come from a wide variety of sources. The history of traditional Chinese medicine (TCM) can be traced back thousands of years in Eastern countries. Modern research has confirmed that TCM contains a variety of active constituents with strong pharmacological effects that play a significant role in the prevention and treatment of cardiac metabolic diseases.⁴

Astragalus membranaceus, the dried roots of *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge.,⁵ is one of the most frequently used TCMs, with a history of use of more than 2000 years. *Astragalus membranaceus* was first recorded in Shen Nong Ben Cao Jing. Modern pharmacological research suggests the *Astragalus membranaceus* has positive effects such as improving cardiac function,⁶ promoting angiogenesis,⁷ regulating blood glucose,⁸ being an anti-tumor agent,⁹ and increasing immunomodulatory activity.¹⁰ The principle active constituents of *Astragalus membranaceus* are saponins, flavonoids, and polysaccharides,¹¹ but it also includes components such as anthraquinones, alkaloids, amino acids, β -sitosterol, and metallic elements.¹² Astragaloside IV (AS-IV) is a lanolin alcohol-derived tetracyclic triterpene saponin extracted from *Astragalus membranaceus*. It is a white powder with the molecular formula $C_{41}H_{68}O_{14}$. The relative molecular weight is 784.97, and the CAS number is 84,687-43-4. The melting point is 299–300°C (in MeOH). AS-IV has a structure similar to steroidal drugs with very low solubility. It is easily soluble in methanol, ethanol, acetone, and sparingly soluble in weakly polar organic solvents such as chloroform or ethyl acetate. $[\alpha] +22.0^\circ$ (c 0.92, MeOH); FAB-MS m/z: 807.0 $[M+Na]^+$, HR-FAB-MS m/z: $C_{41}H_{68}O_{14}Na$ (required 807.4507, $[M+Na]^+$ at m/z 807.4529). IR (film) ν_{max} cm^{-1} : 3395 (OH), 1930, 1038. 1H NMR (400 MHz, C_5D_5N) data and ^{13}C NMR (100 MHz, C_5D_5N) data, as shown in Table 1. AS-IV (8 mg·kg⁻¹) was injected into the tail vein of rats, the content was determined by HPLC-ELSD, and the pharmacokinetic parameters were analyzed by DAS2.0 software. The results are shown in Table 2. The results showed that the two-compartment model was conformed in vivo after the tail vein injection of AS-IV in rats.¹³⁻¹⁵ The absolute bioavailability of AS-IV is 2.2%. Glycosyl hydrolysis can occur through the transformation

of intestinal flora, and it is hardly metabolized in the liver. There is no first-pass effect after oral administration.¹⁶⁻¹⁹ In the Chinese Pharmacopoeia, the content of AS-IV is the standard for quality testing of *Astragalus membranaceus*.²⁰ Figure 1 shows the structural formula of AS-IV. In this review, we discuss the therapeutic implications of the use of AS-IV in CVDs in greater detail. This study analyzes the effects and possible mechanisms of AS-IV on the heart and blood vessels. At the same time, the effects of AS-IV on blood glucose, blood lipids and its antiviral effects are reviewed.

Protect Heart Structure and Function

According to existing literature, *Astragalus membranaceus* preparations (traditional decoctions, granule preparations, and injections) are widely used to treat diseases of the cardiac system, such as heart failure, edium and water retention, and arrhythmias.²¹⁻²³ As the main active ingredient of the Chinese medicine *Astragalus membranaceus*, AS-IV has a good regulatory effect on the heart. It can protect against ischemic and hypoxic cardiomyocytes, protect the heart structure, and enhance heart function.

Protect Ischemic and Hypoxic Cardiomyocytes

Prevention and treatment of myocardial injury caused by ischemia and hypoxia have always been the focus of clinical and scientific research. A large number of research reports have shown that *Astragalus membranaceus* has a significant protective effect on myocardial cell injury caused by ischemia and hypoxia, and its mechanism may be related to antioxidant injury,^{24,25} energy metabolism,^{26,27} and ion balance regulation.^{28,29} Hypoxic-ischemic injury leads to the accumulation of oxygen-free radicals and the reduction of superoxide dismutase (SOD) content, leading to structural damage to the heart.³⁰ The oxidative stress response can cause damage to mitochondria and plays an important role in cardiac pathological processes.³¹ The heart is a high oxygen-consuming, high energy-consuming organ. During the course of life, the heart's orderly diastolic contraction activity relies on cardiomyocytes to increase energy support. There are a large number of mitochondria in cardiomyocytes, which increases available energy for the ordered activity of the heart. Mitochondria produce more than 95% of the adenosine triphosphate (ATP) used by the heart, and the production of ATP is essential for normal cardiac function.³² The

Table 1 ^1H and ^{13}C NMR Spectroscopic Data of AS-IV

No. C	δ_{C}	δ_{H}
1	32.4	
2	30.4	
3	88.7	5.33 dd (12, 4.5)
4	42.8	
5	52.7	1.92 d (8.5)
6	79.4	3.80 ddd (8.5, 8.5, 4)
7	34.8	
8	45.9	
9	21.2	
10	29.2	
11	26.3	
12	33.5	
13	45.2	
14	46.4	
15	46.4	
16	73.5	5.03 m
17	58.4	2.53 d (9)
18	21.3	3H, 1.42 s
19	29.0	0.21 d (4); 0.60 d (4)
20	87.4	
21	27.2	3H, 1.30 s
22	35.0	1.67 m; 3.14 dd (20, 10.5)
23	26.6	
24	81.8	3.88 m
25	71.4	
26	28.3	3H, 1.59 s
27	28.7	3H, 1.30 s
28	28.8	3H, 2.06 s
29	16.8	3H, 1.38 s
30	20.0	3H, 0.94 s
1'	107.8	4.87 d (7.5)
2'	75.7	
3'	78.3	
4'	72.0	
5'	67.2	
1''	105.4	4.92 d (7.5)
2''	75.7	
3''	79.3	
4''	71.4	
5''	78.7	
6''	63.3	

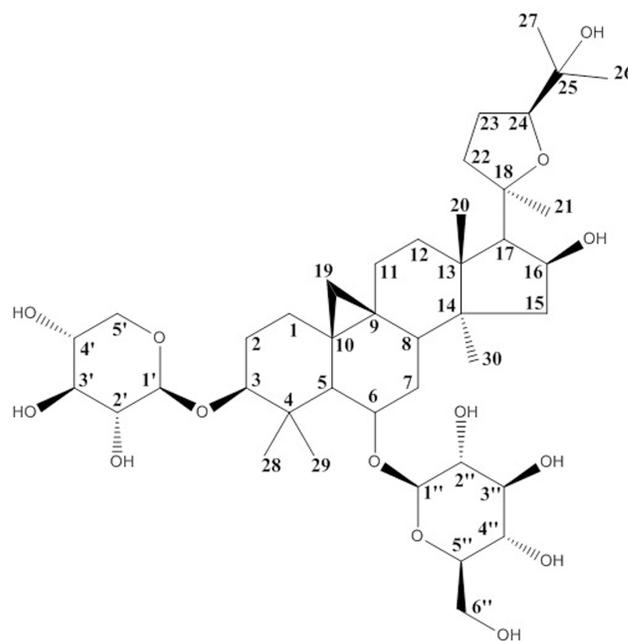
regulation of ion-specific channels and electrophysiological balance are very important for the generation and conduction of electrical pulses, but their regulation is also related to energy regulation.³³

AS-IV can improve cell viability, decrease malondialdehyde (MDA) content, reduce the activity of creatine phosphokinase (CPK) and lactic dehydrogenase (LDH),

Table 2 Pharmacokinetic Parameters of AS-IV (8 mg kg⁻¹) Injected into the Tail Vein of Rats

Parameters	Unit	Value
K ₁₂	min ⁻¹	0.00024
K ₂₁	min ⁻¹	0.002
K ₁₀	min ⁻¹	0.0066
T _{1/2α} (Distribution half-life)	min	110.5
T _{1/2β} (Elimination half-life)	min	331.6
V _c (Apparent volume of distribution of central compartment)	mL kg ⁻¹	0.00032
MRT (Mean residence time)	min	103.9571
V _d (Apparent volume of distribution)	mL kg ⁻¹	175.142
CL (Clearance)	mL/ (min kg)	0.3661
AUC _t (The total area under concentration–time curve)	min/ (μg mL)	11,880.31
AUC _i (The incremental area under concentration–time curve)	min/ (μg mL)	13,707.13

increase the activity of Glutathione peroxidase (GSH-Px) and SOD, and reduce the production of reactive oxygen species (ROS) and the loss of mitochondria.³⁴ The extensive clearance of ROS may be related to the regulation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling pathway.³⁵ AS-IV can increase the activity and expression of SOD-1 under normoxic and hypoxic conditions.²⁴ Quercetin is a natural antioxidant.³⁶ However, in vitro culture of rat cardiomyocytes has

**Figure 1** The structural formula of AS-IV.

shown that AS-IV has a better protective effect on the myocardium than quercetin, and both of them are better than vitamin E.³⁷

The ratio of ATP/adenosine diphosphate (ADP) and ATP/adenosine monophosphate (AMP) is decreased by ischemia and hypoxia.³⁸ It is well known that during ischemia or hypoxia, the increase in ATP levels in the interstitial spaces within the heart is due to its release from many cell types including cardiomyocytes. Results show that ATP is released through the maxi-anion channel.³⁹ AS-IV upregulates the expression of B-cell lymphoma 2 (Bcl-2), promotes the translocation of Bcl-2 to mitochondria, maintains the membrane potential of mitochondria, and inhibits mitochondrial permeability transition pore (mPTP) opening. This compound also inhibits the activation of caspase-3, decreases the expression of Bcl-2 associated X protein (Bax), reduces the release of cytochrome C (Cyt-C), increases ATP production, and ultimately reduces cell apoptosis and attenuates ischemia-hypoxia injury.^{26,27,34,39} When observing cell viability and morphology, it was found that AS-IV could upregulate the gene expression of GATA-4 and the survival factors Bcl-2 and P62 while also inhibiting apoptosis and autophagy genes, such as poly ADP-ribose polymerase (PARP), caspase-3, and Beclin-1. AS-IV can stimulate the expression of the transcription factor GATA-4, thereby enhancing the protective effect on the myocardium.⁴⁰

The imbalance in coronary blood flow mechanisms, including misregulation of ion channels, leads to the disruption of cardiac structure and loss of myocardial function. Coronary ion channels may represent arterial microvascular dysfunction.⁴¹ Ca^{2+} is released from the sarcoplasmic reticulum (SR) via the ryanodine receptors (RyRs), and other ions (especially K^+ , Mg^{2+} and Cl^-) provide counter-ion flux during systole.⁴² Hypoxic-ischemic injury inhibits SR Ca^{2+} -ATPase activity in cardiomyocytes and decreases the mRNA and protein expression of SR Ca^{2+} -ATPase.⁴³ After treatment with AS-IV, the capacity for the decreased kinase activity of protein kinase A (PKA) can be restored. The expression of PKA specific phosphorylated Ser (16) phosphorylated phospholamban (Ser (16)-PLN) is upregulated in cardiomyocytes, restoring the function of SR Ca^{2+} -ATPase (SERCA2a),²⁹ regulating Ca^{2+} homeostasis, decreasing the expression of $[\text{Ca}^{2+}]_i$ and CaSR, increasing the phosphorylation level of extracellular regulated protein kinases (ERK) to inhibit cell apoptosis.^{28,44}

There have been numerous experiments that have been used to study the possible pathways involved in the inhibition of myocardial ischemia-hypoxia injury by AS-IV. Studies have shown that in cardiomyocytes injured by hypoxia/reoxygenation, AS-IV can promote cell proliferation, upregulate the expression of miR-101a, inhibit the expression of transforming growth factor-beta receptor 1 (TGFBR1) and toll-like receptor 2 (TLR2), and inhibit the downstream genes of the mitogen-activated protein kinase (MAPK) signaling pathway. These results indicate that AS-IV may play a role through the miR-101a/TGFBR1/TLR2/MAPK signaling pathway.⁴⁵ Some studies have examined the expression of heme oxygenase (HO-1) by Western blot as well as the expression of Nrf2 and BTB and CNC homology 1 (Bach1) proteins in the nucleus. AS-IV can regulate the expression of Nrf2 and Bach1 proteins and significantly increase the expression of HO-1 protein ($P < 0.01$). Moreover, Phosphatidylinositol-3-kinase (PI3K) inhibitors have been found to have a certain reversal effect on the therapeutic effect of AS-IV. It was concluded that the PI3K/protein kinase B (AKT)/HO-1 signaling pathway may participate in the protective mechanism of ischemia and hypoxia.^{46,47} AS-IV can upregulate the p-AKT/AKT ratio and the phosphorylated glycogen synthase kinase/glycogen synthase kinase 3 β (GSK-3 β) ratio, and the mechanism of alleviating I/R damage may be related to the PI3K/AKT/GSK-3 β signaling pathway.⁴⁸ Similarly, studies have found that the inhibition of PI3K/mammalian target of rapamycin (mTOR) or mTOR can reverse AS-IV-induced downregulation of long non-coding RNA (lncRNA) growth arrest-specific transcript 5 (GAS5) in cardiomyocytes. AS-IV may play a protective role by activating the PI3K/mTOR pathway.⁴⁹ Bcl-2 and Bcl-2-like protein 2 (BCL2L2) correspond to the target genes of miR-23a and miR-92a. Knockdown of miR-23a and miR-92a is associated with the PI3K/AKT and MAPK/ERK signaling pathways. AS-IV may play a protective role in cardiomyocytes by downregulating the target genes of Bcl-2 and BCL2L2 (miR-23a and miR-92a) and activating the PI3K/AKT and MAPK/ERK signaling pathways.⁵⁰ In addition, after AS-IV treatment, the mRNA and protein expression levels of hypoxia-inducible factor-1 α (HIF1 α), the Notch signal receptor 1 (Notch1) and the Notch ligand Jag 1 (Jagged1) are significantly increased in rats ($P < 0.01$ or $P < 0.05$).⁵¹ Upregulation of Hes1 protein expression suggests that the Notch1/Hes1 signaling pathway may be involved in the prevention of myocardial ischemia and hypoxia injury.³⁴ AS-IV downregulates the expression of toll-like receptor 4 (TLR4) and nuclear factor kappa-B

(NF- κ B), suggesting that it may play a role in inhibiting apoptosis and reducing ischemia and hypoxia injury in rats through the TLR4/NF- κ B signaling pathway.⁵² In summary, the protective effect of AS-IV against ischemia and hypoxia injury may involve multiple pathways, such as the MAPK, PI3K/AKT, Notch1, and NF- κ B pathways, and its mechanism is relatively complex. Figure 2 summarizes the effect of hypoxic-ischemic injury on myocardial mitochondria and the protective mechanism of AS-IV.

Regulation of the Heart Structure and Inhibition of Cardiac Hypertrophy and Myocardial Fibrosis

Hypertrophy includes physiological and pathological effects, and early compensatory myocardial hypertrophy is an adaptive response. Over time, pathological cardiac hypertrophy alters cardiac structure, leading to heart failure.^{53,54} Similarly, excessive myocardial fibrosis can also lead to

ventricular remodeling and heart failure.⁵⁵ AS-IV can inhibit ventricular remodeling and improve cardiac function.⁵⁶

There are many experimental studies that have successfully created models of cardiac hypertrophy by taking multiple approaches and have demonstrated the protective effect of AS-IV on cardiac hypertrophy in vivo or in vitro. Recent research has used isoproterenol (ISO) or a calcium-sensing receptor agonist (GdCl₃) to induce hypertrophy in rat and heart H9C2 cells and found that AS-IV can attenuate the cardiac function and mitochondrial structural damage caused by the inducer. Moreover, AS-IV can affect the expression of [Ca²⁺] (i) and calcium-sensing receptor, thereby inhibiting myocardial hypertrophy and apoptosis.⁵⁷ AS-IV may exert an inhibitory effect on ISO-induced cardiac hypertrophy by reducing oxidative stress and calpain-1 activation. These researchers also used the same research subjects induced with ISO. Their results show that AS-IV increased Bcl-2 expression, decreased

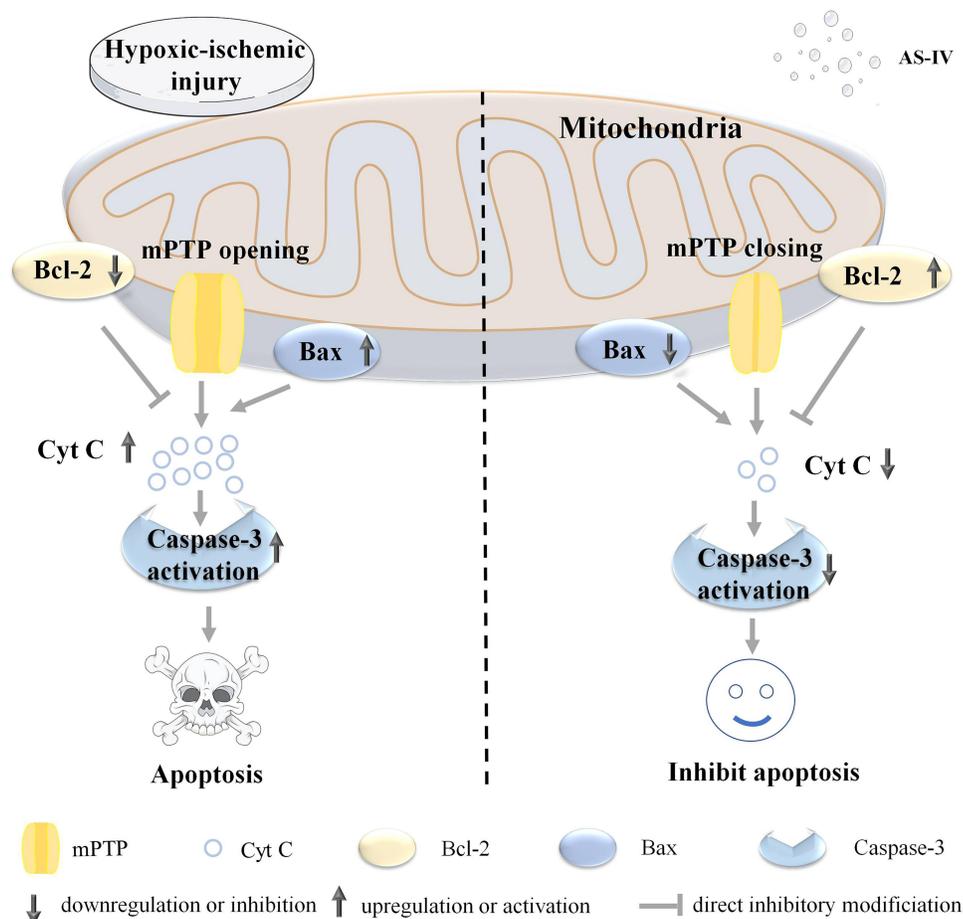


Figure 2 The mechanism of AS-IV protection of cardiomyocytes from hypoxia-ischemia injury. Hypoxic-ischemic injury will lead to the downregulation of Bcl-2 expression, upregulation of Bax expression, opening of mPTP, release of Cyt C, and activation of Caspase-3, leading to apoptosis. The addition of AS-IV can inhibit this series of processes and protect cardiomyocytes.

Bax and calpain-1 protein expression and calpain activity, and increased the activities of mitochondrial superoxide dismutase (mito-SOD) and mitochondrial catalase (mito-CAT).⁵⁸ AS-IV also regulates the Ca^{2+} -mediated calcineurin (CaN) signaling pathway. Lipopolysaccharide (LPS) induces cardiac hypertrophy, increases the level of resting Ca^{2+} , and promotes CaN activation. The addition of AS-IV can reduce cardiac hypertrophy and inhibit CaN activation before lipopolysaccharide induction. It inhibits the level of resting Ca^{2+} similarly to verapamil.⁵⁹ AS-IV may also prevent ISO-induced cardiac hypertrophy by mediating the NF- κ B/peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α) signaling pathway. AS-IV was used in combination with ISO to treat Sprague-Dawley (SD) rats or neonatal rat ventricular myocytes (NRVM). The results show that pathological changes were alleviated and the subunit transfer of transcription factor p65 (p65) and NF- κ B were inhibited.⁶⁰ AS-IV can upregulate Nrf2, stimulate the Nrf2/HO-1 signaling pathway, and improve ventricular function and structure.⁶¹ SD rats and neonatal rat cardiomyocytes were next treated with ISO in this report. In vivo, AS-IV could regulate the changes caused by ISO treatment, increase TLR4 and p65 protein expression, increase NF- κ B inhibitor α (I κ B α), and significantly reduce the expression of atrial natriuretic peptide (ANP), TLR4 mRNA, tumor necrosis factor- α (TNF- α), and interleukin 6 (IL-6) in serum. In vitro, AS-IV could regulate cell size and had a similar effect to propranolol. The mechanism of action may be related to the inhibition of TLR4/NF- κ B signaling pathway and the attenuation of inflammation effects.⁶² Other studies have used an aortic band (AB) surgery-induced mouse myocardial hypertrophy model. IKKepsilon inhibitory factor (SIKE) is enhanced and TANK1-binding kinase 1 (TBK1)/PI3K/AKT activity is inhibited after AS-IV treatment so as to prevent heart hypertrophy.⁶³ AS-IV could inhibit endothelin-1 (ET-1) induced cardiomyocyte hypertrophy and affect the expression of signaling molecules in the vitamin D axis.⁶⁴ Table 3 summarizes the research subjects of all the experiments mentioned above, the induction methods of the respective cardiac hypertrophy models and the possible mechanisms of AS-IV.

Myocardial fibrosis is caused by an excessive accumulation of collagen in the myocardial interstitium and exists in different stages of a variety of cardiomyopathies. In order to determine the therapeutic effects of AS-IV on viral myocarditis, a mouse model of viral myocarditis was established with coxsackievirus B3 (CVB3). Studies

have shown that AS-IV can attenuate the expression of FAS, FASL, caspase-8 and caspase-3, and inhibit CVB3-induced myocardial apoptosis, which may be related to the inhibition of fatty acid synthetase/Fas ligand (FAS/FASL) signaling pathway activation.⁶⁵ For CVB3-induced myocardial fibrosis in dilated cardiomyopathy, AS-IV treatment significantly improved survival. AS-IV can downregulate the expression of transforming growth factor- β 1 (TGF- β 1) and its downstream phosphorylated mothers against decapentaplegic protein 2/3 (pSmad2/3) and Smad4 in the myocardium, as well as reducing the level of type I collagen. The preventive fibrosis effect of AS-IV may be related to the downregulation of the TGF- β 1-Smad signaling pathway.⁶⁶ AS-IV can reduce mortality and improve myocardial fibrosis in mice with CVB3-induced chronic myocarditis. AS-IV can also reduce the collagen volume fraction. Its mechanism of action may be downregulation of the expression of TGF- β 1 and matrix metalloproteinase-1 (MMP-1) and upregulation of MMP-13 and MMP-14 expression.⁶⁷ It was observed that AS-IV significantly downregulated the mRNA expression of NLR family pyrin domain containing 3 (NLRP3), caspase-1, IL-18 and IL-6 in mouse heart tissue. AS-IV may exhibit ISO-induced inhibition of myocardial fibrosis in mice by inhibiting the NLRP3 pathway.⁶⁸ Hypoxia can lead to the upregulation of transient receptor potential melastatin 7 (TRPM7) protein, which is one of the targets of miR-135a. In vivo and in vitro studies have shown that AS-IV can reduce the expression of TRPM7 and its mRNA, inhibit the activation of the TGF- β /Smads pathway, and inhibit myocardial fibrosis.^{69,70} The mechanism by which AS-IV inhibits ISO-induced myocardial fibrosis may be related to ROS-mediated responses. It has been found that both increased ROS content and upregulated cardiostrophin 1 (CT1) expression, both of which were inhibited after the addition of astragaloside, which inhibited cardiac fibroblast proliferation and collagen production.⁷¹ Inhibition of ROS-mediated MAPK activation can also inhibit myocardial fibrosis. AS-IV can significantly inhibit ISO-induced cardiac fibroblast proliferation and collagen I synthesis, reduce ROS levels, and inhibit the phosphorylation of extracellular signal-regulated kinase, p38MAPK, and cJun N-terminal kinase. Acetylcysteine, an ROS scavenger, has a similar effect to AS-IV in regulating ROS.⁷² AS-IV can significantly reduce the cardiac mass index and left ventricular mass index, metabolites of type I collagen, as well as TGF- β 1, Smad 2/3, and Smad 4 protein expression levels ($P < 0.05$), but it can upregulate

Table 3 Mechanisms of AS-IV in the Treatment of Cardiac Hypertrophy

Research Subjects	Induction Methods	Mechanism	Refs
Rats and heart H9C2 cells	Isoproterenol or GdCl3	Regulates CaSR-mediated $[Ca^{2+}]_i$, CaMKII and CaN signaling pathways, reduces heart function and mitochondrial structural damage	[58]
Sprague-Dawley rats and H9C2 cells	Isoproterenol	Reduces oxidative stress and activates calpain-I, displays anti-apoptotic effects	[59]
Primary Cardiomyocytes	Lipopolysaccharide	Inhibits cardiac hypertrophy through the Ca^{2+} -mediated CaN signaling pathway	[60]
Sprague-Dawley rats and neonatal rat ventricular myocytes	Isoproterenol	Modulates NF- κ B/PGC-1 α signaling to prevent cardiac hypertrophy	[61]
Rats and heart H9C2 cells	Abdominal aortic coarctation or angiotensin II	Upregulates Nrf2, stimulates the Nrf2/HO-1 signaling pathway to improve heart structure and function	[62]
Sprague-Dawley rats and neonatal rat cardiomyocytes	Isoproterenol	Inhibits the TLR4/NF- κ B signaling pathway and reduce inflammation	[63]
Mice, inbred C57BL	Aortic banding surgery	Improves IKKepsilon inhibitory factor, inhibits TBK1/PI3K/AKT activity	[64]
Primary rat cardiomyocytes	ET-I	Inhibits ET-I induced cardiomyocyte hypertrophy, affects the expression of signaling molecules in the vitamin D axis	[65]

Smad 7 protein levels ($P < 0.05$). AS-IV combined with electroacupuncture had better effects on regulation than propranolol in some aspects. The attenuation of myocardial hypertrophy and myocardial fibrosis by AS-IV in rats may be related to the TGF- β 1/Smad signaling pathway.⁷³ Table 4 summarizes the research subjects of all the experiments mentioned above, the induction methods of myocardial fibrosis model, and the possible mechanisms of AS-IV.

Enhancement of Heart Function

Previous studies have found that AS-IV has a positive inotropic effect similar to cardiac glycosides.⁷⁴ Gene chip control assays were used to investigate the regulatory effects of AS-IV on myocardial gene expression profiles in rats. It was found that AS-IV could upregulate and enhance myocardial function.⁷⁵ AS-IV could also restore diastolic dysfunction in rats with chronic heart failure, and its mechanism of action was to downregulate calcium-sensitive receptors and protein kinase C- α .⁷⁶ AS-IV inhibited L-type calcium channels, which could reduce extracellular calcium influx, and at the same time promote the release of internal calcium, bidirectionally regulating the level of Ca^{2+} in cardiomyocytes and maintaining a steady state.^{74,77} AS-IV could also inhibit

Na^+/K^+ -ATPase activity, which could produce immediate myocardial contractile effects.^{26,78}

AS-IV alleviates oxidative stress, increases the production of nitric oxide (NO) and cyclic guanosine phosphate (cGMP) in the myocardium, and improves diastolic dysfunction.⁷⁹ AS-IV increases left ventricular systolic pressure, maximum rates of increase and decrease of left ventricular pressure, and significantly improves the survival rate of rats with heart failure.^{80,81} Cardiac output, heart rate, stroke volume, mean aortic pressure, and systolic aortic pressure gradually return to normal levels after treatment.⁸² AS-IV can restore normal cardiac parameters, enhance myocardial contractility, and improve cardiac diastolic dysfunction.

Effects on Blood Vessels

Gene chip control assays revealed that AS-IV had the greatest effect on vascular developmental function.⁷⁵ The effect of astragaloside on vascular regulation was mainly to improve vascular endothelial dysfunction and promote angiogenesis. Vascular endothelial cells are a barrier between circulating blood and the inner wall of blood vessels. A study of SD rats induced by ISO found that AS-IV increased the endothelial nitric oxide synthase (eNOS) dimer/monomer ratio and NO in serum and decreased the nuclear-cytoplasmic protein expression ratio of NF- κ B

Table 4 Mechanisms of AS-IV Action in the Treatment of Myocardial Fibrosis

Research Subjects	Induction Methods	Mechanism	Refs
Mice, inbred C57BL	Coxsackievirus B3	Reduces the expression of FAS, FASL, caspase-8 and caspase-3, inhibits the activation of the FAS/FASL signaling pathway	[66]
Mice, inbred BALB C	Coxsackievirus B3	Downregulates the TGF- β 1-Smad signaling pathway and reduces the level of type I collagen	[67]
Mice, Inbred BALB C	Coxsackievirus B3	Downregulates the expression of TGF- β 1 and upregulates the expression of MMP-13 and MMP-14	[68]
Mice, Inbred BALB C and primary cardiac fibroblasts	Isoproterenol	Downregulates the mRNA expression of NLRP3, caspase-1, IL-18 and IL-6, inhibits the NLRP3 pathway	[69]
Sprague-Dawley rats	Isoproterenol	Reduces the expression of TRPM7 and its mRNA, inhibits the activation of the TGF- β /Smads pathway, and inhibits fibrosis through the miR-135a-TRPM7-TGF- β /Smads pathway.	[71]
Sprague-Dawley rats and primary cardiac fibroblasts	Isoproterenol	Inhibits the increase of ROS content and the upregulation of cardiotrophin I expression	[72]
Sprague-Dawley rats and primary cardiac fibroblasts	Isoproterenol	Inhibits ROS-mediated activation of mitogen-activated protein kinase (MAPK)	[73]
Sprague-Dawley rats	Isoproterenol	Decreases TGF- β 1, Smad 2/3, and Smad 4 protein expression levels, upregulates Smad 7 protein expression level, and regulates the TGF- β 1/Smad signaling pathway	[74]

p65. AS-IV downregulated the expression of IL-1 β , IL-6, and TNF α mRNA. The mechanism may have been through the attenuation of the oxidative stress response and inhibit the ROS-NF- κ B pathway.⁸³ Dysglycemia and hyperhomocysteinemia are risk factors for cardiovascular disease, and AS-IV can also improve the endothelial dysfunction caused by them. For diabetic rats induced by streptozotocin (STZ), AS-IV can reduce the level of ROS, increase the production of NO and the expression of eNOS, and improve the activity of SOD and GSH-px. AS-IV ameliorated endothelial dysfunction in diabetic rats by decreasing oxidative stress and calpain-1.⁸⁴ The effects of AS-IV on human umbilical vein endothelial cells (HUVECs) were similar to those of TLR4 and NF- κ B p65 inhibitors. AS-IV could significantly reduce the content of IL-6 and TNF- α and decrease the expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), TLR4, and nuclear NF- κ B p65. AS-IV may play a protective role through the TLR4/NF- κ B signaling pathway.⁸⁵ Rats fed with fructose develop metabolic syndrome. High doses of AS-IV could improve glucose tolerance and endothelium-dependent vasodilation as well as increase the levels of NOx and cGMP; this mechanism may be associated with the NO/cGMP-related pathways.⁸⁶ AS-IV significantly

ameliorated homocysteine-induced inactivation of the nitric oxide synthase (NOS) signaling pathway by increasing SOD activity, which was similar to SOD pretreatment. AS-IV may be beneficial for the treatment of the endothelial dysfunction caused by the NO/NOS pathway disorder in hyperhomocysteinemia.⁸⁷ Table 5 summarizes the research subjects of all the experiments mentioned above, the induction methods of endothelial dysfunction, and possible mechanisms of AS-IV.

AS-IV promotes angiogenesis, increases vascular density, and promotes the mRNA expression of CD31 and vascular endothelial growth factor (VEGF). AS-IV induces Janus kinase (JAK) and signal transducer, and is an activator of transcription 3 (STAT3) phosphorylation, which may promote angiogenesis possibly related to the JAK-STAT3 pathway.⁸⁸ AS-IV increases the mRNA and protein expression levels of VEGF and basic fibroblast growth factor (bFGF) ($P < 0.01$ or $P < 0.05$). AS-IV can also significantly increase microvessel density ($P < 0.05$).⁸⁹ AS-IV can alleviate ultrastructural damage and promote angiogenesis, promote cell proliferation and tube formation, and induce the activation of the phosphatase and tensin homologue deleted on chromosome (PTEN)/PI3K/Akt signaling pathway.⁹⁰ After AS-IV administration, myocardial morphology is significantly improved and the

Table 5 Mechanisms of AS-IV in the Treatment of Endothelial Dysfunction

Research Subjects	Induction Methods	Mechanism	Refs
Sprague-Dawley rats	Isoproterenol	Reduces eNOS-mediated oxidative stress and inhibits the ROS-NF-κB pathway	[84]
Sprague-Dawley rats and Human umbilical vein endothelial cells	Streptozotocin	Reduces oxidative stress and calpain-1, improves endothelial dysfunction	[85]
Sprague-Dawley rats and Human umbilical vein endothelial cells	Streptozotocin	Reduces the content of IL-6 and TNF-α, decreases the expression of VCAM-1, ICAM-1, TLR4, and nuclear NF-κB p65, regulates the TLR4/NF-κB signaling pathway	[86]
Sprague-Dawley rats	Fructose	Improves glucose tolerance and endothelium-dependent vasodilation, increases the levels of NOx and cGMP	[87]
Human umbilical vein endothelial cells	Homocysteine	Increases ROS activity, ameliorates the inactivation of NOS, and regulates the NO/NOS pathway	[88]

number of new blood vessels is increased. The mRNA and protein expressions of Protein kinase D1 (PKD1), Histone Deacetylase 5 (HDAC5), and VEGF in myocardial tissue are significantly increased. AS-IV may promote angiogenesis through the PKD1-HDAC5-VEGF pathway.⁹¹ TCM has a coordinated and synergistic effect, and multiple medicines are used together for better efficacy. AS-IV combined with tanshinone IIA (an active ingredient of *Salvia miltiorrhiza* Bge) can significantly increase the proliferation and tube formation ability of EC-like cells compared with either drug alone. Tanshinone IIA and AS-IV can promote the angiogenesis of EC-like cells by upregulating the expression of connexin 37 (Cx37), Cx40, and

Cx43.⁹² The search for vascular substitutes has always been an area of intense research. TCM in the fiber scaffold can provide abundant biological factors. AS-IV and ferulic acid (the main component of *Angelica sinensis*) in a ratio of 7:3 could activate the cell viability of endothelial and smooth muscle cells, promote extracellular matrix secretion, increase vascular density, and reduce inflammatory responses.⁹³ Table 6 summarizes the research subjects of all the above experiments, the methods of promoting angiogenesis, and the possible mechanisms of AS-IV.

Other Effects of AS-IV

Antiviral Effects

Through the high-throughput screening of classic prescriptions from The Treatise on Cold-Induced and Miscellaneous Diseases, effective antiviral compounds were recently identified. It was found that AS-IV could activate p65 phosphorylation and nuclear translocation and had antiviral effects.⁹⁴ AS-IV can effectively alleviate myocardial fibrosis and inhibit myocardial cell apoptosis in the treatment of viral myocarditis. AS-IV upregulates the expression of Interferon γ (IFN- γ) mRNA, reduces the viral clearance of CVB3, and inhibits the proliferation of CVB3, thus exerting antiviral effects.⁹⁵ The effectiveness of AS-IV in the intervention of viral myocarditis was also systematically reviewed, and the results indicated that it might play a role through anti-myocardial remodeling, anti-myocardial fibrosis, anti-viral, anti-inflammatory, or anti-oxidation mechanisms.⁹⁶ AS-IV decreases the protein expressions of Bax and caspase-3 and increases Bcl-2 protein expression. The mechanism may involve the inhibition of human adenovirus type 3 (HAdV-3) replication, and the virus inhibition rate was positively correlated with the concentration of AS-IV.⁹⁷ In addition, AS-IV could also inhibit the secretion of hepatitis B virus surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) and reduce serum duck hepatitis B virus (DHBV) DNA level. *Astragalus membranaceus*, a TCM, helps to increase the negative conversion rate of HBeAg and Hepatitis B virus (HBV) DNA.⁹⁸

Regulation of Blood Glucose and Lipid Levels

Dysglycemia and dyslipidemia are risk factors for cardiovascular disease, and regulating blood glucose and lipid stabilization helps to maintain cardiovascular health. AS-IV significantly increases the content of hepatic glycogen and insulin, decreases the content of blood glucose glycosylated serum protein, and significantly improves pancreatic

Table 6 Mechanisms of AS-IV Promotion of Angiogenesis

Research Subjects	Intervention Methods	Mechanism	Refs
Sprague-Dawley rats	Ligation of left coronary artery	Induces phosphorylation of JAK and STAT3 and regulates the JAK-STAT3 pathway	[89]
Wistar rats	Ligation of left coronary artery	Increases the mRNA and protein expression levels of VEGF and bFGF, increases microvessel density	[90]
Sprague Dawley rats and Human umbilical vein endothelial cells	Ligation of left coronary artery	Reduces ultrastructural damage and promotes angiogenesis, promotes cell proliferation and tube formation, and induces the activation of the PTEN/PI3K/Akt signaling pathway	[91]
Sprague-Dawley rats	Ligation of left anterior descending branch	Increases the mRNA and protein expression of PKDI, HDAC5 and VEGF, and regulates the PKDI-HDAC5-VEGF pathway	[92]
Mesenchymal stem cells isolated from the femurs and tibias of Sprague Dawley rats	VEGF and bFGF promote the differentiation of MSCs into EC-like cells	Enhances the proliferation and tube formation ability of EC-like cells, and upregulates the expression of Cx37, Cx40, and Cx43	[93]

(Continued)

Table 6 (Continued).

Research Subjects	Intervention Methods	Mechanism	Refs
Primary endothelial cells and smooth muscle cells, Sprague Dawley rats	Place the drug-loaded stent under the back of the rat	Increases cell viability and extracellular matrix secretion of endothelial and smooth muscle cells, increases vascular density and decreases inflammatory response after drug loading	[94]

pathological changes in streptozotocin-induced diabetic mice.⁹⁹ By downregulating the expression of IL-6 and TNF- α and inhibiting the NLRP3 inflammasome in the pancreas of gestational diabetic mice, AS-IV can reduce glucose and insulin levels in gestational diabetic mice.¹⁰⁰ Moreover, it can inhibit the expression of integrin-linked kinases in diabetic rats and restore the expression of integrin $\alpha\beta 1$ to reduce diabetic nephropathy.¹⁰¹

The protective mechanism of AS-IV on myocardial injury in type 2 diabetes may be achieved by regulating abnormal energy and lipid metabolism, regulating the release of PGC-1 α and nuclear respiratory factor 1 (NRF1), reversing hyperglycemia-induced oxidative stress and autophagy, and improving the accumulation of cardiac lipids.^{102–104} AS-IV intervenes in apoE (-/-) mice raised on a high-fat diet, and studies found that the levels of triacylglycerol (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were downregulated and the levels of HDL-C were increased in the blood of mice. Thus, AS-IV can regulate blood lipids and protect against vascular injury.¹⁰⁵

Discussion

In recent years, clinical and pathological research on CVDs has developed rapidly, and great achievements have been made in the research and development of therapeutic methods and drug research. However, the incidence and mortality of CVDs are still high and seeking

treatments with high efficiency, low toxicity, and few side effects is still the focus of research. As a characteristic therapy, TCM plays an important role in the treatment of CVDs. *Astragalus membranaceus*, as a commonly used TCM, has obvious protective effects on the heart, brain, liver, kidney, and lung. In addition, *Astragalus membranaceus* has anti-inflammatory, antioxidant, and immune-enhancing effects, which are good therapeutic effects against cancer and immune diseases.^{106–108}

Single drugs or compound preparations containing *Astragalus membranaceus* are widely used in the treatment of CVDs. Astragalus injection, the main component of which is *Astragalus membranaceus*, where the content of AS-IV is as high as $11.30 \text{ mg}\cdot\text{mL}^{-1}$, is often used in the treatment of CVDs. It is used to treat coronary heart disease, angina pectoris, and viral myocarditis, and can improve myocardial injury indicators [Cardiac troponin I (cTnI), high-sensitivity C-reactive protein (hs-CRP), creatine kinase-MB (CK-MB)], reduce TNF- α , IL-6, hs-CRP levels, improve immune function, improve blood lipid metabolism (reduce TC, LDL-C, TG; increase high-density lipoprotein cholesterol (HDL-C)), reduce blood agglutination, and decrease blood cell aggregation index, fibrinogen levels, and blood cell viscosity.^{109–111} There are many compound Chinese patent medicine preparations that use *Astragalus membranaceus* as the monarch herb, such as Qili Qiangxin Capsules, Qishen Yiqi Dripping Pills, Naoxintong Capsules, Yangxinshi Tablets, Buxinqi Oral Liquid, and Xintong Oral Liquid, which all can be used to treat coronary heart disease, angina pectoris, heart failure, and adverse cardiovascular events after intervention. Different Chinese patent medicines can be used according to TCM syndrome differentiation.^{112–117}

The main active ingredient of *Astragalus membranaceus* is AS-IV, which is sparingly soluble in water and has an oral bioavailability of less than 3%. Structural modification and new formulations to improve the bioavailability of oral drugs are commonly used methods at present that can increase stability. Astragalosidic acid, a novel water-soluble derivative of AS-IV, also has obvious cardioprotective effects, with twice the relative bioavailability of AS-IV. It has better permeability and is easier to absorb in the intestine. Moreover, high-dose administration has no obvious acute toxicity. Improving the oral availability of AS-IV is a key direction of new drug research and development.^{16,19} There are few reports on the toxicology of AS-IV, and it is impossible to determine the possible chronic accumulation caused

by its long-term use. Although of great significance, the limited number of studies have been mostly based on animal or cell experiments, and there is insufficient evidence for clinical application of the effective ingredients of *Astragalus membranaceus*. The human body is a living body, and the target pathways are more complicated than model organisms. At present, the targets and signaling pathways for CVDs are complex, and the research is relatively scant in humans. The research on the pharmacological effects and mechanism of AS-IV on a certain sites is not very deep, and there is a lack of in-depth study of network regulation relationships. The dosage of AS-IV used in each study varies greatly, and the safe range and most effective dose of AS-IV still needs to be further determined.

In conclusion, this article briefly analyzed the structure and pharmacokinetics of AS-IV and expounded on the cardiovascular protective mechanisms from its regulatory effects on the heart, blood vessels, blood sugar, and blood lipid levels. AS-IV can eliminate ROS, increase SOD activity, and help cells resist oxidative damage, regulate mitochondrial energy metabolism, and ion homeostasis. AS-IV also plays a protective role against ischemia-hypoxic damage by regulating multiple pathways such as the MAPK, PI3K/AKT, Notch1, and NF- κ B pathways. AS-IV can act on ion channels or reduce the inflammatory response to inhibit myocardial hypertrophy, but also inhibits FAS/FASL and TGF- β /Smads pathway activation and reduces the level of collagen and collagen volume fraction to anti-myocardial fibrosis. Its positive inotropic effect can significantly improve myocardial diastolic dysfunction and restore normal cardiac parameters.

The effect on vascular development is more obvious. AS-IV can prevent vascular endothelial dysfunction by weakening oxidative stress response and reducing inflammation, increase the ability of cell proliferation and tube formation, increase blood vessel density, and promote angiogenesis. It has a wide range of inhibitory effects on a variety of viruses, inhibits virus proliferation, and improves the body's immunity. The risk factors of CVDs also see significant improvement after AS-IV treatment, which can regulate metabolic abnormalities, improve lipid accumulation, and reduce vascular injury. From multiple levels, different dimensions of disease development play a therapeutic role, which is worthy of further promotion and application.

Conclusion

The study of the therapeutic effects and mechanisms of *Astragalus membranaceus* and its active ingredients has attracted much attention in the pharmacokinetic field. AS-IV displays good therapeutic effects, especially in the cardiovascular field. It can significantly reduce myocardial injury caused by ischemia and hypoxia, improve energy metabolism, improve endothelial dysfunction, promote angiogenesis, improve immune function, and regulate blood glucose and blood lipid levels. The mechanism by which AS-IV exerts its therapeutic effect on CVDs is complicated, and some therapeutic effects that may involve a combination of multiple pathways are still unclear. AS-IV has a wide range of therapeutic effects and has good development prospects. Based on current research, it can be applied to hypoxic and ischemic injury, physical damage caused by viral diseases, or novel proangiogenic agents. The research on new drugs and mechanisms of AS-IV continues to progress, and more new alternative drugs derived from AS-IV are expected in the future.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data. All authors took part in drafting the article and revising it critically for important intellectual content. All authors agreed on the journal to which the article will be submitted. All authors gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (No. 81973836), and the China Academy of Chinese Medical Sciences-Traditional Chinese Medicine Science and Technology Achievement Leading Project (No. ZZ13-ZD-04).

Disclosure

All authors declare that there are no conflicts of interest in publishing this work in whole or in part and report no conflicts of interest for this work.

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