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Review

Recent pharmacological advances in the treatment of cardiovascular events with Astragaloside IV

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of death and disability globally. A wide range of CVDs have been reported, each of which diverges significantly, exhibiting sophisticated types of pathogenesis (e.g., inflammatory, oxidative stress, and disorders in cardiomyocyte metabolism). Compared with conventional treatments in modern medicine, traditional Chinese medicine (TCM) can exhibit comparative advantages in the treatment of CVDs. TCM can be utilized to develop effective strategies for addressing the challenges of CVD, with fewer side effects and higher therapeutic efficiency. Astragaloside IV (AS-IV) has been confirmed as one of the major active ingredients found in Astragalus membranaceus (a Chinese herbal medicine that has been extensively employed clinically for the treatments of CVDs). Since recent studies have shown that AS-IV in CVD treatments has achieved promising results, the substance has aroused great attention and further discussions in the field. The present review aims to summarize the recent pharmacological advances in employing AS-IV in the treatment of CVDs.

1. Introduction

Cardiovascular disease (CVD) refers to a common disease that seriously jeopardizes people's lives and health. It has been widely reported in elderly individuals aged over 50 years and with the characterization of high morbidity, disability, and mortality [1]. The morbidity and mortality of CVD rank first in China, Europe, the U.S. and other relatively developed countries. Existing research suggests that CVD accounts for over 31% of deaths worldwide [2]. Notably, with the acceleration in aging in the social population, the above-mentioned situation will become increasingly serious, and the morbidity and mortality rates will continue to increase [3]. Numerous types of CVDs have been reported, for instance, heart failure (HF), myocardial infarction (MI), pulmonary arterial hypertension (PAH), and atherosclerosis (AS). These diseases are public health issues that have severely threatened human health worldwide and are yet to be solved. In recent years, although increasingly more drugs have been applied to the clinical treatments of cardiovascular events, the incidence rate and mortality are still increasing.

Abbreviations: AS-IV, astragaloside IV; CVD, cardiovascular disease; AS, atherosclerosis; HF, heart failure; MI, myocardial infarction; PAH, pulmonary arterial hypertension; TCM, traditional Chinese medicine; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; MRAs, mineral corticosteroid receptor antagonists; SUMO, Small ubiquitin-like modifier; Spen1, specific protease 1; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVSED, left ventricular end-systolic dimension; BNP, brain natriuretic peptide; LVW/BW, left ventricular body mass to body weight; LV, left ventricle; AMI, acute myocardial infarction; CHF, chronic heart failure; NF-κB, nuclear factor kappa B; BMECs, bone marrow mesenchymal stem cells; I/R, ischemia-reperfusion; MCT, monocrotaline; Tfh cells, T follicular helper cells; Tfr cells, T follicular regulatory cells; CCN1, cysteine-rich 61; TNF, tumor necrosis factor; IL, interleukin; HPASMC, human pulmonary artery smooth muscle cells; MD, Myocardial dysfunction; CLP, cecum ligation and puncture; DCM, diabetic cardiomyopathy; HIF-1α, hypoxia-inducible factor 1α; Ox-LDL, oxidized low-density lipoprotein; HUVECs, human umbilical vein endothelial cells; LDH, lactate dehydrogenase; PBA, phenyl butyric acid; HO-1, heme oxygenase-1; NLR, nucleotide-binding domain leucine-rich repeat-containing receptor; Nrf-2, nuclear factor red lineage-2-related factor 2; LPC, lysophosphatidic choline; CF, Cardiac fibrosis; LVH, left ventricular hypertrophy; ISO, isoprenaline; DOX, doxorubicin; ADR, adriamycin; VSMC, vascular smooth muscle cell; BLM, bleomycin.

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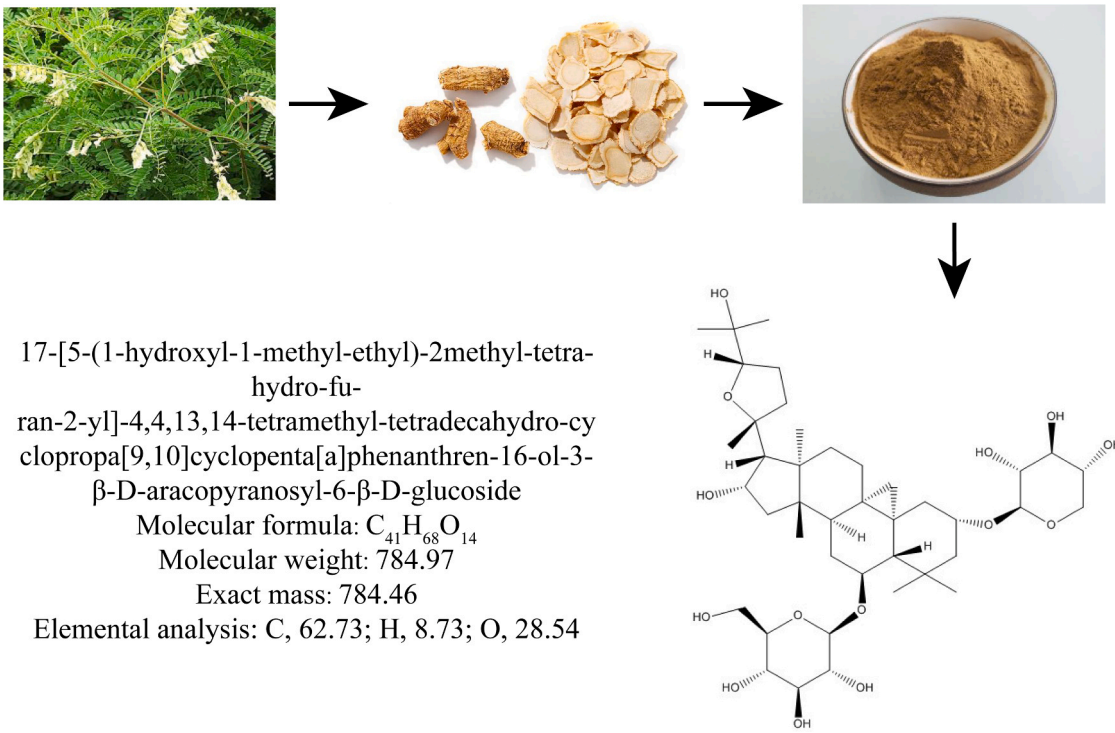

Fig. 1. The structure and main source of AS-IV. AS-IV is an active compound originally extracted from Astragalus membranaceus. It belongs to the group of pentacyclic triterpenoids, as a cyclic astragalosol with β-D-xylopyranosyl and β-D-glucopyranosyl residues attached at the O-3 and O-6 positions, respectively. The molecular model of AS-IV is exhibited in the figure. Detailed AS-IV information was sourced from PubChem

Therefore, it is of great clinical significance to explore new drugs for cardiovascular events.

Traditional Chinese medicine (TCM) has a history of over 2000 years and has been widely applied clinically. Modern society and international communication have made great progress over the past few years. In this context, TCM has emerged to be popular worldwide with herbal medicine being extensively accepted globally. As revealed by existing evidence, TCM may serve as a complementary and alternative method for primary and secondary CVD prevention [4]. TCM exhibits numerous advantages, such as multiple targets, lower cost, and fewer side effects. Despite the widespread application of TCM, its explicit role in preventing and treating a single disease remains unclear since scientific evidence is rare. Thus, in-depth trials need to be performed to verify the precise effect of TCM on CVD.

Astragalus membranaceus, one of the sources of Radix Astragali [5], which refers to 'Huang Qi', was categorized as an Upper Herb in the Divine Farmer's Classic of Materia Medica, the oldest surviving Chinese materia medica. It was described to have properties of lightening the body, tonifying qi and lengthening the lifespan [6]. In clinic, Astragalus membranaceus was commonly used in multiple herbal formulas [7–12], or acted alone in the practice of TCM [13–15], treating a wide variety of diseases and body disorders [16–20]. Moreover, the potential use of this herb and its chemical constituents in the treatment of CVD across diversified clinical applications has been extensively investigated over the past few years. Astragaloside IV (AS-IV) has been proven to be the predominant component extracted from Astragalus membranaceus and there is evidence indicating that AS-IV can mediate the cardiovascular protective effects of astragalus [7–12]. Besides its cardioprotective effects, which have been extensively studied, AS-IV has also been studied to have anti-cancer, hepatoprotective, neuroprotective, and immune-enhancing effects [21–26].

Multiple studies have verified that AS-IV exhibits pharmacological effects on CVD due to its antioxidant, immuno-regulation, anti-inflammatory, and anti-apoptotic properties, as well being effective in treating respiratory diseases [6,26]. Moreover, AS-IV can alleviate infarction-induced cardiomyocyte injury by enhancing mitochondrial morphology and function [27,28]. In addition, AS-IV has shown notable pharmacological effects on anti-myocardial fibrosis [29]. Furthermore, AS-IV regulates calcium balance [30] and protects the heart through numerous signaling pathways [31]. This study aims at reviewing the recent progress regarding the use of AS-IV in the treatment of CVD and providing evidence for its potential clinical application. It also aims to review the cardiovascular protection provided by AS-IV and the mechanism of AS-IV in cardiovascular diseases, such as heart failure, myocardial infarction, and myocardial ischemia–reperfusion injury, systematically summarizing the cardiovascular protective effects of AS-IV.

Table 1
Physicochemical properties of Astragaloside IV.

Content	Description
Name	Astragaloside IV
CAS number	84687–43–4
Molecular formula	$C_{41}H_{68}O_{14}$
IUPAC Name	(2 R,3 R,4 S,5 S,6 R)− 2-[[(1 S,3 R,6 S,8 R,9 S,11 S,12 S,14 S,15 R,16 R)− 14-hydroxy-15-[(2 R,5 S)− 5-(2-hydroxypropan-2-yl)− 2-methyloxolan-2-yl]− 7,7,12,16-tetramethyl-6-[(2 S,3 R,4 S,5 R)− 3,4,5-trihydroxyoxan-2-yl]oxy-9-pentacyclo[9.7.0.01,3.03,8.012,16]octadecanyl]oxy]− 6-(hydroxymethyl)oxane-3,4,5-triol
Molecular weight	785.0 g/mol
Topological Polar SurfaceArea	228Å^2
LogP	1.96
Physical description	A crystalline solid
Color	White crystalline powder
Flash Point	495.5 ℃
Melting Point	295–296 ℃
Boiling Point	895.7 ℃
Solubility	DMF: 20 mg/ml; DMSO: 30 mg/ml; DMSO:PBS (pH7.2) (1:1): 0.5 mg/ml
Density	1.39 g/cm^3

2. Chemical structure and pharmacological properties of AS-IV

Astragaloside IV (PubChem CID 13943297) (Fig. 1) is a white-to-yellow crystalline powder isolated from Astragalus membranaceus var. mongholicus. It belongs to the group of pentacyclic triterpenoids, as a cyclic astragalosol with β-D-xylopyranosyl and β-D-glucopyranosyl residues respectively attached at the O-3 and O-6 positions. It is a triterpenoid saponin and a pentacyclic triterpenoid functionally related to cyclic flavonoids. AS-IV plays various roles as an anti-inflammatory agent [21], anticancer [22] and antitumor agent [32], kidney protector [23], neuroprotective agent [24,25,33], antioxidant agent [34], and pro-angiogenic agent [35], and possesses properties to treat respiratory diseases [26]. The detailed physicochemical properties of AS-IV are summarized in Table 1.

3. Pharmacokinetics and toxicology of AS-IV

Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion of a drug, the main parameters of which are mean time to peak concentration (Tmax), half-life (T1/2), mean residence time (MRT), clearance (CL), and bioavailability (F). A deepened understanding of drug pharmacokinetics may help us to assess the nature of a specific drug and the prospects of its application. The pharmacokinetic profile of AS-IV has been previously characterized in studies using rats and Beagle dogs as the experimental subjects. It was found that the Tmax, T1/2, MRT, and CL were 0.75, 3.8 and 4.62 h, and 6.16 L kg^{-1}- h^{-1}, respectively, in rats administered 20 mg/kg AS-IV orally; whereas, after the oral administration of AS-IV to beagle dogs, it was observed that the Tmax, T1/2, MRT, and CL were 1.0, 3.83 and 4.35 h, and 0.010 L kg^{-1}-min^{-1}, respectively [36–38]. In addition, it was discovered that AS-IV has low bioavailability in vivo after oral administration in rats (3.66%) and beagles (7.4%) [37], which is mainly due to its poor intestinal permeability, high molecular weight, low lipophilicity, and its paracellular transport properties [39], [40]; therefore, the oral administration of AS-IV is not recommended clinically. By assaying the drug content in different tissues after the intravenous administration of AS-IV, it was revealed that the highest AS-IV concentrations were found in the liver and kidney, followed by the lungs, heart, and spleen. AS-IV is difficult to detect in the brain, suggesting that it may have difficulty in penetrating the blood–brain barrier [41]. In addition, AS-IV was found to be more than 83% bound to plasma proteins, with a recovery rate of approximately 50% in urine and feces [42,43].

AS-IV causes no significant adverse effects or preclinical toxicity. A study conducted by Gui et al. showed that the oral administration of AS-IV did not affect hepatic or renal function [44]. Experiments on animals also confirmed that treatment with AS-IV does not result in toxicity or side effects in adult animals, with safe doses in rats and beagles equivalent to 70 or 35 times the human dose (0.57 g/kg) [45]. However, AS-IV was found to have dose-dependent maternal toxicity. Significant delays in the hair development and neurological development of pups were observed after treatment on maternal rats at a dose of 1.0 mg/kg/d, suggesting that AS-IV should be used with caution in the treatment of CVD in pregnant populations [46]. In addition, Zhu et al. also found a risk of maternal toxicity in AS-IV treatment by intravenous injection in maternal rats and New Zealand white rabbits, whereas its teratogenicity was not detected [47]. Since relevant studies are limited, and support from clinical evidence is particularly lacking, further investigation is still required. AS-IV is a relatively safe chemical component to apply clinically.

4. Effect and mechanism of AS-IV in cardiovascular events

4.1. Heart failure

Heart failure (HF) refers to a pathophysiological process or syndrome where the systolic or diastolic function of the myocardium is severely impaired by a wide variety of pathogenic factors [48]. HF is currently recognized as a common CVD affecting approximately 1–2% of adults worldwide, thus triggering an absolute or relative decrease in cardiac output [49]. As the terminal point of all types of CVD [50], HF seriously threatens human health. Extensive research has suggested that AS-IV is an active component in treating HF, with the effect evaluated by measuring cardiovascular parameters on rats [51]. Advanced studies have unveiled the underlying mechanisms. Liu et al. studied the protective effect and mechanism of AS-IV against HF. It has been confirmed that small ubiquitin-like modifier (SUMO)-specific protease 1 (SENP1) is involved. As indicated by the results, AS-IV can improve cardiac function, reduce myocardial ROS and H_2O_2 levels, and inhibit the reduction in mitochondrial membrane potential while reducing cardiomyocyte apoptosis in HF mice. The above results also reveal that AS-IV can reduce oxidative stress in cardiomyocytes, decrease mitochondrial damage, inhibit ventricular remodeling, and ultimately enhance cardiac function by inhibiting HF-induced SENP1 overexpression [52]. Additionally, Sui et al. found that AS-IV could prevent heart failure by counteracting oxidative stress through the Nrf2/HO-1 pathway [53]. Moreover, Wang et al. suggested that AS-IV can prevent LPS-induced cardiac dysfunction by targeting miR-1 and ultimately inhibiting calcium-mediated apoptosis and autophagy, thus presenting new ideas regarding the application of AS-IV in the treatment of cardiac dysfunction [54]. In addition, Li et al. studied the effects of AS-IV on rat or mice models with HF using data retrieval and meta-analysis. Their results showed that AS-IV increased left ventricular fractional shortening (LVFS) and left ventricular ejection fraction (LVEF). Furthermore, the left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), and B-type brain natriuretic peptide systolic dimension were also reduced. LVESD, B-type brain natriuretic peptide (BNP), and left ventricular weight to body weight (LVW/BW) levels significantly improve cardiac function. Accordingly, the application of AS-IV shows great potential for the treatment of HF [55], and is related to antioxidant stress and anti-cardiomyocyte apoptosis.

4.2. Myocardial infarction and myocardial ischemia–reperfusion injury

Myocardial infarction (MI) refers to a type of heart attack in which blood flow to the heart is reduced due to the formation of plaque in the inner walls of the arteries, such that the heart muscle is injured under the effect of insufficient oxygen supply [56]. Although clinical treatments can reduce damage to the heart and improve patients' lives, MI still carries a greater risk of heart failure [57]. Some studies have suggested that AS-IV can play a subsidiary role in treating MI. For example, it has been proven that a combination of remote ischemic conditioning (RIC) and AS-IV treatment can be a more practical and effective method for heart-protection against MI compared with individual treatments [58]. The introduction of AS-IV in later treatments for MI should be considered to improve the prognosis. Zhang et al. investigated the mechanism of myocardial injury protection using AS-IV after myocardial infarction. The protective effect of AS-IV against hypoxic injury in cardiac myocytes can be mediated by maintaining mitochondrial homeostasis in a SIRT3-dependent manner [59]. Sun et al. assessed the effect of AS-IV on MI, with a diabetic mice model selected instead. His study demonstrated that AS-IV prevented myocardial infarction cell apoptosis and restored cardiac function, its reason believed to be due to the regulation of the MAPK signaling pathway [60]. Zhang et al. suggested that AS-IV can alleviate MI-induced myocardial fibrosis and cardiac remodeling by inhibiting the ROS/cysteine aspartase-1/GSDMD signaling pathway [29]. Shi et al. confirmed that AS-IV can also mitigate AMI. The mechanism of AS-IV in preventing acute AMI-induced chronic HF (CHF) was investigated, and AS-IV was found to ameliorate AMI by reducing inflammation and blocking the TLR4/MyD88/NF-κB signaling pathway [61]. Furthermore, Sha et al. explored the role played by exosomes (MSC-Exo) from bone marrow mesenchymal stem cells (BMMECs) in the

mechanism of MI mitigation with the use of AS-IV. Their results revealed that AS-IV can restore myocardial contractile function, ameliorate myocardial fibrosis and angiogenesis, reduce inflammatory factors, and induce apoptosis in rats after AMI [62]. In summary, these studies show that improving mitochondrial energy metabolism, inhibiting cardiomyocyte apoptosis, and inhibiting myocardial fibrosis can improve myocardial infarction.

Unfortunately, following MI, the restoration of coronary blood flow may cause secondary injury to the ischemic myocardium, most likely in the form of myocardial ischemia–reperfusion (I/R) injury. Autophagy is regulated by ROS and takes on critical significance in myocardial I/R injury. Huang et al. found that SOD was down-regulated and $O2^{-}$ was up-regulated in H_2O_2-induced H9C2 cardiomyocyte injury in vitro, as well as in myocardial I/R injury in vivo. AS-IV has been verified to reverse this alteration. AS-IV can attenuate I/R-induced autophagy by reducing the ability of AS-IV to attenuate myocardial I/R injury by mitigating I/R-induced autophagy accumulation [63].

4.3. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) exhibits adverse remodeling of the artery tree, leading to increased vascular resistance, with a subsequent increase in right ventricular afterload, which would eventually develop to HF [64]. Non-specific clinical manifestations and a lack of pathological knowledge have led to a poor prognosis correlated with a delay in diagnosis and the initiation of subsequent therapy. Sildenafil has been the most used drug in PAH treatment thus far. As multiple studies have shown that AS-IV can play a promising role in dealing with PAH [65,66], the introduction of AS-IV may possibly optimize the current treatment of PAH. Li et al. found that AS-IV treatment can significantly enhance cardiac function in monocrotaline (MCT)-induced mice. AS-IV is believed to regulate Tfh and Tfr cell responses, thereby inhibiting PAH symptoms, such as pulmonary vascular remodeling. AS-IV can lead to the decreased differentiation of Tfh cells (T follicular helper cells) and IL-21 production while increasing the differentiation of Tfr cells (T follicular regulatory cells) and the production of TGF-β and IL-10. Chronic hypoxia promoted germinal center B-cell responses, which were inhibited by AS-IV. AS-IV also inhibited the proliferation, migration, and adhesion of PASMCs in vitro. In addition, AS-IV significantly decreased RhoA protein levels and up-regulated p27 protein levels in PASMCs under hypoxic conditions. The moderating effect of AS-IV was confirmed to inhibit the phosphorylation of the mTOR signaling pathway [67]. Moreover, Yao et al. explored the protective effects and mechanisms of AS-IV on hypoxia-induced PASMC proliferation and pulmonary vascular remodeling. In their research, AS-IV effectively reversed hypoxia-induced pulmonary vascular remodeling and PASMC proliferation following the Notch signaling pathway [68]. Sun et al. studied the effect exerted by AS-IV on PAH. Their results indicated that AS-IV can down-regulate the expression levels of NLRP-3, caspase-1, ASC, IL-18, IL-1β, and calpain-1 protein *in vitro* and *in vivo*, such that monoclonal antibody-induced PAH can be inhibited via the NLRP-3/calpain-1 pathway [69]. Furthermore, Jin et al. also investigated the possible therapeutic effect of AS-IV on MCT-induced PAH. The study showed that AS-IV attenuated MCT-induced PAH by facilitating inflammation, pulmonary artery endothelial cell dysfunction, pulmonary artery smooth muscle cell proliferation, as well as apoptosis resistance [70]. Moreover, Liu et al. suggested that AS-IV can up-regulate the expression of CCN1 (cysteine-rich 61) in the advanced state of PAH, such that the ERK1/2 signaling pathway can be activated, PAH-induced apoptosis can be reduced, and PAH can be ameliorated [71]. Tian et al. employed rat PAH models induced by MCT. The results from in vivo experiments suggested that AS-IV can attenuate elevated pulmonary artery pressure and its structure in MCT-induced rat modifications. In addition, AS-IV can avoid the MCT-induced increase in the serum levels of tumor necrosis factor (TNF)-α and interleukin (IL)− 1β and their gene expression in the pleura. Furthermore, AS-IV can promote apoptotic resistance in human pulmonary artery smooth muscle cells (HPASMC) while attenuating hypoxia-induced proliferation. AS-IV can up-regulate the expression of caspase-3, caspase-9, p21, p27, and Bax while down-regulating Bcl-2, phosphorylated ERK, HIF-1α, and protein appearance in HPASMC, confirming the protective effect of AS-IV on pulmonary arterial pressure [72].

4.4. Hypertension

Hypertension refers to a common cardiovascular disease arising from elevated blood pressure, constituting the underlying mechanism of cardiovascular morbidity and mortality. Statistics reveal that nearly 1.4 billion people worldwide are subjected to hypertension [66]. Prescribing anti-hypertensive medication is a common method used to control hypertension. AS-IV's role in alleviating hypertension by improving pro-inflammatory reaction and leptin resistance was previously discovered [73], confirming that AS-IV can also play a role in the pharmacological methods of treating hypertension. A study by Jing et al. demonstrated AS-IV's role in alleviating L-NAME-induced hypertensive heart disease. They investigated the anti-hypertensive and cardio-protective effects of AS-IV on hypertension induced by L-NAME in rats through network pharmacology and experimental pharmacology. It was revealed that AS-IV can enhance cardiovascular and cardiac function, alleviate cardiac hypertrophy, and enhance histopathological changes in cardiac tissue by down-regulating ANP and BNP expression. In addition, AS-IV can protect endothelial function by up-regulating eNOS expression, attenuating oxidative stress by increasing antioxidant enzyme activity, and inhibiting cardiac inflammation by down-regulating the expression of IL-6 and TNF-α [74].

4.5. Cardiac dysfunction

Myocardial dysfunction (MD) is usually characterized by a reversible decrease in cardiac ejection fraction (EF), ventricular dilatation, and a reduced cardiac response to fluid resuscitation and catecholamines. The effect of AS-IV on chronic intermittent hypoxia-induced myocardial injury has already been studied, and its function of modulating Ca^{2+} homeostasis has been demonstrated [75]. Thus, AS-IV is certainly capable of mitigating cardiac dysfunction, while advanced studies have shown that the underlying mechanisms can vary. Su et al. assessed the role of AS-IV in cecum ligation and puncture (CLP)-induced cardiac insufficiency. They discovered that AS-IV could improve SIMD through modulation of the NOX4/JNK/BAX signaling pathway [76]. Furthermore, Li et al. confirmed that AS-IV restored DCM (diabetic cardiomyopathy) dysfunction, and reduced cardiomyocyte injury and myocardial dysfunction by inhibiting CD36-mediated iron death in DCM rats [77]. In addition, Xin et al. suggested that AS-IV takes on critical significance in sepsis-induced cardiac insufficiency and survival outcomes. The possible mechanisms for the protective effect of sepsis-induced cardiac insufficiency depend on the activation of the IKK/NF-κB signaling pathway in cardiomyocytes [78]. In addition, Wang et al. explored the underlying mechanisms of the effect of AS-IV on LPS-induced cardiac dysfunction. The results indicated that AS-IV can attenuate LPS-induced cardiac insufficiency by inhibiting miR-1-mediated inflammation and autophagy [79]. Moreover, Li et al. measured the effect of AS-IV on hypoxia-injured H9c2 cardiomyocytes. Their study found that AS-IV may alleviate post-hypoxic H9c2 cardiomyocyte injury by activating the JAK2/STAT3-mediated HIF-1α (hypoxia-inducible factor 1α) signaling pathway [80]. Furthermore, Zhang et al. studied the protective effect of AS-IV on oxidized low-density lipoprotein (ox-LDL)-induced cardiomyocyte injury. The results revealed that AS-IV can protect cardiomyocytes from oxidative damage by regulating HDAC activity, such that ox-LDL-induced low levels of eNOS can be reversed, which was manifested as a decrease in BNP concentration [81].

4.6. Atherosclerosis

Atherosclerosis (AS) refers to a chronic inflammatory disease of blood vessels that is mainly fueled by lipids [82]. It is the basic syndrome of CVD, which has been widely reported in chronic inflammation in large and medium-sized arteries, and it is prone to causing the formation of easily ruptured plaques, resulting in vascular obstruction [83]. It was found that Tanshinone IIA (TS IIA) and AS-IV have a combined effect on atherosclerotic plaque stability, which shows the potential of the introduction of AS-IV in treating AS [84]. This has now been corroborated by multiple studies. Shao et al. explored the role of AS-IV and circular RNA_0000231 (circ_0000231) in AS using the AS cell model. The results indicated that AS-IV can inhibit apoptosis, inflammation, and oxidative stress in AS cells, while restoring the viability and migratory capacity of oxidized ox-LDL-mediated HUVECs (human umbilical vein endothelial cells). AS-IV protected HUVECs from ox-LDL-induced injury by targeting the circ_0000231/miR-135a-5p/CLIC4 axis [85]. Furthermore, Zhang et al. reported that AS-IV had the ability to protect against atherosclerosis in $LDLR^{-/-}$ mice through the MAPK/NF-κB signaling pathway, attenuating atherosclerosis by suppressing inflammation, and reducing the levels of inflammatory cytokines in serum, aortic, and liver tissues, and the NF-κB p65 levels in aortic roots. AS-IV was also found to inhibit JNK, ERK1/2, p38, and NF-κB, as well as the phosphorylation of inflammatory proteins (iNOS, VCAM-1, and IL-6) [86]. Moreover, Tian et al. found that AS-IV reduced ox-LDL-induced lipid content, reversed the ox-LDL-induced reduction in RAW264.7 macrophage cell viability, and elevated lactate dehydrogenase (LDH) leak and apoptosis, similar to the effects of 4-phenylbutyric acid (PBA, an ER stress inhibitor). AS-IV was discovered to effectively protect macrophages from ox-LDL-induced apoptosis mediated by ER stress-CHOP by promoting autophagy [87]. In addition, Chen et al. investigated the protective effects of AS-IV in ox-LDL-induced HUVECs. They highlighted that AS-IV can up-regulate the mRNA expression of Nrf2 and HO-1, and down-regulate the supernatant levels of TNF-α and IL-6, such that ox-LDL-induced endothelial cell injury can be prevented. As a result, apoptosis, oxidative stress, and inflammatory responses can be reduced [88].

4.7. Vascular endothelial cell dysfunction

As a vital component of the arterial intima, endothelial cells form a barrier between blood and tissue, while regulating vascular function and maintaining a stable internal environment. When endothelial cells are consistently damaged, pathological variations in the blood vessels are generally induced, such that they become susceptible to further damage from peroxidation, thus inducing a wide variety of cardiovascular diseases. Past studies have confirmed the beneficial effect of AS-IV on protecting vascular endothelial dysfunction [89], while more recent studies have provided supplementary evidence. Zhao et al. explored the potential mechanism of the effect of AS-IV on vascular endothelial function (VED). Their results indicated that AS-IV can ameliorate chronic intermittent hypoxia-induced VED through the calpain-1/SIRT1/AMPK signaling pathway [90]. Furthermore, Leng et al. investigated the protective effect of AS-IV on endothelial dysfunction and explored the underlying molecular biological mechanisms. The results showed that AS-IV rescued high-glucose-induced endothelial dysfunction by inhibiting the P2X7R-dependent p38 MAPK signaling pathway. Sepsis is an impaired host response to infection that can lead to life-threatening organ dysfunction. The nucleotide-binding domain leucine-rich repeat-containing receptor (NLR) family protein NLRP3 plays a key role in host defense [91]. Su et al. measured the role of AS-IV in regulating mitochondrial function and inhibiting NLRP3 inflammatory activation, finding that AS-IV inhibits LPS-activated HUVEC scorching by inducing a ROS/NLRP3-mediated inflammatory response [92]. Sheng et al. compared the effects of lysophosphatidic choline (LPC) and AS-IV on vascular endothelial cell viability. The results indicated that LPC inhibited cell viability and promoted apoptosis and senescence with increasing concentrations. Furthermore, the LPC treatment-triggered decrease in cellular activity, up-regulated levels of iron ions and lipid ROS and enhanced cellular senescence can be achieved. All the above-mentioned manifestations were notably reversed by AS-IV. AS-IV treatment notably alleviated the mitochondrial morphological changes induced by LPC treatment. Moreover, AS-IV partially up-regulated the expression levels of SLC7A11 and GPX4, while LPC decreased the SLC expression levels, suggesting that AS-IV has positive implications for the treatment of endothelial cell apoptosis caused by iron death [93].

4.8. Myocardial hypertrophy

Myocardial hypertrophy refers to an adaptive compensatory response that occurs primarily during prolonged periods of pressure overload and maintains adequate cardiac output in the early stages. If the stimulus persists, myocardial hypertrophy will progress to irreversible myocardial systolic dysfunction (e.g., CHF) [94]. Previously, it was revealed that AS-IV can attenuate cardiac hypertrophy, collagen accumulation, and abnormal cardiac functions in mice [95], therefore AS-IV can certainly play a role in treating myocardial hypertrophy. Advanced studies have provided more evidence. Zhang et al. studied the effect of AS-IV on mechanical-stress-induced myocardial hypertrophy. As indicated by a study that placed a focus on autophagy and inflammation, AS-IV can prevent mechanical-stress-induced myocardial hypertrophy by activating autophagy and reducing inflammation [96]. Zhang et al. studied the effect of AS-IV on myocardial hypertrophy in vivo and established a rat model of intrauterine ischemia (IHU). The experimental results showed that AS-IV can reduce the increase in systolic and diastolic blood pressure caused by IHU. AS-IV also down-regulates the activation of ERK1/2 and the expression of Egr1, suggesting that it can regulate the pathological process of myocardial hypertrophy through the protein kinase Cβ type isoform 2/Egr-1 pathway [97].

4.9. Cardiac fibrosis

Cardiac fibrosis (CF) is characterized by an excessive proliferation of cardiac fibroblasts and an accumulation of extracellular matrix, which eventually becomes an irreversible factor in HF. The prevention and regression of myocardial fibrosis take on critical significance in improving the survival of HF patients. Du et al. aimed at evaluating whether the antifibrotic effects of AS-IV are correlated with variations in the gut microbiota and fecal metabolites. The results revealed that AS-IV treatment prevented ISO (isoprenaline)-induced cardiac insufficiency, myocardial injury, histopathological changes, and myocardial fibrosis. AS-IV depletion increased the abundance of Akkermansia, Defluviitaleaceae_UCG-011, and Rikenella, and modulated intestinal metabolites in the feces. Among 141 altered intestinal metabolites, amino acid production was drastically altered. Furthermore, significant correlations have been found between several specific gut microbes and altered fecal metabolites, thus leading to the enhanced abundance of AS-IV, Defluviitaleaceae_UCG-011, and Rikenella, and the modulation of amino acid metabolism, which may contribute to the antifibrotic and cardioprotective effects of AS-IV [98].

4.10. Doxorubicin-induced cardiotoxicity

Doxorubicin (DOX) (i.e., Adriamycin (ADR)) refers to a powerful antineoplastic agent that has been extensively employed in clinical practice for treating hematological malignancies and solid tumors. Although DOX is considered a first-line cancer treatment drug, its cardiotoxicity can trigger cardiomyopathy, eventually progressing to HF. Previous research suggested that the damage caused by DOX is permanent, at the cellular level [99]. Recent studies have found that AS-IV can reverse DOX-induced myocardial damage. Luo et al. confirmed that

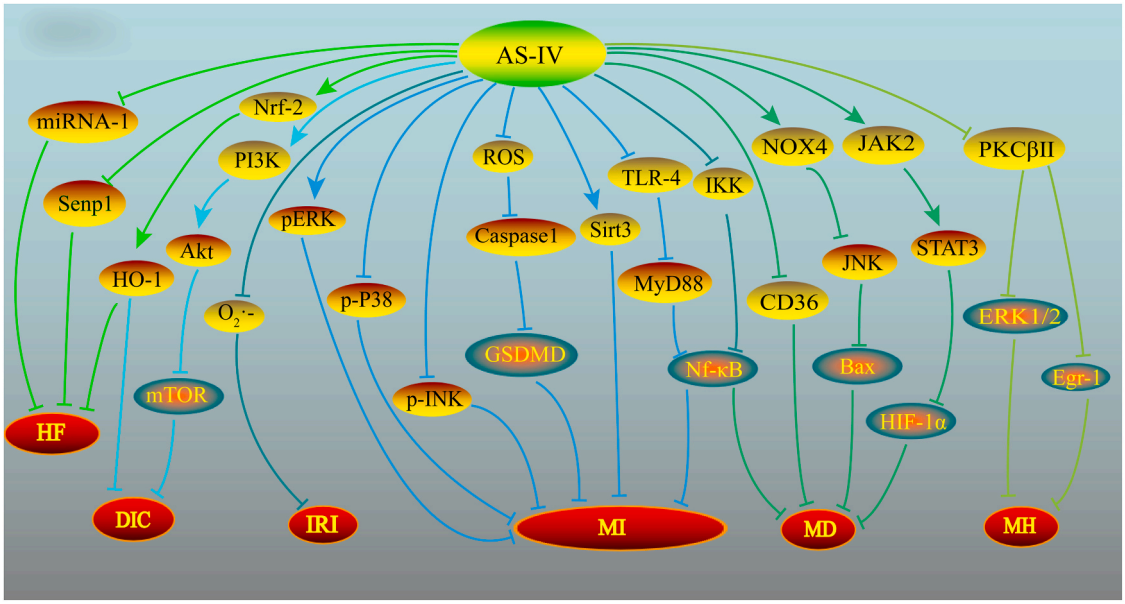

Fig. 2. Schematic showing the effects and mechanisms of AS-IV in cardiovascular events related to myocardium. The myocardium diseases subjective to AS-IV include HF, DIC, IRI, MI, MD and MH. HF, Heart failure; DIC, Doxorubicin-induced cardiotoxicity; IRI, Ischemia-reperfusion injury; MI, Myocardial infarction; MD, Myocardial dysfunction; MH, Myocardial hypertrophy.

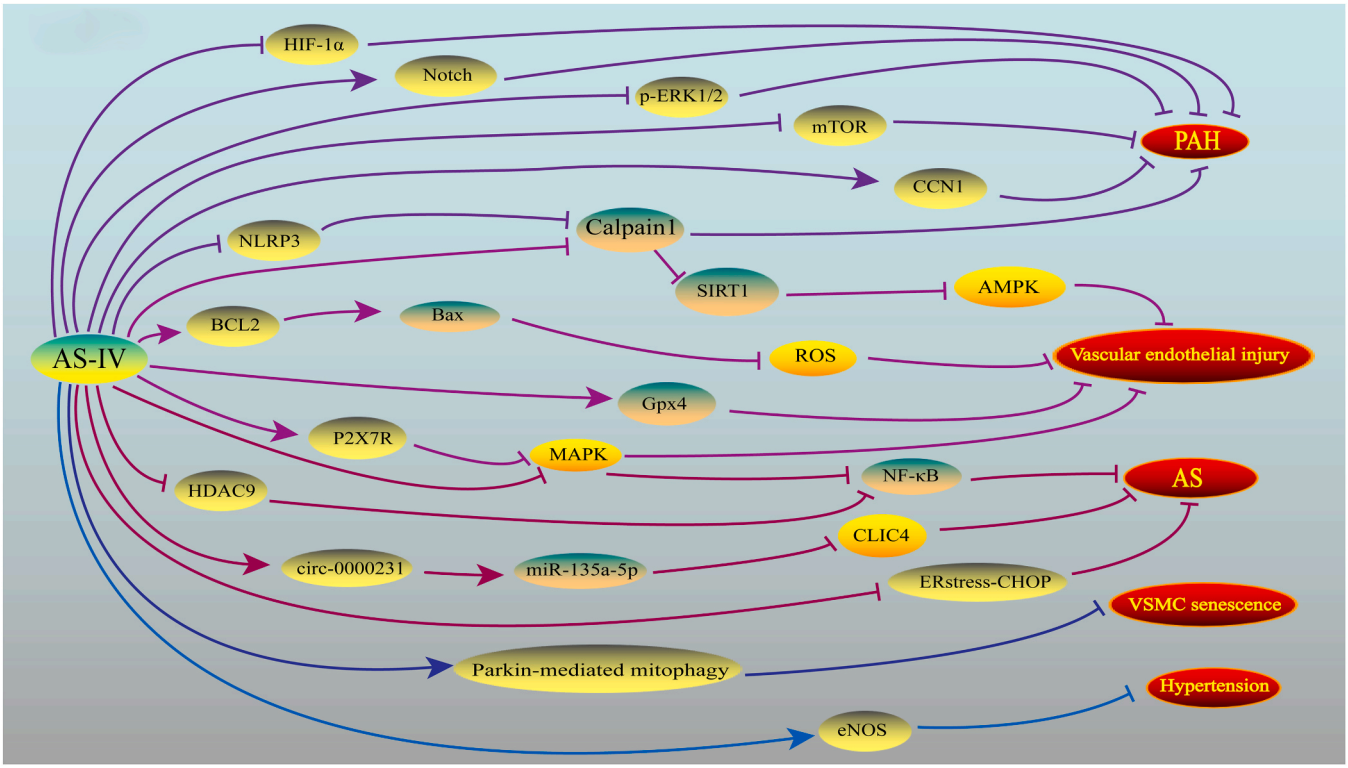

Fig. 3. Schematic showing the effects and mechanisms of AS-IV in cardiovascular events related to blood vessels. The blood vessel diseases subjective to AS-IV include PAH, vascular endothelial injury, AS, VSMC senescence and hypertension. PAH, Pulmonary arterial hypertension; AS, Atherosclerosis; VSMC senescence, Vascular smooth muscle cell senescence.

AS-IV can reduce DOX-induced cardiac injury by activating the PI3K/Akt signaling pathway [100]. Chen et al. explored the protective effect of AS-IV against DOX-induced myocardial injury. The results indicated that AS-IV acts as an agent by inhibiting scorch death, therefore its significant cardioprotective effects against DOX cardiotoxicity may be correlated with Nrf-2/HO-1 activation [101]. Moreover, Luo et al. explored the functional effects of AS-IV on DOX-induced cardiomyopathy, suggesting that AS-IV may protect against DOX-induced myocardial fibrosis, partly due to its anti-iron death effect through an enhanced Nrf2 signaling pathway [102]. Feng et al. measured the effect of AS-IV on both animal and cellular HF models induced by DOX. Their results suggested that AS-IV treatment can lead to elevated EF levels and

Table 2
Cardiovascular protective effects of Astragaloside IV.

Research Model	Research Subjects	Intervention Methods (*In vitro*)	Intervention Methods (*In vivo*)	Effects	Targets or pathways	References
Heart failure	HL-1 cells, Male C57BL/6 J mice	ISO (20 μmol/l), AS-IV (25, 50, 100, 200 μmol/l)	Surgical operation, AS-IV (40 mg/kg)	Cardiac contractile function↑, Cardiomyocyte hypertrophy↓, Mitochondrial damage↓, Apoptosis↓, Oxidative stress↓	Senp1 expression↓	J. Liu et al. (2021)[52]
Heart failure	H9c2 cells, Male SD rats	LPS (10 μg /ml), AS-IV (10 μg/ml)	ISO (20 μmol/l), LPS (10 mg/kg/d), AS-IV (80 mg/kg/d)	Rat survival rate↑, cardiac function↑, Infarct size↓, Oxidative Stress↓	Nrf2/HO-1 pathway↑	Y. B. Sui et al. (2020)[53]
Heart failure	H9C2 cells, Male SD rats	AS-IV (50 μg/ml)	AS-IV (10 mg/kg/d)	Cardiac function↑, Heart injury markers↓, Apoptosis↓, Autophagy↓, Calcium-related parameters (CaMKII↓, PLB↑, RYR2↑, Serca2A↑), Mitochondrial energy metabolism-related proteins (PGC-1↑, Tfam↑)	miRNA-1↓	Q. Wang et al. (2021)[54]
Myocardial infarction	H9c2 cells, Male C57BL/6 mice	Hypoxia, AS-IV (1 μM)	Surgical operation, Bet (18 mg/kg), AS-IV (10 mg/kg)	Cardiac function↑, Angiogenesis↑, Mitochondrial injury↓, Apoptosis↓, Cell Viability↑	Sirt3↑	W. Zhang et al. (2022)[59]
Myocardial infarction	H9c2 cells, Male C57BL/6 mice	High glucose and high-fat, Hypoxia, AS-IV (10 or 50 ng/ml)	Streptozotocin injection, High glucose/high fat diet, AS-IV (10 or 50 mg/kg/d)	Myocyte apoptosis↓, Cardiac contractile function↑, Cardiac fibrosis↓, Inflammation↓	JNK and p38 pathway↓, ERK pathway↑	C. Sun et al. (2021)[60]
Myocardial infarction	Bone marrow-derived macrophages, Male C57BL/6 mice	Nigericin, LPS (1 μg/ml), AS-IV (100 μM)	Surgical operation, AS-IV (40 mg/kg/d)	Cardiac function↑, Myocardial injury↑, Myocardial fibrosis↓, Myocardial hypertrophy↓, Inflammatory infiltration↓, BMDMs pyroptosis↓	ROS/caspase-1/GSDMD pathway↓	X. Zhang et al. (2022)[29]
Myocardial infarction	SD rats	None	Surgical operation, AS-IV (80 mg/kg/d)	Hemodynamic disorder↓, Cardiac function↑, Morphological aberration↓, Cardiac fibrosis↓	TLR4/MyD88/NF-κB pathway↓	H. Shi et al. (2021)[61]
Myocardial infarction	H9c2 cells, Male SD rats	AS-IV (15 μM)	Surgical operation	Cardiac function↑, Myocardial fibrosis↓, Angiogenesis↑, Inflammatory↓, Apoptosis↓	Bone marrow mesenchymal stem cells -derived exosomes↑	Z. Sha et al. (2023)[62]
Myocardial ischemia-reperfusion injury	H9C2 cells, Male C57BL/6 mice	Tert-butyl hydroperoxide, CQ (10 μM), 2-ME (10 μM), AS-IV (50 μM)	Surgical operation, AS-IV (20 mg/kg)	Infract size↓, Apoptosis↓, Autophagy↓	O2•− ↓	K. Y. Huang et al. (2021)[63]
Pulmonary arterial hypertension	Pulmonary artery smooth muscle cells, Male C57BL/6 mice	Hypoxia	Chronic hypoxia, AS-IV (20, 40, 80 mg/kg/d)	Pulmonary vascular remodeling↓, Tfh cell differentiation↑, Germinal center B cell responses↓, PASMCs proliferation, migration and adhesion↓	mTOR pathway↓	C. Li et al. (2022)[67]
Pulmonary arterial hypertension	Pulmonary artery smooth muscle cells, Male SD rats	Hypoxic, 48 h, AS-IV (5, 10, 20 μM)	Hypoxia, AS-IV (2 mg/kg/d)	Pulmonary arterial hypertension ↓, Right ventricle hypertrophy↓, Pulmonary vascular remodeling↓, PASMC proliferation↓	Jagged-1↓, Notch-3↓, Hes-5↓, Notch pathway↑	J. Yao et al. (2021)[68]
Pulmonary arterial hypertension	Human pulmonary artery smooth muscle cells, Male SD rats	Monocrotaline, pyrrole, AS-IV (50, 100 μmol/L)	Monocrotaline intraperitoneal injection, MCT (60 mg/kg), AS-IV (40, 80 mg/kg/d)	NLRP-3↓, Caspase-1↓, ASC↓, IL-18↓, IL-1β↓, Calpain-1↓	NLRP-3/calpain-1 pathway↓	Y. Sun et al. (2021)[69]
Pulmonary arterial hypertension	Human pulmonary artery endothelial cells, Human pulmonary artery smooth muscle cells, Male SD rats	Hypoxia, AS-IV (10, 20, 40 μM)	Monocrotaline intraperitoneal injection, MCT (60 mg/kg), AS-IV (10, 30 mg/kg/d)	Pulmonary artery pressure↓, Pulmonary artery structural remodeling↓, Right ventricular hypertrophy↓, PASMC proliferation↓, PASMC apoptosis↑, HPAEC dysfunction↓, Inflammatory↓	HIF-1α↓, p-ERK1/2↓	H. Jin et al. (2021)[70]
Pulmonary arterial hypertension	Human pulmonary artery endothelial cells, Male SD rats	Hypoxia/ Monocrotaline pyrrole, MCTP (60 μg/ml), AS-IV (10, 20, 40 μM)	Hypoxia/ Monocrotaline intraperitoneally injection, MCT (60 mg/kg), AS-IV (20, 40, 80 mg/kg/d)	Hemodynamic parameter↓, Vascular wall area ratio↓, Vascular wall thickness ratio↓, α- SMA↓, Apoptosis↓, Cell viability↑	CCN1 pathway↑, ERK1/2 pathway↑	Y. Liu et al. (2023)[71]

(*continued on next page*)

Table 2 (*continued*)

Research Model	Research Subjects	Intervention Methods (*In vitro*)	Intervention Methods (*In vivo*)	Effects	Targets or pathways	References
Pulmonary arterial hypertension	Rats, Primary HPAECs, HPASMCs	Hypoxia, AS-IV (10, 20, 40, 80 μM)	Monocrotaline intraperitoneal injection, MCT (60 mg/kg), AS-IV (10, 30 mg/kg/d)	Pulmonary artery pressure↓, TNF-α↓, IL-1β↓, HPASMC proliferation↓, HPASMC apoptosis↑, PAEC dysfunction↓	p21↑, p27↑, HIF-1α↓, p-ERK1/2↓	XinTian et al. (2022)[72]
Hypertensive heart disease	H9C2 cells, Male SD rats	L-NAME, AS-IV (20, 40, 80 μg/ml)	L-NAME, intraperitoneal injection, AS-IV (20, 40 mg/kg/d)	Cardiovascular Parameters↓, Cardiac marker enzymes↓, Cardiac hypertrophy markers↓, Endothelial function↑, Inflammation↓, Oxidative stress↓	eNOS↑	H. Jing et al. (2021)[74]
Sepsis-induced myocardial dysfunction	Rat cardio myoblasts, H9c2 cells, Male SD rats	LPS (10 μmol/ml), AS-IV (100 μmol/ml)	Cecal ligation and puncture surgery, AS-IV (30 mg/kg/d)	Rat survival rate↑, Cardiac function↑, Cardiac enzyme markers↓, Inflammation↓, Apoptosis↓	NOX4/JNK/BAX pathway↓	Y. Su et al. (2022)[76]
Diabetic cardiomyopathy	H9c2 cells, Male SD rats	Palmitic acid, AS-IV (20, 40, 80 mM)	High-fat diet, Streptozotocin intraperitoneal injection, AS-IV (20, 40, 80 mg/kg/d)	Cell ferroptosis↓, Intracellular lipid accumulation↓, Myocardial injury markers↓, Cardiac contractile function↑	CD36 pathway↓	X. Li et al. (2023)[77]
Sepsis-induce myocardial dysfunction	Male SD rats	None	Cecal ligation and puncture surgery, AS-IV (40 mg/kg/d)	Rat survival rate↑, Cardiac function↑, Myocardial injury↓, Apoptosis↓, Inflammatory cytokines↓, Oxidative stress↓	IKK/NF-κB Pathway↑	X. Huang et al. (2021)[78]
LPS-Induced Cardiac Dysfunction	H9c2 cells, Male SD rats	LPS (10 μg/ml), AS-IV (10 μg/ml)	LPS (10 mg/kg/d), AS-IV (80 mg/kg/d)	Heart dysfunction↓, Pathological changes↓, Inflammatory↓, Autophagy↓	miRNA-1↓	Q. Wang et al. (2022)[79]
Hypoxia-injured cardiomyocytes injury	H9c2 cells	Hypoxia, AS-IV (12.5 μM)	None	Cell survival↑, Apoptosis↓	JAK2/STAT3/HIF-1α pathway↑	B. Li et al. (2021)[80]
Myocardial cell injury	HL-1 cells	Ox-LDL (25 μg protein/ml), AS-IV (12.5, 50 μM)	None	Apoptosis↓, BNP↓, iNOS↓, eNOS↑	Histone deacetylase↓	W. Zhang et al. (2021)[81]
Atherosclerosis	Human umbilical vein endothelial cells	Ox-LDL, AS-IV (50, 75, 100 μM)	None	Apoptosis↓, Inflammation↓, Oxidative stress↓, Ox-LDL injury↓	circ_0000231/miR-135a-5p/CLIC4 axis	X. Shao et al. (2021)[85]
Atherosclerosis and hepatic steatosis	LDLR$^{-/-}$male mice	None	High fat diet, AS- IV (10 mg/kg)	Serum lipids↓, Plaque area↓, Plaque stability↑, α-SMA↑, Caspase 3↑, Inflammatory cytokines↓	MAPK/NF-κB pathway↓	Y. Zhang (2022)[86]
Atherosclerosis	RAW264.7 macrophages, Apoe$^{-/-}$ mice	Ox-LDL (100 μg/ml)	Atherogenic high-fat diet, AS-IV (40 mg/kg/d)	Cell viability↑, Lipid content↓, Apoptosis↓, Lactate dehydrogenase leakage↓, ER stress↓, Autophagy↑	ER stress-CHOP signaling pathway↓	H. Tian et al. (2022)[87]
Atherosclerosis	Human umbilical vein endothelial cells	Ox-LDL (25, 50, 100 μg/ml), AS-IV (10, 20, 40 μM)	None	Cell viability↑, Apoptosis↓, Inflammation↓, Oxidative stress↓	HDAC9/NF-κB pathway↓	D. Chen et al. (2023)[88]
Vascular endothelial injury	Human coronary artery endothelial cells, Calpain-1 knockout and wild-type C57BL/6 mice	Chronic intermittent hypoxia, MDL-28170 (20 μM) SRT1720 (4 μM) AS-IV (100 μM)	Chronic intermittent hypoxia, AS-IV (40, 80 mg/kg/d)	Endothelial dependent vasomotion↑, Nitric oxide↑, Oxidative stress↓, Inflammation↓, Mitochondrial dysfunction↓	calpain-1/SIRT1/AMPK pathway↓	F. Zhao et al. (2022)[90]
Vascular endothelial injury	Rat aortic endothelial cells, SD rats	High glucose, AS-IV (100 μM)	Streptozotocin intraperitoneal injection, AS-IV (40, 80 mg/kg/d)	Endothelial function↑, NO↑, eNOS↑, Inflammation↓, Oxidative stress↓	P2×7R/P38 MAPK pathway↓	B. Leng et al. (2020)[91]
Vascular endothelial cell injury	Human umbilical vein endothelial cells	LPS + AS-IV (100 μmol/ml)	None	Cell viability↑, ROS↓, Pyroptosis↓	BCL2/BAX pathway↑, BCL2/BAX/ROS pathway↓	Y. Su et al. (2022)[92]
Vascular endothelial injury	Human umbilical vein endothelial cells	Bleomycin , LPC (0.4 μM), AS-IV (50 μM)	None	LPC↓, Apoptosis↓, senescence↓, Ferroptosis↓, Mitochondrial morphology↑	ROS↓, GPX4↑, SLC7A11↑	S. Sheng et al. (2021)[93]
Myocardial hypertrophy	Rat primary cardiomyocytes, Male SD rats	Mechanically stretching primary cardiomyocytes, AS-IV (100 μM)	Surgical operation, AS-IV (40, 80 mg/kg/d)	Cardiac function↑, Cardiac hypertrophy↓, Autophagy↑, Inflammation↓	Autophagy↑, Inflammation↓	T. Zhang et al. (2020)[96]

(*continued on next page*)

Table 2 (*continued*)

Research Model	Research Subjects	Intervention Methods (*In vitro*)	Intervention Methods (*In vivo*)	Effects	Targets or pathways	References
Myocardial hypertrophy	8–week-old male and female rats	None	IUH, AS-IV (20, 40, 80 mg/kg)	HW/BW↓, LVM/BM↓, HM/TL↓, LVM/TL↓, Pathological changes↓, Blood pressure↓,	PKCβII/Egr-1 pathway↓	T.Zhang et al. (2023)[97]
Cardiac fibrosis	Male C57BL/6 mice	None	Isoprenaline injection, AS-IV (100 mg/kg/d)	Cardiac dysfunction↓, Myocardial enzyme↓, Cardiac fibrosis↓, Gut Microbial dysbiosis↓, Fecal metabolic disorders↓	Akkermansia↑, Defluviitaleaceae_UCG-011↑, Rikenella↑, Amino acid metabolism↑	X. Q. Du et al. (2022)[98]
Adriamycin cardiotoxicity	H9c2 cells, Male SD rats	Adriamycin, AS-IV (100 μM)	Adriamycin intraperitoneally injection, AS-IV (1.0 mg/kg/d)	Myocardial injury↓, Oxidative stress↓, Cardiac function↑, Apoptosis↓, Autophagy↓	PI3K/Akt/mTOR pathway↑	L. F. Luo et al. (2021) [100]
Doxorubicin cardiotoxicity	H9C2 cells, Male Wistar rats	DOX	DOX intraperitoneal injection, AS-IV (40 mg/kg/d)	Cardiac function↑, Cardiac injury indicators↓, Myocardial fibrosis↓, Inflammatory↓, Oxidative Stress↓, Mitochondrial injury↓, Pyroptosis↓	Nrf2/HO-1 pathway↑	X. Chen et al. (2023) [101]
Adriamycin cardiotoxicity	Male SD rats	None	Adriamycin intraperitoneal injection, AS-IV (10 mg/kg/d)	Myocardial fibrosis↓, Cardiac dysfunction↓, Oxidative stress↓, Cardiac ferroptosis↓	Nrf2 pathway↑	L. F. Luo et al. (2021) [102]
Doxorubicin cardiotoxicity	H9C2 cells, Male Wistar rats	Dox (1 mmol/L), AS-IV (50, 100 mmol/L)	DOX intraperitoneal injection, AS-IV (1.0 mg/kg/d)	Left ventricular ejection fraction↑, Enlarged cardiomyocyte↓, Apoptosis↓, Necrosis↓	Nrf2/HO-1 pathway↑	W. Feng et al. (2022) [103]
Vascular senescence	Vascular smooth muscle cells, Male BABL/C mice	Bleomycin, Mdivi-1 (1 μM), AS-IV (10, 50, 100 μM)	D-galactose injection, AS-IV (20, 40, 80 mg/kg/d)	Vascular smooth muscle cell senescence↓, Mitochondrial injury↓, Mitophagy↑	Parkin-mediated mitophagy↑	H. Li et al. (2022) [104]

reduced cardiomyocyte size, as well as down-regulating the expression of nuclear factor red lineage-2-related factor 2 (Nrf-2) and its downstream gene heme oxygenase-1 (HO-1). Regarding the specific mechanism, as revealed by their results, DRP1/mitofusin1/2 expression can be regulated by AS-IV, while the Nrf2/HO-1 signaling pathway can be activated [103].

4.11. Other CVDs

Vascular smooth muscle cell (VSMC) senescence also refers to a major pathological mechanism in CVD. A study by Li et al. suggested that AS-IV could attenuate bleomycin (BLM)-induced VSMC senescence. AS-IV effectively ameliorated BLM-induced mitochondrial damage in senescent VSMC and D-gal-induced senescent mice, increased MMP, and mediated mitochondrial autophagy. Furthermore, Parkin expression can enhance the anti-aging function of AS-IV [104].

5. Conclusions and perspectives

The studies reviewed above show the wide range of the cardioprotective effects of AS-IV as it exhibits various biological functions (e.g., anti-inflammatory, anti-oxidative stress, anti-apoptosis, anti-fibrosis, and modulation of the cardiomyocyte metabolism) (Figs. 2, 3, Table 2). In the study of the role of AS-IV in cardiovascular events, the collection of phenotypic information is more and more abundant, the exploration of molecular mechanisms is more and more in-depth which is closely related to the latest research progress in molecular biology. The above-described studies suggested that AS-IV can inhibit apoptosis, inflammation, and oxidative stress in AS cells; restore the viability and migratory capacity of ox-LDL-challenged HUVEC; reduce the levels of inflammatory cytokines in serum, aortic, and liver tissues, and NF-κB p65 levels in artery roots; prevent mechanical-stress-induced myocardial hypertrophy by activating autophagy and reducing inflammation; and play a subsidiary role in treating PAH. In addition, AS-IV is a promising drug to use in the treatment of CHF. Mechanistically, other than the studies of classical cellular signaling pathways, researchers have begun to focus on the role of non-coding RNA, including micro-RNA and circular RNA, in the cardioprotective effects of AS-IV. Studies have revealed that the cardioprotective effects of AS-IV may be mediated in part via micro-RNA and circular RNA. With more advanced technologies for the study of non-coding RNA have been developed, more comprehensive and in-depth functions and mechanisms in the cardiac system have become more describable, which would bring a greater hope to expand our knowledge and be instrumental in the research regarding the role of AS-IV on cardiovascular evens.

Studies have shown that AS-IV has a certain protective effect in a variety of CVDs models. However, the clinical application of AS-IV on CVDs is still limited. So far, only one clinical study reported that AS-IV supplementation can enhance human exercise endurance and promote muscle growth following eccentric exercise-induced injury. This is partly because the direct targets of AS-IV have not been identified. Notably, the above-mentioned studies indicate that AS-IV exhibits a multi-target effect in treating cardiovascular evens. Therefore, it is worth noting that the multi-target effect of AS-IV may lead to potential side effects, which is important but may have been overlooked by researchers or not demonstrated in shorter trial cycles. Therefore, it is necessary to explore the direct targets of AS-IV. However, the direct target of AS-IV action is still unknown. At present, the research on the direct targets of active ingredients in traditional Chinese medicine has attracted much attention. With the help of network pharmacology, molecular docking and drug target databases, the prediction of drug targets can be initially realized and further validated by combining with techniques such as surface plasmon resonance or isothermal titration thermal analysis. In addition, traditional Chinese medicine monomers can be modified with the help of medicinal chemistry to increase the pharmacological activity and reduce the side effects of drugs. Moreover, the combination of different TCM monomers can show more efficient

pharmacological effects. These can provide ideas for further investigation of the role and mechanism of action of AS-IV in cardiovascular events which will also provide theoretical references for the application of AS-IV to the clinic.

Furthermore, all the above-described studies remain in the preclinical phase and have not yet been verified clinically. Therefore, further research is still needed to investigate the functions, molecular mechanisms, and therapeutic values of AS-IV in cardiovascular events. Our review should be helpful to those who are conducting related research.

CRediT authorship contribution statement

Zehui Xu, the first author, provided the idea and wrote the complete article. **Houle Zhou**, Co First Author, drew pictures and revised the article. **Yihan Zhang**, Co First Author, responsible for collecting literature and revising the article. **Ziji Cheng**, Co First Author, responsible for literature collection and article revision. **Wan Melisandre**, Co First Author, responsible for article revision. **Wanting Qin,** responsible for literature collection. **Peiyu Li**, responsible for figure plotting. **Jiaming Feng**, responsible for literature collection. **Shuijin Shao**, responsible for article revision. **Wenlong Xue**, Co Corresponding author put forward suggestions for revision. **Haidong Guo**, Co Corresponding author put forward suggestions for revision. **Baonian Liu**, corresponding author, responsible for article revision and financial support.

Declaration of Competing Interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

Data Availability

No data was used for the research described in the article.

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