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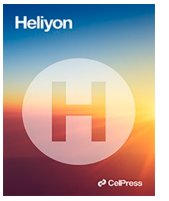

Review article

A systematic review of astragaloside IV effects on animal models of diabetes mellitus and its complications

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ABSTRACT

Context: Diabetes mellitus (DM) is one of the fastest-growing diseases worldwide; however, its pathogenesis remains unclear. Complications seriously affect the quality of life of patients in the later stages of diabetes, ultimately leading to suffering. Natural small molecules are an important source of antidiabetic agents.

Objective: Astragaloside IV (AS-IV) is an active ingredient of Astragalus mongholicus (Fisch.) Bunge. We reviewed the efficacy and mechanism of action of AS-IV in animal and cellular models of diabetes and the mechanism of action of AS-IV on diabetic complications in animal and cellular models. We also summarized the safety of AS-IV and provided ideas and rationales for its future clinical application.

Methods: Articles on the intervention in DM and its complications using AS-IV, such as those published in SCIENCE, PubMed, Springer, ACS, SCOPUS, and CNKI from the establishment of the database to February 2022, were reviewed. The following points were systematically summarized: dose/concentration, route of administration, potential mechanisms, and efficacy of AS-IV in animal models of DM and its complications.

Results: AS-IV has shown therapeutic effects in animal models of DM, such as alleviating gestational diabetes, delaying diabetic nephropathy, preventing myocardial cell apoptosis, and inhibiting vascular endothelial dysfunction; however, the potential effects of AS-IV on DM should be investigated.

Conclusion: AS-IV is a potential drug for the treatment of diabetes and its complications, including diabetic vascular disease, cardiomyopathy, retinopathy, peripheral neuropathy, and nephropathy. In addition, preclinical toxicity studies indicate that it appears to be safe, but the safe human dose limit is yet to be determined, and formal assessments of adverse drug reactions among humans need to be further investigated. However, additional formulations or structural modifications are required to improve the pharmacokinetic parameters and facilitate the clinical use of AS-IV.

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1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by chronic blood sugar elevation. However, its pathogenesis remains unclear. The current argument regarding the pathogenesis of DM is primarily related to insulin secretion and fat disorders [1]. Currently, DM is considered an epidemic with an increasing disease burden worldwide [2]. Furthermore, DM is more likely to develop in adults aged >35 years. Epidemiological studies predict that 693 million adults will be diagnosed with DM by 2045 [3]. Furthermore, DM is regarded as the third major noncommunicable disease after cardiovascular disease and cancer [4], and its complications seriously affect the quality of life of patients and can even threaten life [5,6]. Diabetes-related complications often appear in patients approximately 10 years after the onset of the disease [7] and mainly involve chronic damage and dysfunction of the eyes, kidneys, heart, blood vessels, and nerves [8]. Complications such as diabetic nephropathy (DN) and diabetic cardiomyopathy (DCM) seriously affect the quality of life and safety of patients [9]. Although remarkable progress has been made in treating DM, problems such as the poor efficacy of a single drug and prominent adverse reactions remain. For example, thiazolidinediones (TZDs), including rosiglitazone and pioglitazone, are antidiabetic drugs that increase insulin sensitivity by activating peroxisome proliferator-activated receptors (PPARs) [10]. However, TZDs can regulate bone metabolism and may adversely affect bone [11]. Studies have found that the use of TZDs was associated with decreased bone mineral density [12] and that women over 65 years of age treated with TZDs had the highest risk of fractures [13]. In addition, rosiglitazone use was associated with an increased risk of stroke, heart failure, and all-cause mortality, and an increased risk of a composite of acute myocardial infarction, stroke, heart failure, and all-cause mortality in patients aged 65 years or older [14]. Furthermore, patients treated with pioglitazone have a slightly increased risk of bladder cancer, and pioglitazone should be discontinued in patients with type 2 DM (T2DM) who are newly diagnosed with bladder cancer [15]. Saxagliptin is a dipeptidyl peptidase-4 inhibitor. It is used alone or in combination with other oral hypoglycemic agents to treat T2DM [16]. Although saxagliptin improves blood glucose control, it also increases hospitalization owing to heart failure [17]. Other methods are needed to reduce cardiovascular risk in individuals with diabetes [18].

Astragalus mongholicus (Fisch.) Bunge (AM) is a traditional Chinese medicine used to treat various diseases since ancient times [19]. AM is a detoxifier and diuretic that reduces swelling and drains pus [20,21]. AM is often used as a hypoglycemic agent in the formulation of hypoglycemic drugs, the biologically active ingredients often used in animal experiments to evaluate their health benefits in DM [22]. Astragaloside IV (AS-IV) is one of the main active components of AM and a quality control index for AM quality [23]. AS-IV has a wide range of pharmacological effects, including enhanced immunity, antiviral and antioxidative stress effects, antifibrotic effects, and protection of the heart and kidneys [24]. AS-IV has received remarkable attention recently for preventing and treating diabetes and its complications owing to its functions, such as lowering blood sugar, reducing insulin resistance, and protecting the kidneys [25]. The chemical structure of AS-IV is shown in Fig. 2.

Numerous pharmacological studies have investigated the effects of AS-IV on diabetes and its complications. To better explain the efficacy and mechanism of action of AS-IV in treating diabetes and its complications, animal studies on the use of AS-IV in the treatment of DM published from the establishment of the database to February 2022 were systematically reviewed. Furthermore, a detailed study on the pharmacological effects of AS-IV on diabetic complications was performed to propose a possible mechanism of action for the antidiabetic effects of AS-IV. Finally, the data on the safety of AS-IV is summarized to provide ideas and evidence for its future clinical application.

2. Methods

2.1. Literature search strategy

First, we searched for studies on DM using PubMed, Web of Science, ScienceDirect, CNKI, and Wanfang databases. a. For searching relevant studies, “AS-IV” was used alone or paired with terms such as “diabetes,” “diabetic nephropathy,” “diabetic cardiomyopathy,” “diabetic neuropathy,” “diabetic angiopathy,” “diabetic foot,” “gestational diabetes,” “safety,” “toxicological,” and “pharmacology.” Only Chinese and English studies were searched to avoid language barriers and translation costs and increase time efficiency. b. The inclusion criteria in this review were as follows: (1) test subjects were animals or cells that are diabetes or diabetic complication models, (2) AS-IV treatment was used as an intervention, (3) articles on the safety or toxicity of AS-IV, and (4) published and unpublished (dissertations and master’s theses) studies in any language until February 2022.

2.2. Inclusion and exclusion of literature

The inclusion criteria in this review were as follows: (1) studies on the effect of AS-IV on DM; (2) preclinical and clinical studies with reasonable scientific evidence; and (3) studies that aimed to determine the potential mechanism of action. The exclusion criteria for literature search were: (1) inappropriate study models; (2) inappropriate interventions; (3) inappropriate outcomes (e.g., incomplete data on study results); and (4) inappropriate types of studies.

A total of 52 articles were eligible for inclusion. Of these, two studies explored T2DM, three explored gestational diabetes, nine explored diabetic vascular endothelial disease, four explored diabetic cardiomyopathy, three explored diabetic retinopathy, two explored diabetic peripheral neuropathy, and 29 explored diabetic nephropathy (Fig. 1).

3. Key findings

A systematic summary of the mechanisms underlying AS-IV and its complications is provided in Table 1. Furthermore, illustrations of the mechanism of action of AS-IV against DN, diabetic vascular endothelial disease, diabetic vascular endothelial disease, diabetic peripheral neuropathy, and diabetic retinopathy (DR) are shown in Figs. 2 and 3.

3.1. AS-IV against diabetes mellitus

DM is a systemic metabolic disease, mainly caused by chronic blood sugar elevation and immune and environmental factors [26] (see Fig. 4). DM is divided into type 1 diabetes, T2DM, gestational diabetes, and other types of diabetes, with T2DM accounting for 90% of DM cases [27,28]. Antidiabetic studies on AS-IV have mainly focused on patients with T2DM and gestational diabetes.

3.2. Possible mechanisms by which AS-IV lowers blood sugar levels in T2DM

AS-IV lowers blood sugar levels in patients with T2DM. Chronic hyperglycemia is a typical feature of diabetes [29]. Increased free fatty acid (FFA) concentration or intracellular fat content in the body exacerbates insulin resistance and impairs beta cell function [30]. When hyperglycemia and hyperlipidemia occur simultaneously, diabetic complications are significantly aggravated [31]. Han [32] administered 30–120 mg/kg AS-IV via gavage to high-sugar and high-fat-fed diabetic rats for eight weeks. Based on their experimental results, the serum levels of fasting blood glucose, triglycerides, total cholesterol, serum alanine aminotransferase, serum aspartate aminotransferase, liver index, and hepatocyte apoptosis rate decreased in diabetic rats, whereas liver histopathology improved.

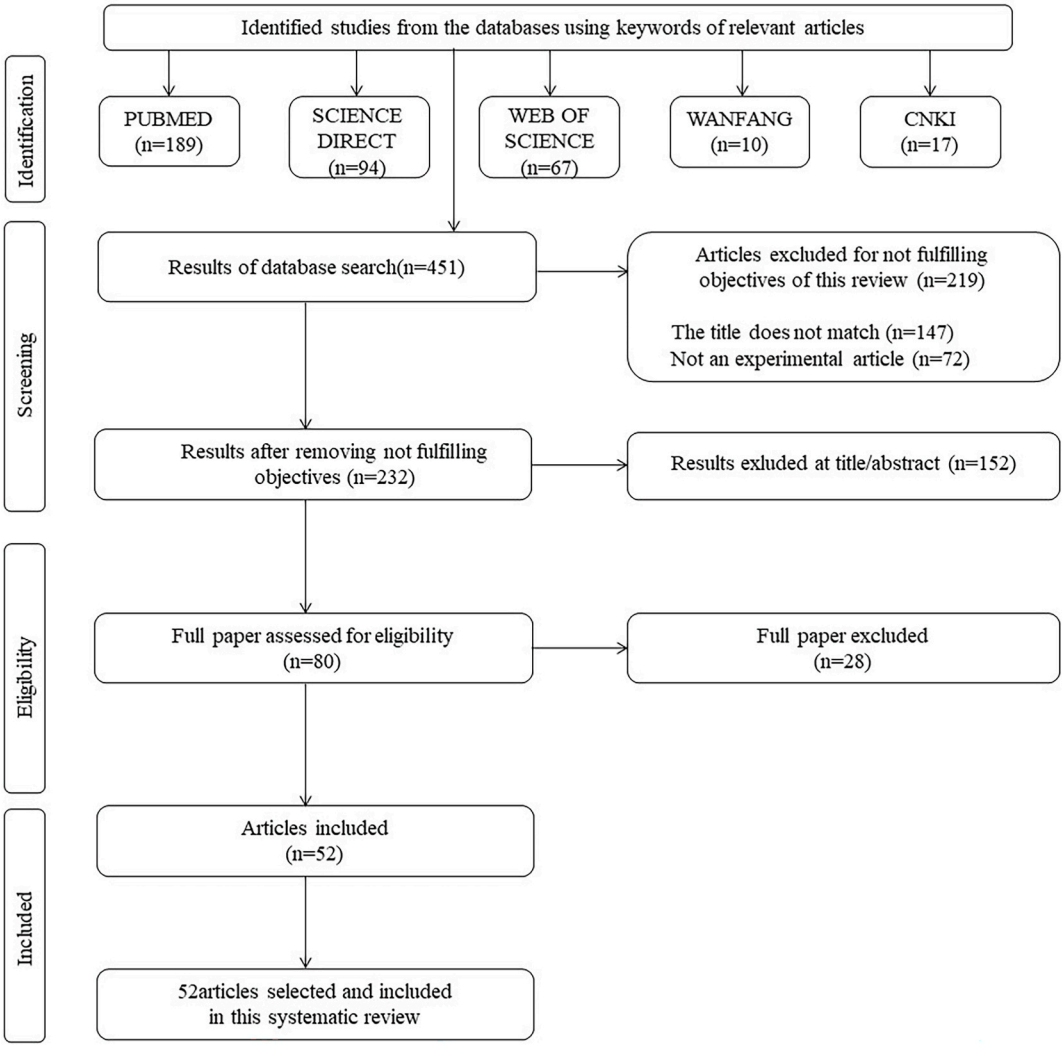

Fig. 1. The flowchart provides an overview of the study search and selection process.

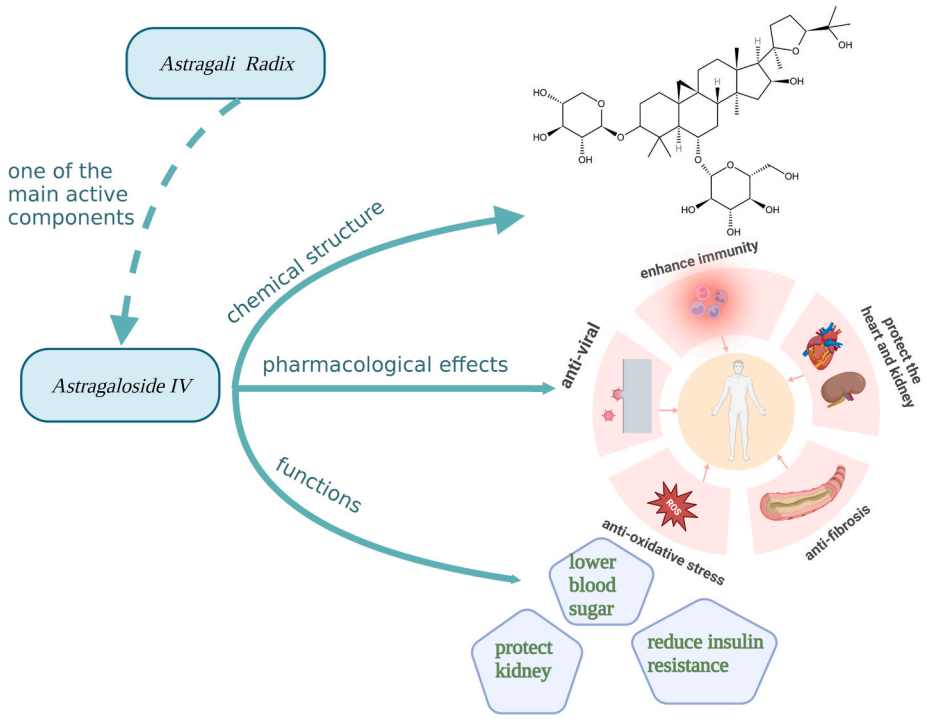

Fig. 2. Introduction to *Astragaloside IV* (AS-IV). AS-IV is one of the main active components of *Astragali radix*. AS-IV has a wide range of pharmacological effects, including enhancing immunity, exhibiting antiviral, antioxidative stress, antifibrosis activities, protecting the heart and kidney, lowering blood sugar levels, and reducing insulin resistance.

3.3. Possible mechanisms by which AS-IV alleviates insulin resistance

Insulin resistance is the primary cause of T2DM. Protein tyrosine phosphatases are key negative regulators of the insulin signaling pathway and are closely associated with the development of insulin resistance [33]. Zhou [34] established a model of insulin resistance in HepG2 cells using a high insulin concentration (1 μM). HepG2 cells cultured in high insulin concentrations were treated with 6.4–102.4 μM of AS-IV. The experimental results revealed that AS-IV inhibited protein tyrosine phosphatase 1 B and improved insulin resistance in HepG2 cells.

3.4. Possible mechanisms by which AS-IV prevents gestational diabetes mellitus (GDM)

GDM refers to diabetes that occurs during pregnancy in patients with normal glucose metabolism. GDM is the most common metabolic disorder during pregnancy [5]. Individuals with GDM display symptoms such as polydipsia, polyuria, polyphagia, and genital itching [35]. Currently, GDM is regarded as a high-risk disease and its complications not only harm pregnant women but also their babies [36]. C57BL/KsJ-Lepdb/+ (db/+) mice are commonly used as animal models of GDM because they can effectively simulate the various symptoms of pregnant women with GDM [37].

Researchers have employed the C57BL/KsJ-Lepdb/+ (db/+) mouse model to examine the effects of AS-IV on GDM. Zhang et al. [38] reported that 20 mg/kg AS-IV reduced liver gluconeogenesis and relieved GDM. AS-IV downregulated the expression of inflammatory genes and upregulated the expression of antioxidant genes in C57BL/KsJ-Lepdb/+ (db/+) mice. Moreover, Zhou et al. [39] found that 20 mg/kg AS-IV inhibited placental oxidative stress, inflammatory cytokine production, and activation of the toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) pathway in C57BL/KsJ-Lepdb/+ (db/+) mice. These researchers speculated that AS-IV could reduce placental oxidative stress and inflammation to fight GDM, which may be related to the TLR4/NF-κB signaling pathway. Zhang et al. [40] orally administered 15–30 mg/kg AS-IV to C57BL/KsJ-Lepdb/+ (db/+) mice to investigate the mechanism of action of AS-IV in GDM. AS-IV was found to downregulate the expression of the murine inflammation genes, interleukin 6 (*IL-6*) and tumor necrosis factor-alpha (*TNF-α)*, and inhibit the expression of inflammasome-related protein containing NLR family pyrimidine domain-3 (NLRP3) in the pancreas of GDM mice.

3.5. Possible mechanisms by which AS-IV prevents diabetes complications

(Insert Fig. 3 near here)

Table 1
Mechanism of AS-IV action against diabetes and its complications.

Disease	Animal/cell model	Dosage	Target/pathways/mechanism	Adminstration route	Referfence
Type 2 diabetes	STZ-induced diabetic rats	30–120 mg/kg	Triglyceridesl/serum alanine aminotransferase	intragastric administration	32
	HepG2 cell	6.4–102.4 μM	Insulin resistance/PTP1B	dissolve into culture medium	34
Gestational diabetes	C57BL/KsJ-Lepdb/+female mice	20 mg/kg	cAMP	orally gavage	38
	C58BL/KsJ-Lepdb/+female mice	20 mg/kg	TLR4/NF-κB pathway	orally gavage	39
	C59BL/KsJ-Lepdb/+female mice	15–30 mg/kg	NLRP3	orally gavage	40
Diabetic vascular endothelial disease	STZ-induced diabetic rats	40–80 mg/kg	P38 MAPK Signaling Pathway	orally gavage	47
	STZ-induced diabetic rats	40–80 mg/kg	ROS/SOD/GSH-px/calpain-1	orally gavage	48
	HG-induced HUVECs	25–100 μm	JNK signaling pathway	dissolve into culture medium	49
	(ox-LDL)-induced EPCs	10–200 μm	LOX-1/NLRP3 pathway	dissolve into culture medium	52
	STZ-induced diabetic rats	40 or 80 mg/kg	TLR4/NF-κB signaling pathway.	intragastric administration	53
	endothelial cells	100 mmol/l	VEGF/vWF	dissolve into culture medium	54
	high glucose-induced HMCs	6 μmol/L	SUMOylation pathway	dissolve into culture medium	55
	H2O2-inducedHUVECs	5–800 μmol/l	TGF-β1/Smad2 signaling pathway	dissolve into culture medium	56
	STZ-induced diabetic rats	50 mg/kg	Ox-LDL/NF-κB P65/MCP-1/TNF-α.	intragastric administration	57
Diabetic cardiomyopathy	T2DM rats	80 mg/kg	Improve myocardial contraction and relaxation	intragastric administration	62
	STZ-induced diabetic rats	10–40 mg/kg	PGc-1α	intraperitoneal injection	63
	H9C2(2-1) cell	100 μM	miR-34a-mediated autophagy pathway	dissolve into culture medium	64
	bone marrow mesenchymal stem cells	10–200 mM	NF-kB pathway	dissolve into culture medium	65
Diabetic retinopathy	STZ-induced diabetic rats	20–60 mg/kg	miR-128	intragastrically administered	70
	HG-induced RPE cell	2–20 μm	MnSOD	dissolve into culture medium	71
	db/db mice	4.5 or 9 mg/kg	ERK1/2,NF-kB	oral gavage	72
Diabetic Peripheral Neuropathy	STZ-induced diabetic mice	3–12 mg/kg	Na+, K + ATPase	oral gavage	73
	STZ-induced diabetic rats	60 mg/kg/d	SIRT1/p53 signaling pathway	intragastric administration	74
Diabetic nephropathy	STZ-induced diabetic mice	2.5–10 mg/kg	ILK/α3β1	oral gavage	82
	diabetic KK-Ay mice	40 mg/kg	miR-21 overexpression	oral gavage	83
	STZ-induced diabetic mice	3–12 mg/kg	SERCA2b/AMPKα	oral gavage	84
	STZ-induced diabetic rats	5 mg/kg/d	lncRNA-TUG1/TRAF5 pathway	oral gavage	85
	db/db diabetic mice	2–18 mg/kg/d	PPARγ-Klotho-FoxO1 axis	oral gavage	86
	db/db diabetic mice	1 g/kg	Drp-1/Fis-1/MFF	mix with standard food	87
	STZ-induced diabetic mice	5 g/kg	MEK1/2-ERK1/2-RSK2 signaling pathway	mix with standard food	88
	db/db diabetic mice	1 g/kg	Akt/mTOR/NFκB/Erk1/2 signaling pathways	mix with standard food	89
	STZ-induced diabetic mice	10 mg/kg	eIF2α/PERK/GRP78/ORP150/caspase-3.	oral gavage	90
	HG-induced podocyte	10–40 μM	calcineurin/NFAT signaling pathway	dissolve into culture medium	91
	db/db diabetic mice	2–18 mg/kg	Ca2+-ATPase (SERCA)	intragastric administration	92
	STZ-induced diabetic mice	5–10 mg/kg	PERK- ATF4-CHOP pathway	oral gavage	93
	HG-induced podocyte	2.5–10 mg/kg	Bax and Bcl-2	oral gavage	94

(*continued on next page*)

Table 1 (*continued*)

Disease	Animal/cell model	Dosage	Target/pathways/mechanism	Adminstration route	Referfence
	T2DM rats	40–80 mg/kg	p-PERK/ATF4/CHOP	intragastric administration	95
	HK-2 cells	10–80 mM	Nrf2/ARE signaling pathway	dissolve into culture medium	99
	STZ-induced diabetic mice	2.5–10 mg/kg/d	IL-1β/TNF-α/ERK1/2/TRPC6	intragastric administration	100
	Palmitic acid -induced HK-2 cell	10–40 μmol/L	Bcl-2/Nrf2	dissolve into culture medium	101
	human tubular epithelial cells	0–200 μM	p38 MAPK signaling pathway	dissolve into culture medium	102
	NRK-52E cell	0.8–80 μg/ml	ROS/α-SMA	dissolve into culture medium	103
	STZ-induced diabetic rats	20–80 mg/kg/d	CD36	intragastric administration	104
	high glucose-induced HMCs	5–100 μM	NADPH oxidase/ROS/Akt/nuclear factor-κB(NF-κB)pathway	dissolve into culture medium	105
	STZ-induced diabetic rats	80 mg/kg	AGEs/IL-1β/IL-18	gavage	106
	STZ-induced diabetic rats	40 mg/kg	α-actinin-4/ILK	gavage	107
	STZ-induced diabetic mice	5–10 mg/kg	NF-jB	oral gavage	108
	NRK-52E cell	20–100 μg/ml	TGF-β/Smad pathway	dissolve into culture medium	111
	HG-induced rat MCs	0–100 μg/ml	TGF-β1/Smad/miR-192 signaling pathway	dissolve into culture medium	112
	high glucose-induced HK-2 cells	50–200 μg/ml	mTORC1/p70S6K signaling	dissolve into culture medium	113
	HG-induced MC and KK-Ay mice	40 mg/kg/day	SIRT1-NF-κB pathway	oral gavage	114
	diabetic KK-Ay mice *in vivo*.	25–100 μm	NF-κB p65/Sirtuin 1	gavage	115

3.5.1. Diabetic vascular disease

Diabetic vascular disease is the primary cause of DM complications. Diabetic vascular diseases are divided into macro and microvascular diseases [41]. Diabetic macroangiopathy is defined as various cardiovascular diseases caused by atherosclerosis, including the aorta, coronary artery, and peripheral arteriosclerosis of the limbs. Microvessels are blood vessels with a lumen diameter of less than 100 μm. The main pathological manifestations of diabetic microangiopathy include basement membrane thickening and disturbances in the microcirculation [42]. Microvascular damage is the main cause of damage to the body and can affect ventricular contraction and relaxation, causing retinopathy and glomerulosclerosis in patients with diabetes and leading to complications such as DN, DR, and neuropathy [43,44]. There is no clear explanation regarding the pathogenesis of diabetic macroangiopathy or microangiopathy. Despite differences in the pathogenesis of diabetic macro and microangiopathy, endothelial dysfunction has been recognized as a causative factor of both complications [45]. AS-IV exhibits various vascular pharmacological activities, particularly protective effects against vascular endothelial dysfunction, and has attracted considerable attention [46].

Several studies have investigated endothelial dysfunction. Leng et al. [47] explored the mechanism by which AS-IV improves diabetic endothelial dysfunction. They found that 100 μM AS-IV significantly improved endothelium-dependent relaxation in streptozotocin (STZ)-induced diabetic mice, enhancing the expression of P2X7R and p-p38 mitogen-activated protein kinase (MAPK) via the inhibition of the p38 MAPK signaling pathway. Additionally, 40–80 mg/kg AS-IV was orally administered to STZ-induced diabetic rats for eight weeks. This increased nitric oxide production and endothelial nitric oxide synthase expression in the thoracic aorta of rats. Furthermore, AS-IV decreased the level of reactive oxygen species (ROS) and increased the activities of superoxide dismutase (SOD) and glutathione peroxidase in rats by reducing oxidative stress and calpain-1, thereby ameliorating endothelial dysfunction of the thoracic aorta in diabetic rats [48]. In addition, You et al. [49] proposed that AS-IV could inhibit the process of endothelial dysfunction in diabetic macrovascular complications by suppressing apoptosis and the inflammatory response of human umbilical vein endothelial cells (HUVECs) under high-glucose (HG) conditions by inhibiting the c-Jun NH2-terminal kinase (JNK) pathway. Based on their experimental results, 25–100 μM AS-IV intervened in HG-induced HUVECs and reduced cell apoptosis and inflammation by suppressing the JNK signaling pathway.

The inflammatory infiltration and glycosylation pathways are key factors in advanced glycation pathways [50]. The formation and aggregation of advanced glycosylation end products are closely related to the aging process and acceleration of diabetic macrovascular disease [51]. Accordingly, researchers began using these two factors to assess the effects of AS-IV on diabetic vascular diseases.

After treating oxidized low-density lipoprotein-induced endothelial progenitor cells with 10–200 μM AS-IV, Qian et al. [52] have found that activation of the NLRP3 inflammasome induced by oxidized low-density lipoprotein was inhibited, and ROS production was reduced. Thus, the lectin-like oxidized low-density lipoprotein receptor-1/NLRP3 pathway may be a key factor in the protective effects of AS-IV on endothelial progenitor cells. According to Leng et al. [53], 40–80 mg/kg AS-IV via gavage could effectively protect vascular endothelial dysfunction in STZ-induced diabetic rats through the TLR4/NF-κB signaling pathway, as revealed by the lowered content of IL-6 and TNF-α and the suppressed expression of vascular cell adhesion molecule-1 and TLR4. Luo et al. [54] obtained different

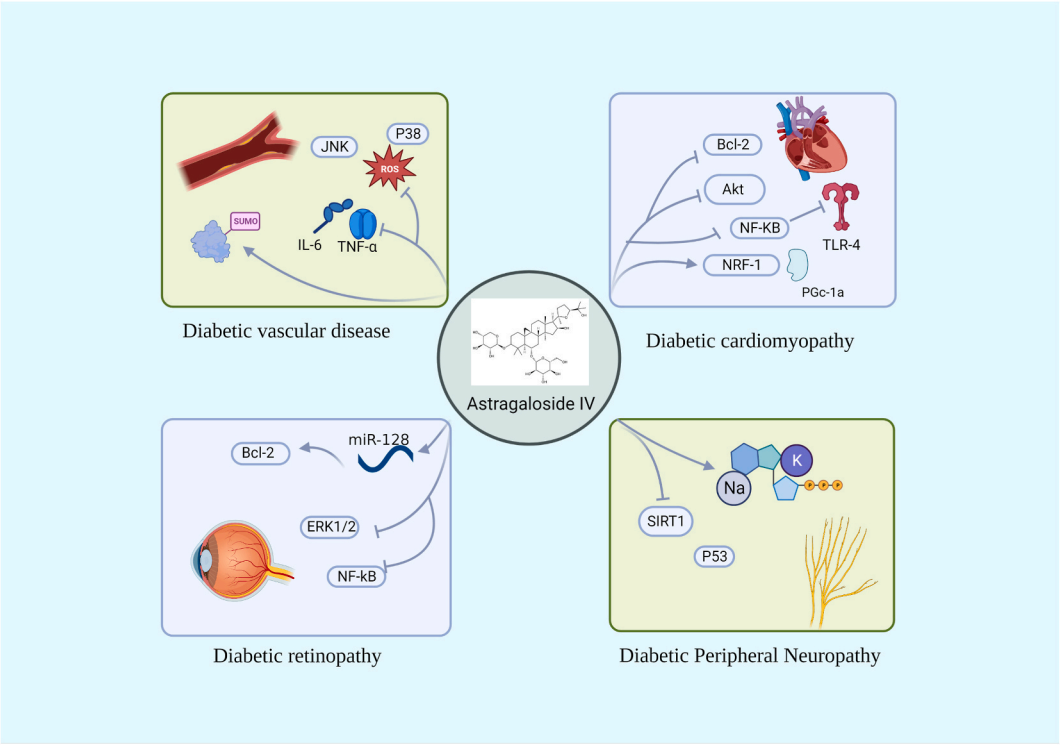

Fig. 3. Mechanism of *Astragaloside IV* (AS-IV) action against diabetic vascular endothelial disease, diabetic vascular endothelial disease, diabetic peripheral neuropathy, and diabetic retinopathy. Illustration of the therapeutic mechanism of AS-IV in diabetic vascular disease, cardiomyopathy, retinopathy, and peripheral neuropathy. In diabetic vascular disease, AS-IV improves vascular endothelial lesions by inhibiting the P38 and JNK signaling pathways and reducing inflammation via activation of the SUMOylation pathway. Similarly, AS-IV can reduce the expression of Bcl2 and pAKT/AKT proteins to protect cardiomyocytes and attenuate the expression of TLR4 in bone marrow mesenchymal stem cells through the NF-kB signaling pathway. AS-IV regulates the release of peroxisome proliferator-activated receptor γ coactivator 1-α (PGc-1α) and nuclear respiratory factor 1 (nrF 1). In retinopathy, AS-IV mainly inhibits ERK1/2 phosphorylation and NF-kB activation and upregulates the expression of miR-128, increasing Bcl-2 protein. AS-IV inhibits diabetic peripheral neuropathy mainly by elevating Na+/K + ATPase and protects against neuropathy by inhibiting SIRT1/p53 signaling.

results using the same animal model. This study showed that 100 mmol/L AS-IV promoted wound healing in STZ-induced diabetic mice, with an increased number of endothelial cells and increased expression of vascular endothelial growth factor and von Willebrand factor. Wang et al. [55] reported that 6 μmol/L AS-IV significantly shortened the healing time of rat skin wounds compared with that in the control. Furthermore, the vascular network at the edge of the skin resection was more abundant with less inflammatory cell infiltration. Based on their in-depth research, these results were achieved through AS-IV activation of the SUMOylation pathway.

Ma et al. [56] intervened in H_2O_2-induced HUVECs using 5–800 μmol/L AS-IV to determine the role of the transforming growth factor-β1 (TGF-β1)/suppressor of mothers against decapentaplegic (Smad)2 signaling pathway in endothelial cell apoptosis induced by oxidative stress. Their findings demonstrated that AS-IV decreased the expression of NADPH oxidase 4 via the TGF-β1/Smad2 signaling pathway to protect diabetic vascular endothelial cells from apoptosis. Yin et al. [57] reported that ferulic acid combined with 50 mg/kg AS-IV could effectively alleviate vascular endothelial dysfunction in STZ-induced diabetic rats, resulting in the activation of monocyte chemoattractant protein-1 (MCP-1), TNF-α, and NF-κB P65 was inhibited.

3.5.2. Diabetic cardiomyopathy (DCM)

DCM has long been observed in patients with diabetes with hyperglycemia and hyperlipidemia and contributes to a series of pathological changes, such as the deposition of lipids and calcium salts in the coronary arteries, arteriolar sclerosis in the myocardial wall, and myocardial microvascular stenosis, ultimately leading to changes in the structure and function of the heart [58,59]. People with DCM often experience heart palpitations, dizziness, precordial pain, shortness of breath, cyanosis, edema, and intermittent claudication. Patients also show obvious signs of heart enlargement, tachycardia, bradycardia, arrhythmia, etc. [60]. According to many studies, DCM pathogenesis is related to signaling pathways induced by HG and oxidative stress [61]. Accumulating evidence from recent animal experimental studies supports the prevention of cardiomyocyte apoptosis via oxidative stress and autophagy pathways using AS-IV.

Wang et al. [62] discussed the preventive effects of AS-IV on cardiomyopathy caused by T2DM. Based on their results, 80 mg/kg AS-IV improved the systolic and diastolic functions of the heart in T2DM rats and pathological changes in the heart tissue. Finally, these

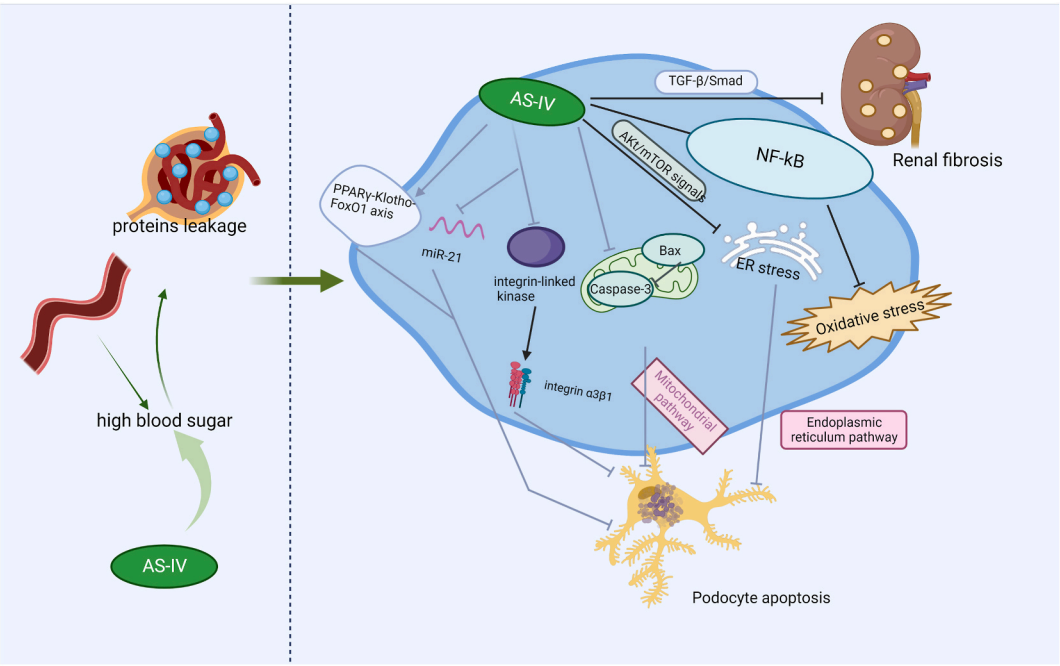

Fig. 4. Mechanism of *Astragaloside IV* (AS-IV) action against diabetic nephropathy. AS-IV regulates protein leakage in diabetic nephropathy by controlling blood glucose levels. Podocyte apoptosis is mainly hindered via the inhibition of apoptosis and resistance to oxidative stress. The mitochondrial pathway reduces Caspase-3 production by inhibiting Bax, whereas the ER pathway mainly inhibits podocyte apoptosis by inhibiting AKt and mTOR pathway-related signals. Some minor pathways, such as inhibition of miR-21 overexpression and integrin-linked kinase expression in diabetic rats, restore integrin α3β1 expression. Antioxidative stress is inhibited by the NF-kB pathway. Alternatively, it directly regulates TGF-β or SMAD to inhibit renal fibrosis.

studies suggested that these effects may be related to improved lipid metabolism in cardiomyocytes. Zhang et al. [63] administered 10–40 mg/kg AS-IV to STZ-induced diabetic mice *in vitro*. Based on their experimental results, AS-IV regulates the release of PPARγ coactivator 1-α and nuclear respiratory factor 1 to adjust energy metabolism for reduced myocardial damage. Using the same model, Zhu et al. [64] found that 100 μM AS-IV significantly reduced B-cell lymphoma 2 (Bcl2) and phosphorylated protein kinase B (AKT)/AKT protein expression via the miR-34a-mediated autophagy pathway, thereby protecting H9C2 (2-1) cell from damage. Furthermore, lipid peroxidation and increased SOD activity were inhibited in rats. In contrast, Li et al. [65] administered 1 g/kg AS-IV to 20 patients with diabetes for four weeks and collected blood samples. The expression levels of TLR4, TNF-α, and MCP-1 were decreased, and AS-IV was identified to attenuate the expression of TLR4 in bone marrow mesenchymal stem cells via the NF-kB signaling pathway.

3.5.3. Diabetic retinopathy (DR)

DR is the leading cause of blindness and the most important manifestation of diabetic microvascular disease [66,67]. The pathogenesis of DR is as follows: the normal interaction between the retinal neural and vascular components is disrupted, leading to vascular permeability, neovascularization, and loss of proper neural function [68]. DR is accompanied by pathological changes such as selective loss of pericytes, thickening of the basement membrane, formation of microangiomas, proliferation of endothelial cells, and formation of new blood vessels. Accordingly, AS-IV can reverse DR by reducing the apoptosis of retinal pigment cells. In the current study, the relationship between abnormal retinal miRNA expression profiles and DR was a central issue [69].

Wang et al. [70] revealed that 20–60 mg/kg AS-IV protected retinal pigment epithelium (RPE) cells from apoptosis by upregulating miR-128 expression in STZ-induced diabetic rats. Furthermore, the expression levels of Bcl-2 and Fas ligand were increased in STZ-induced diabetic rats.

Qiao et al. [71] determined the potential effects of AS-IV on HG-induced RPE cells. Based on their findings, 2–20 μM AS-IV could increase the activity of total SOD, manganese-dependent SOD, catalase, and glutathione peroxidase to protect HG-induced RPE cells. Ding et al. [72] reported that 4.5 or 9 mg/kg AS-IV can relieve retinal ganglion cell dysfunction in db/db mice by decreasing the activity of retina aldose reductase and inhibiting extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) phosphorylation and NF-kB activation.

3.5.4. Diabetic peripheral neuropathy

Diabetic peripheral neuropathy is one of the most common chronic complications in patients with diabetes and leads to pain, paresthesia, and sensory loss. AS-IV exerted protective effects against diabetic peripheral neuropathy in STZ-induced diabetic rats by

elevating Na^+/K^+ ATPase [73]. Recently, AS-IV was reported to reduce mitochondria-dependent apoptosis by suppressing the sirtuin 1 (SIRT1)/p53 signaling pathway in STZ-induced diabetic rats with diabetic peripheral neuropathy [74].

3.5.5. Diabetic nephropathy (DN)

DN, the main microvascular complication of diabetes, is one of the most serious complications of the disease [75]. DN mainly refers to diabetic glomerulosclerosis, a glomerular disease characterized by vascular damage. Patients with DN display symptoms such as foamy urine, dizziness, fatigue, nausea, and discomfort [76]. According to current studies, DN pathogenesis remains unclear but mainly includes metabolic disorders, abnormal glucose metabolism, oxidative stress, endoplasmic reticulum stress, inflammatory response, and autophagy, with metabolic disorders regarded as a prerequisite [77,78]. Renal tubular mesangial cell (MC) proliferation, inflammatory cell infiltration, and renal fibrosis are common pathological manifestations of DN [79]. Based on these key points and an increasing number of animal experiments, AS-IV can relieve the symptoms of DN and inhibit renal fibrosis by protecting kidney podocytes and exhibiting anti-apoptotic, antioxidative, anti-inflammatory, and other protective effects on kidney cells.

One of the most important mechanisms of action of AS-IV in treating DN is the protection of renal podocytes. Podocytes are visceral epithelial cells that primarily regulate filtration in the advanced glomeruli [80]. The podocyte foot process distributed around the glomerular capillaries is an important podocyte structure, and its disappearance is a key factor leading to DN progression [81].

Chen et al. [82] explored the therapeutic effects of AS-IV on podocytes in diabetic rats. They administered 2.5–10 mg/kg AS-IV to STZ-induced diabetic mice for 14 weeks. The experimental data revealed that the symptoms of rat podocyte loss and disappearance of the podocyte foot process were improved, which may be related to the inhibited expression of integrin-linked kinase and restored expression of integrin α3β1 in diabetic rats by AS-IV. Wang et al. [83] showed that 40 mg/kg AS-IV inhibited podocyte dedifferentiation and MC activation by suppressing miR-21 overexpression in diabetic KK-Ay mice, thereby improving kidney function. Guo et al. [84] revealed that 3–12 mg/kg AS-IV effectively prevented the deterioration of STZ-induced diabetic mouse podocyte damage in DN, attenuates sarcoplasmic/endoplasmic reticulum Ca2+-ATPase (SERCA) 2-dependent endoplasmic reticulum stress, and promoted autophagy induction of AMP-activated protein kinase. Lei et al. [85] investigated the protective mechanism of AS-IV against podocyte damage in DN. After treating STZ-induced diabetic mice with 5 mg/kg/day AS-IV for 12 weeks, the researchers found increased levels of urinary albumin and TNF receptor-associated factor 5 and decreased levels of taurine upregulated gene 1 in mice. These researchers concluded that AS-IV inhibited podocyte apoptosis in diabetic rats via the long noncoding RNA-taurine upregulated gene 1/TNF receptor-associated factor 5 pathway.

Excessive apoptosis in renal podocytes is the most common mechanism underlying podocyte injury. AS-IV inhibits podocyte apoptosis induced by mitochondrial and endoplasmic reticulum pathways, thereby exerting a protective effect on podocytes.

Xing et al. [86] administered 2–18 mg/kg/d AS-IV to db/db mice and HG-cultured podocytes to explore the protective mechanism of AS-IV against DN podocyte apoptosis. These researchers found an increased expression of klotho in glomerular podocytes. Furthermore, kidney function and podocyte damage were ameliorated in the db/db mice. Therefore, these researchers proposed that AS-IV may protect podocytes from apoptosis in DN by activating the PPARγ-klotho-forkhead box O1 axis. After the administration of 1 g/kg AS-IV to db/db diabetic mice, Liu et al. [87] found that the expression of dynamin-related protein 1, mitochondrial fission protein 1, and mitochondrial fission factor was significantly reduced in db/db diabetic mouse kidneys, which delayed the progression of nephropathy. This may be due to the restoration of the mitochondrial quality control network. Song et al. [88] added 5 g/kg AS-IV to the standard chow diet of STZ-induced diabetic mice and found that it could effectively relieve early DN. Accordingly, these researchers suggested that the mechanism of AS-IV may be related to the inhibition of the mitogen-activated protein kinase kinase 1/2-ERK1/2-ribosomal S6 kinase 2 signaling pathway.

3.5.6. Endoplasmic reticulum stress is the main manifestation of the endoplasmic reticulum-induced apoptosis pathway

Similar to Liu et al. [87] and Xing et al. [86], Sun et al. [89] used the same model to explore the protective effects of dietary supplementation with AS-IV on renal injury in db/db diabetic mice. AS-IV inhibited the activation of diabetes-related Akt/mTOR, NF-κB, and Erk1/2 signaling pathways, with no detectable liver toxicity. Wang et al. [90] proposed that the reversal of DN by AS-IV may be related to a reduction in endoplasmic reticulum stress. Their proposal was due to the prevention of eukaryotic Initiation Factor 2 alpha, protein kinase R-like endoplasmic reticulum kinase (PERK), and JNK phosphorylation in STZ-induced diabetic mice and significant inhibition of the expression of glucose-regulated protein 78 and 150 kDa oxygen-regulated protein by 10 mg/kg AS-IV. AS-IV also reduced C/EBP homologous protein (CHOP) expression and cleaved caspase-3 levels, thereby reducing podocyte apoptosis. Yao et al. [91] found that the expression of transient receptor potential channel 6 (TRPC6) was inhibited, and Ca^{2+} concentration decreased significantly in HG-induced podocytes treated with 10–40 μM AS-IV. Therefore, it was speculated that AS-IV utilizes the calcineurin/nuclear factor of activated T cells signaling pathway to downregulate TRPC6 to protect against HG-induced podocyte damage. Guo et al. [92] revealed that the administration of 2–18 mg/kg AS-IV via gavage could restore SERCA activity, significantly inhibit SERCA2 expression, and suppress endoplasmic reticulum stress-induced podocyte apoptosis in a dose-dependent manner in db/db mice. As a result, AS-IV reduced damage in patients with DN. Chen et al. [93] found that 5 and 10 mg/kg of AS-IV increased the expression of glucose-regulated protein 78 and estrogen receptor-related apoptotic proteins in diabetic rats. Accordingly, they concluded that AS-IV had a protective effect on podocyte apoptosis induced by endoplasmic reticulum stress, which was mainly related to the inhibition of the PERK-activating transcription factor 4-CHOP pathway. Gui et al. [94] determined the effects of AS-IV on podocytes under diabetic conditions *in vivo* and *in vitro*. Briefly, cultured podocytes were exposed to an HG environment and treated with 2.5–10 mg/kg AS-IV. The *in vivo* and *in vitro* results showed that AS-IV partially restored the balance between bcl-2-like protein 4 and Bcl-2 expression and inhibited the activation of caspase-3 to prevent podocyte apoptosis, suggesting that AS-IV may be a new type of antioxidant. Ju et al. [95] found that AS-IV (40 and 80 mg/kg) could alleviate renal tubular epithelial cell apoptosis in DN rats by

inhibiting endoplasmic reticulum stress-induced apoptosis and downregulating the expression of p-PERK, activating transcription factor 4, and CHOP.

Oxidative stress is another important mechanism that underlies diabetic kidney injury. AS-IV protected renal epithelial cells and MCs from oxidative stress [96]. Oxidative stress refers to a state in which the body produces increased levels of ROS under various stimuli that exceed the body's degradation ability, causing oxidative damage to biological macromolecules and affecting the body's normal activities [97]. In hyperglycemia, glomerular MCs and tubular epithelial cells increase ROS production, which in turn aggravates kidney damage in patients with diabetes [98]. Therefore, antioxidants are considered key drugs for the treatment of DN. Simultaneously, research on nephropathy caused by the antioxidant-active substances of AS-IV has become a hot topic.

According to Wang et al. [99], 10–80 μM AS-IV significantly reversed HG-induced apoptosis and oxidative stress in HK-2 cells by regulating the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element signaling pathway, resulting in increased viability, and suppressed the apoptosis of HK-2 cells. Moreover, He et al. [100] revealed that 2.5–10 mg/kg AS-IV could prevent kidney damage in STZ-induced diabetic mice caused by iatrogenic hyperinsulinemia, mainly by suppressing oxidative stress, IL-1β and TNF-α overproduction, downregulating ERK1/2 activation, and upregulating TRPC6 expression. Chenet al. [101] revealed that 10–40 μmol/L AS-IV protected renal tubular epithelial cells from damage by inhibiting the apoptosis of palmitic acid-induced HK-2 cells, resulting in lowered expression of bcl-2-like protein 4 and cleaved caspase-3 and increased expression of Bcl-2 and phosphorylated Nrf2. Wang et al. [102] sought to determine whether AS-IV has an inhibitory effect on HG-induced human tubular epithelial cells. Based on their findings, 0–200 μg/mg AS-IV inhibited the expression of TGF-β1 and the activation of the p38 MAPK pathway in HG-induced human tubular epithelial cells and increased the production of hepatocyte growth factor in cells. Thus, Wang et al. [102] suggested that AS-IV relieves diabetic kidney damage and may be related to the suppression of p38 MAPK signaling pathway activation and hepatocyte growth factor overproduction. Qi et al. [103] studied the mechanism of action of AS-IV in the albumin (GA)-induced epithelial-to-mesenchymal transition of NRK-52E cells. After administering 0.8–80 μg/mL AS-IV to NRK-52E cells, these researchers found that AS-IV reduced the expression of α-smooth muscle actin and increased the expression of E-cadherin in NRK-52E cells, which was mainly mediated by the inhibition of oxidative stress in renal proximal tubular cells.

Su et al. [104] administered 20–80 mg/kg AS-IV to STZ-induced diabetic rats and detected palmitate-induced human glomerular MCs (HMCs). AS-IV suppressed the expression of CD36 to mediate FFA uptake and lipid accumulation, thereby reversing oxidative stress and fibrosis in palmitate-induced HMCs. Sun et al. [105] treated HG-induced human MCs with 5–100 μM AS-IV and found the following changes in the cells: increased activity of NADPH oxidase, decreased expression of NADPH oxidase 4 protein, and inhibited phosphorylation of Akt and inhibitor of kappa B-alpha. Finally, Sun et al. proposed that AS-IV mainly protects HG-induced human MCs by suppressing the NADPH oxidase/ROS/Akt/NF-κB pathway.

Inflammation may be one of the most important factors leading to DN, and AS-IV alleviates DN by reducing inflammatory damage. Hyperglycemia can stimulate intrinsic kidney cells to produce inflammatory mediators that mediate damage. From this perspective, many animal experiments have shown that AS-IV is effective against DN.

Zhang et al. [106] recently revealed that the administration of 80 mg/kg AS-IV via gavage inhibited the expression of renal inflammation-related genes in STZ-induced diabetic mice, improving the severity of DN. Furthermore, the expression levels of IL-1β and IL-18 were found to be significantly reduced. According to Lu et al. [107], 40 mg/kg AS-IV is advantageous for reducing urinary albumin excretion and improving the adhesion function of eosinophils, thereby reversing DN. Their experimental results revealed a significant decrease in the expression of IL and α-actin-4 in STZ-induced diabetic rats. Gui et al. [108] suggested that AS-IV is a new type of anti-inflammatory drug and showed that 5–10 mg/kg AS-IV reduced the serum levels of TNF-α, MCP-1, and intercellular adhesion molecule 1 in STZ-induced diabetic mice. AS-IV also inhibited NF-kB-mediated inflammatory gene expression to reverse DN in rats.

Renal fibrosis is an important pathological condition associated with DN. AS-IV protects renal function by relieving DN symptoms and inhibiting renal fibrosis [109]. According to several studies, the TGF-β/Smad signaling pathway is a key signaling pathway for inducing diabetic renal fibrosis [110]. Therefore, inhibiting this pathway can delay the progression of diabetic renal fibrosis. The effects of AS-IV on DN have been thoroughly assessed in many animal studies and are associated with the TGF-β/Smad signaling pathway.

Wang et al. [111] probed the protective mechanism of AS-IV in the proximal tubule epithelial cells of the kidney. Overall, 20–100 μg/mL AS-IV inhibited the TGF-β/Smad pathway in NRK-52E cells to mitigate HG-induced epithelial-to-mesenchymal transition in renal proximal tubule epithelial cells. In an *in vitro* model, Mao et al. [112] treated HG-induced rat MCs with 0–100 μg/mL AS-IV. Their results suggested that the expression of TGF-β1, Smad3, and α-smooth actin decreased as the expression of Smad7 mRNA and protein increased, thereby suppressing the proliferation of MCs and improving renal fibrosis in rats, which may be related to the TGF-β1/Smad/miR-192 signaling pathway.

AS-IV regulates other signaling pathways to protect against renal fibrosis. Chen et al. [113] revealed that 50–200 μg/mL AS-IV blocked the mTORC1/p70S6K signaling pathway in HK-2 cells to protect HG-mediated renal tubular epithelial-mesenchymal transition, resulting in the downregulation of snail and twist. Wang et al. [114] sought to determine whether AS-IV regulated the proliferation of MCs in DN by specifically regulating the autophagy inducer, SIRT1. The results revealed that 40 mg/kg/day AS-IV significantly improved renal function and fibrosis in diabetic KK-Ay mice. Furthermore, AS-IV suppressed HG-induced MC activation and enhanced autophagy via the SIRT1-NF-κB pathway *in vivo*. Wang et al. [115] revealed that 25–100 μM AS-IV reduced NF-κB p65 subunit acetylation and increased SIRT1 expression, contributing to the suppression of glucose-induced podocyte epithelial-mesenchymal transition and enhanced autophagy in KK-Ay mouse models of diabetes *in vivo*. As a result, renal fibrosis and function improved in KK-Ay mice. Overall, these studies proposed that AS-IV may be a renoprotective agent.

4. Toxicology

Toxicological studies on the traditional Chinese medicine AM found that its extract is safe and does not exhibit obvious toxicity or side effects [116]. Previous studies have evaluated the safety of AS-IV as an active ingredient in AM. Xu et al. [117] administered 0.5–1 mg/kg AS-IV to female rats from pre-mating to day 6 of gestation. Perinatal toxicity in rats was assessed from gestational days 15–21 and lactation days 1–21. Compared with the control group, hair development, eye opening, and cliff parry reflex time were prolonged in newborn mice in the experimental group; however, no difference was found in the memory and learning ability of mice. Jiang et al. [118] conducted experiments similar to those of Xu et al. [117]. These researchers established two experimental groups: rats in group one were intravenously administered 0.25–1 mg/kg AS-IV every day from day 6–15 of pregnancy, and New Zealand white rabbits in group two were administered 0.5–2.0 mg kg/kg AS-IV daily from gestation day 8–17. Based on the experimental results, the percentage of fetal death in the 0.5 and 1.0 mg/kg rat groups was significantly higher than that in the control group, whereas the remaining groups had neither fetal toxicity nor malformed fetuses. Yu et al. [119] conducted subchronic toxicity studies on AM extracts in rats and dogs. These researchers converted AS-IV and astragalus polysaccharide into a dry freeze-dried powder, which was administered to rats and dogs. The behavioral activities and general conditions of the rats and dogs were normal, and no abnormalities in hematology, blood biochemical parameters, or absolute and relative weights of the major organs were found. These researchers concluded that the safe dose range of the AM extract for rats is 5.7–39.9 g/kg, and that for beagle dogs is 2.85–19.95 g/kg.

5. Discussion and future outlook

DM and its complications pose a huge burden on public health worldwide. Despite multiple efforts to develop novel therapeutics, these often fail to manage DM or its complications. Natural small molecules are an important source of antidiabetic agents. This review aimed to summarize and analyze studies on AS-IV, a bioactive compound with potential antiviral, antioxidative, and antifibrotic effects, for treating DM and its complications.

AS-IV has antioxidant effects in DM complications. For instance, AS-IV can inhibit the apoptosis of HK-2 cells by regulating the Nrf2/antioxidant response element, p38MAPK, ERK1/2, and other signaling pathways to protect renal tubular epithelial cells from damage. In addition, AS-IV inhibits the activity of peroxisome proliferators in diabetic mice to protect rat cardiomyocytes from apoptosis. AS-IV has been previously found to reduce oxidative stress and ROS levels in diabetic vascular lesions, improving thoracic aortic endothelial dysfunction in diabetic rats. Moreover, pharmacological studies have revealed that AS-IV exerts protective effects against brain damage and on the central nervous system, cardiovascular system, and kidneys by inhibiting oxidative stress [94,120,121]. Thus, AS-IV is a potential antioxidant agent. AS-IV inhibits mitochondrial/endoplasmic reticulum pathway-induced podocyte apoptosis. Thus, we speculate that AS-IV may be a novel podocyte apoptosis inhibitor. Moreover, AS-IV was found to have significant regulatory effects on the NF-κB, TGF-β/Smad, and p38 MAPK signaling pathways, thereby exerting anti-inflammatory, antifibrotic, and antivascular endothelial dysfunction effects. Previous studies found that AS-IV can regulate the NF-κB, TGF-β/Smad, and p38 MAPK signaling pathways, thereby delaying ischemia and perfusion injury caused by liver fibrosis and transplantation [122,123]. The NF-κB, TGF-β/Smad, and p38 MAPK signaling pathways may be more sensitive to AS-IV. Finally, although only three studies reported the effect of AS-IV on GDM, combined with this safety evaluation, pups were not found to be at risk. AS-IV also has a hypoglycemic effect in mice with GDM.

Based on our analysis, we believe that the oxidative stress pathway associated with the action of AS-IV on ROS warrants further investigation. Antioxidants should be part of the process of treating diabetes, and based on the analysis of experimental and clinical studies, modern therapeutic strategies for the treatment of diabetes aim to develop new approaches to personalized antioxidant therapy, including targeting sources of ROS in combination with new methods of antioxidant delivery [124]. Furthermore, TZDs are PPAR-γ agonists, and AS-IV and TZDs are similar in alleviating diabetes by modulating NF-κB [125]. Similar to AS-IV, metformin, the main drug used to treat T2DM [126], increases AMP-activated protein kinase activity and phosphorylation to control blood glucose levels [127]. AS-IV also acts on many important targets of diabetic complications, including PPARγ, NF-κB, ROS, and ERK1/2. Therefore, AS-IV is a potential drug for the treatment of diabetes and its associated complications. Further research is required to obtain reasonable LD50 and NOAEL data for drug discovery and development.

Moreover, we identified 11 *in vivo* and *in vitro* models, with STZ-induced diabetic rats being the most frequently used. A previous review reported that STZ-induced diabetes in mice is currently the most effective chemical animal model for DM research [128]. Therefore, this model could improve the accuracy of similar studies in the future. Combined with the safety assessment of AS-IV, 10–120 mg/kg AS-IV was found to be directly administered to STZ-induced diabetic rats, 2.5–0 mg/kg was found to be directly administered to STZ-induced diabetic mice, 2–18 mg/kg was directly administered to db/db diabetic mice, and 10–200 μg/ml AS-IV in culture fluid or medium was administered to other cell models. These results suggest a safe and standard method of administration and dosage for future pharmacological research on AS-IV, ultimately avoiding unnecessary waste.

Increasing attention is being paid to plant-active natural products with unique chemical structures and various pharmacological effects [129]. With continued advances in high-throughput screening technology, AS-IV, as a plant-active natural product, has become an indispensable source of new drugs [130,131]. Natural active ingredients, such as AS-IV, have been demonstrated to often act on multiple targets rather than on a single target [132]. However, the low bioavailability of AS-IV alone limits its clinical use. The lack of target specificity may reduce the therapeutic effect of AS-IV upon administration to a living body. Therefore, new formulations or structural modifications are needed to improve the pharmacokinetic parameters and promote the clinical application of AS-IV. Traditional Chinese medicine is widely known as a key source of bioactive agents for DM and its complications [133,134]. They may exert synergistic effects when used in combination with other chemical drugs. For example, AS-IV and ligustrazine were

previously found to antagonize ischemia-reperfusion injury in a rat model of acute cerebral ischemia [135]. A previous study found that the combined use of atorvastatin and AS-IV could more effectively reduce the inflammatory response in mice than either of the two agents [136]. AS-IV and polyurethane concurrently increase the levels of neuronal regeneration indicators and promote Schwann cell proliferation in mice [137]. Therefore, combination therapy with AS-IV may prevent and treat diabetes and its associated complications. However, there is a complicated problem in that co-delivery interactions may occur when multidrug therapy is applied, such as affecting their absorption and metabolism in the body [138,139]. Therefore, attention should be paid to the effective ingredients of the drug to explore whether its combination with AS-IV is beneficial for DM. We are supposed to conduct preclinical experiments before medication administration to observe if there are obvious side effects. In addition, it is important to determine the duration of combined medication. However, given the current data and considering the safety and efficacy, we believe that further preclinical studies are needed before discussing the next steps in clinical trials.

This review has several limitations. For example, no literature reports on the direct targets and specific molecules of AS-IV for treating diabetes were included in this review. Instead, this systematic review comprised preclinical studies, which should provide a theoretical basis and safety evidence for clinical trials. Current research tends to focus on cellular analyses and animal studies. Therefore, pharmacology, pharmacodynamics, and toxicology studies should be reviewed to provide a theoretical basis and safety evidence for clinical trials. In addition, the potential effect of AS-IV on DM should be investigated, and additional formulations or structural modifications are needed to improve the pharmacokinetic parameters and promote the clinical application of AS-IV.

6. Conclusion

In this review, AS-IV was found to alleviate gestational diabetes in mice by downregulating the expression of inflammatory genes and reducing hepatic gluconeogenesis. AS-IV can delay DN by protecting podocytes and exhibiting antioxidant and anti-inflammatory effects. AS-IV prevents cardiomyocyte apoptosis through oxidative stress and autophagy pathways, and AS-IV inhibits vascular endothelial dysfunction to protect diabetic vascular endothelium from damage. In addition, preclinical toxicity studies indicate that it appears to be safe, but the safe human dose limit is yet to be determined, and formal assessments of adverse drug reactions among humans need to be further investigated. AS-IV also prevents the aggravation of diabetic retinal pigment epithelial lesions by reducing retinal pigment epithelial cell apoptosis. Overall, AS-IV is a potential drug for the treatment of diabetes and its complications.

Disclosure statement

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CRediT authorship contribution statement

Caiyan Qu: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Xiyue Tan:** Writing – review & editing, Writing – original draft. **Qichao Hu:** Writing – review & editing. **Jiao Tang:** Data curation. **Yangyang Wang:** Data curation. **Caiying He:** Data curation. **ZiJia He:** Data curation. **Bin Li:** Data curation. **Xiaoxu Fu:** Data curation. **Quanyu Du:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:QuanyuDu reports financial support was provided by Hospital of Chengdu University of Traditional Chinese Medicine. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AS-IV	Astragaloside IV
AM	Astragalus membranaceus
AMPKα	AMP-activated protein kinase
ATF4	activating down-stream transcript factor 4
CHOP	C/EBP homologous protein
DCM	diabetic cardiomyopathy
DN	diabetic nephropathy

DR	Diabetic retinopathy
Drp-1	dynamin-related protein 1
eNOS	endothelial nitric oxide synthase
EPCs	endothelial progenitor cells
Erk1/2	extracellular signal-regulated kinase 1 and 2
Fis-1	fission protein 1
FFA	free fatty acid
GDM	Gestational diabetes mellitus
GRP78	glucose-regulated protein 78
HG	high glucose
IL-6	interleukin-6
JNK	c-Jun NH2-terminal kinase
HUVECs	human umbilical vein endothelial cell
MCs	mesangial cells
MFF	mitochondrial fission factor
Nrf2	nuclear factor erythroid 2 like 2
NLRP3	NLR family pyrin domain containing-3
NF-κB	nuclear factor-κB
NO	nitric oxide
ox-LDL	oxidized low-density lipoprotein
ORP150	oxygen-regulated protein
P38MAPK	P38 mitogen-activated protein kinase
PERK	protein kinase R-like ER; kinase
PTP1B	protein tyrosine phosphatase 1B
P2X7R	P2X7 receptor
ROS	reactive oxygen species
RPE	retinal pigment epithelial
SERCA2b	serca2-dependent endoplasmic reticulum stress
SOD	superoxide dismutase
STZ	streptozotocin
T2DM	type 2 diabetes
TRPC6	transient receptor potential channel 6
TLR4	toll-like receptor 4
TNF-α	tumor necrosis factor alpha
TGF- β 1/Smad2	transforming growth factor- β1
VCAM-1	vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

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