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Review Article

Astragaloside IV in type 2 diabetic vascular complications: from traditional mechanisms to an emerging epitranscriptomic (m6A) perspective

Yanbo Kang[1], Yangyingqi Dai[2], Liping Yin[1]

[1]*Department of Endocrinology, Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610000, Sichuan, China;* [2]*Department of Dermatology, Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610000, Sichuan, China*

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Abstract: Type 2 diabetes mellitus (T2DM) is a significant health problem of global concern, largely attributable to its catastrophic micro- and macro-vascular complications. Astragaloside IV (AS-IV), a major bioactive saponin extracted from Astragalus membranaceus, has emerged as a multi-target therapeutic candidate due to its anti-inflammatory, antioxidant, anti-fibrotic, and pro-survival properties. Dysregulation of N6-methyladenosine (m6A) RNA methylation, as one of the most prevalent epitranscriptomic modifications, has been proposed as a critical contributor to the pathogenesis of diabetic vascular complications, including chronic inflammation, aberrant cell death, and impaired tissue repair. This review integrates these two research fields and proposes a novel concept that modulation of m6A epitranscriptome represents a central mechanism underlying the vascular protective action of AS-IV. New evidence indicates that AS-IV can directly regulate key elements of the m6A machinery, including the upregulation of the methyltransferase methyltransferase-like 3 (METTL3) to enhance sirtuin 1 (SIRT1) expression in diabetic wounds or suppressing the fat mass and obesity-associated protein (FTO) demethylase to suppress inflammatory signaling in diabetic retinopathy. AS-IV acts as a pharmacological modulator of m6A methylation, linking its conventional biological activities to epitranscriptomic regulation. Elucidation of the AS-IV-m6A axis may provide deeper mechanistic understanding and facilitate the development of epitranscriptome-targeted therapies for diabetic vascular complications.

Keywords: Astragaloside IV, type 2 diabetes mellitus, vascular complications, m6a RNA methylation, epitranscriptomics, diabetic nephropathy, diabetic retinopathy

Introduction

Diabetes mellitus type 2 (T2DM) represents a major global public health challenge. According to the International Diabetes Federation, more than half a billion individuals worldwide are affected by diabetes, and this number is projected to increase exponentially over the coming decades [1, 2]. The disease burden of T2DM arises not only from chronic hyperglycemia itself, but more critically from progressive vascular injuries, including both microvascular complications (e.g., nephropathy, retinopathy, neuropathy) and macro-vascular diseases (e.g., atherosclerosis, coronary artery disease, peripheral arterial disease) [3]. These complications are leading causes of end-stage renal disease, blindness, and non-traumatic lower-limb amputation, and are associated with markedly increased morbidity, mortality, and healthcare expenditures [4, 5]. Despite the use of glucose-lowering agents and interventions targeting hypertension and dyslipidemia, a significant residual risk of diabetic vascular complications persists. The complex and multifactorial pathophysiology of diabetic vascular injury underscores the urgent need for novel interventions capable of simultaneously modulating multiple molecular pathways involved in disease progression [6, 7].

Natural products have long served as an important source of multi-target therapeutic agents. Among these, Astragaloside IV (AS-IV), a major

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bioactive saponin extracted from the traditional medicinal plant Astragalus membranaceus, has attracted considerable scientific attention [7-9]. Preclinical studies have demonstrated that AS-IV exerts a broad spectrum of pharmacologic effects, including anti-inflammatory, antioxidant, anti-apoptotic, and anti-fibrotic activities [10-16]. These protective effects have been consistently observed in multiple models of diabetic complications, in which AS-IV modulates key pathogenic pathways involved in diabetic cellular damage, such as suppression of nuclear factor-kappa B (NF-κB) and transforming growth factor-β1 (TGF-β1), and activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and Sirtuin 1 (SIRT1) pathways [17, 18]. The capability of AS-IV to concurrently target multiple pathological processes highlights its therapeutic potential for diabetic vascular disease.

Concurrently, molecular biology has undergone a paradigm shift regarding the emergence of epitranscriptomics, a discipline that focuses on post-transcriptional RNA modifications that regulate gene expression without altering the underlying RNA sequence [19]. N6-methyladenosine (m6A) is the most abundant, dynamic, and reversible modification on eukaryotic messenger RNA (mRNA). m6A marks are deposited by methyltransferase "writer" complexes, removed by demethylase "eraser" enzymes, and interpreted by specific "reader" proteins, thereby determining the fate of target transcripts, including their stability, translation efficiency, and splicing patterns [20, 21]. Accumulating evidence has shown that dysfunction of this m6A machinery is profoundly implicated in the pathogenesis of a broad spectrum of human diseases, such as cancer, neurological disorders, and, most importantly, metabolic and cardiovascular diseases [22, 23]. Given the central involvement of m6A modification in inflammation, angiogenesis, and cell death, it is increasingly recognized as an important regulatory hub in the pathophysiology of T2DM vascular complications.

Considering the multi-target vascular protective effects of AS-IV and the emerging role of m6A RNA methylation as a master regulator in diabetic vascular pathology, a question arises: can the therapeutic action of AS-IV be extended to modulation of the m6A epitranscriptome? This unresolved issue constitutes the primary knowledge gap addressed in the present review.

In this review, we first summarize the well-established mechanisms by which AS-IV ameliorates diverse vascular complications of T2DM. Then, we review current evidence linking dysregulated m6A RNA methylation to the development of these pathological processes. Lastly, we integrate these two disciplines to propose a novel conceptual framework in which m6A RNA methylation acts as a mediator of the vascular protective effects of AS-IV, highlighting emerging evidence that links AS-IV with the regulation of key m6A regulators and identifying new directions for epitranscriptome-targeted therapeutic strategies.

Traditional mechanisms underlying the protective effects of astragaloside IV against T2DM vascular complications

The therapeutic rationale of AS-IV lies in its robust ability to counteract the core pathological pathways activated in the diabetic milieu, including chronic inflammation, oxidative stress, apoptosis, and fibrosis. AS-IV exerts its effects across diverse cell types and modulates a complex network of signaling pathways disrupted under hyperglycemic and dyslipidemic conditions. AS-IV confers broad vascular protection through coordinated actions that preserve endothelial integrity, suppress pathological cell death and tissue remodeling, and regulate immune responses. This section systematically summarizes the established mechanisms, explaining the mechanism by which AS-IV mitigates both microvascular complications (diabetic nephropathy [DN], retinopathy [DR]) and macrovascular pathologies (diabetic foot ulcers [DFU] and atherosclerosis [AS]) (**Figure 1**).

Diabetic nephropathy (DN)

DN is a leading cause of end-stage renal disease, characterized by structural and functional damage to both glomerular and tubular compartments. AS-IV exhibits strong reno-protective properties by targeting several pathological processes in various renal cells, including podocytes, mesangial cells, and the tubular epithelial cells [24].

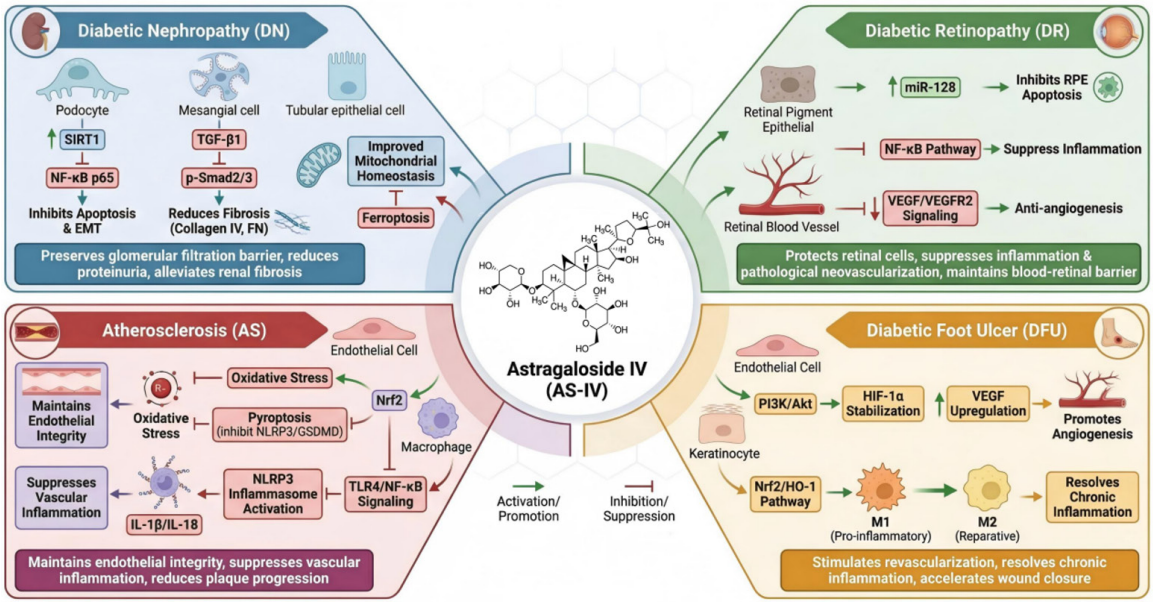

Figure 1. Schematic illustration of the multitarget protective effects of AS-IV against vascular complications of T2DM. The central node depicts the chemical structure of AS-IV and its protective actions against four major vascular complications of T2DM: DN, DR, AS, and DFU. DN: AS-IV preserves the glomerular filtration barrier and attenuates renal fibrosis. Mechanistically, it activates the SIRT1/NF-κB axis to suppress apoptosis and EMT, inhibits the TGF-β1/Smad2/3 fibrotic pathway, and maintains mitochondrial homeostasis (inhibition of ferroptosis) in podocytes and tubular epithelial cells. DR: AS-IV preserves the blood-retinal barrier by upregulating miR-128 to reduce RPE cell apoptosis, inhibiting NF-κB-mediated inflammation, and suppressing pathological angiogenesis through suppression of VEGF/VEGFR2 signaling. DFU: In contrast to DR, AS-IV promotes angiogenesis in wound tissue through activation of the PI3K/Akt/HIF-1/VEGF signaling cascade. It also accelerates wound healing by activating the Nrf2/HO-1 pathway, thereby promoting macrophage polarization toward the reparative M2 type. AS: AS-IV preserves endothelial integrity and inhibits plaque development. It activates Nrf2 to reduce oxidative stress, inhibits pyroptosis through the NLRP3/GSDMD signaling, and NLRP3 inflammasome activation, thereby reducing the release of pro-inflammatory cytokines IL-1β and IL-18. Green arrows indicate activation or upregulation, while red T-bars indicate inhibition or suppression. Notes: T2DM, Type 2 Diabetes Mellitus; DFU, Diabetic Foot Ulcer; DN, Diabetic Nephropathy; DR, Diabetic Retinopathy; EMT, Epithelial-Mesenchymal Transition; VEGF, Vascular Endothelial Growth Factor; VEGFR2, Vascular Endothelial Growth Factor Receptor 2; Akt, Protein Kinase B; HIF-1, Hypoxia-Inducible Factor-1; PI3K, Phosphatidylinositol 3-Kinase; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; GSDMD, Gasdermin D; IL-1β, Interleukin-1β; IL-18, Interleukin-18; HO-1, heme oxygenase-1; TGF-β1, Transforming Growth Factor-β1.

Maintenance of podocyte integrity represents a central mechanism of AS-IV-mediated renal protection. Under high-glucose conditions, podocytes undergo apoptosis, epithelial-mesenchymal transition (EMT), disruption of glomerular filtration barrier, and proteinuria. AS-IV has been shown to suppress glucose-induced podocyte apoptosis and EMT by promoting autophagy, an important cellular homeostatic process. This is mediated through activation of SIRT1, a key metabolic sensor that deacetylates and inactivates the p65 subunit of NF-κB, thereby attenuating inflammatory and apoptotic signaling. AS-IV preserves the viability and function of podocytes through SIRT1-dependent inhibition of NF-κB activity [25].

Mesangial cell dysfunction also plays a pivotal role in DN development. Hyperglycemia triggers mesangial cell proliferation and overproduction of extra cellular material (ECM), leading to glomerulosclerosis. AS-IV counteracts these pathological changes by suppressing inflammatory and fibrotic signaling pathways. AS-IV inhibits NF-κB pathway activation and reduces the expression of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in human glomerular mesangial cells subjected to high-glucose incubation [26, 27]. Moreover, AS-IV effectively inhibits the TGF-β1/Smad signaling pathway the canonical driver of renal fibrosis [24]. AS-IV suppresses the synthesis of ECM components such as collagen IV and fibronectin by downregulating the expression of TGF-β1 and preventing the phosphorylation of Smad2/3, which is consistent with experimental results that

AS-IV prevents the diabetic nephropathy via multi-scale regulation [28].

Beyond inflammation and fibrosis, AS-IV also modulates mitochondrial homeostasis and emerging forms of regulated cell death in DN. AS-IV enhances mitochondrial function by regulating the mitochondrial quality control network, including suppression of mitochondrial fission related proteins and downregulation of aberrantly activated PINK1/PARKIN-mediated mitophagy, thereby reducing oxidative stress [29]. The latest studies further indicate that AS-IV alleviates DN by inhibiting ferroptosis, partially through modulation of the gut microbiota [30].

Diabetic retinopathy (DR)

DR is the most frequent microvascular complication of diabetes and remains a leading cause of blindness in adults. DR pathogenesis is characterized by chronic low-grade inflammation, oxidative stress, and pathological neovascularization, which collectively compromise the integrity of the blood-retinal barrier (BRB) and result in gradual vision loss. AS-IV has emerged as a promising therapeutic candidate for delaying DR progression by targeting these key pathological processes, particularly through protecting retina cells and suppressing angiogenic and inflammatory signaling pathways [31].

Retinal pigment epithelial (RPE) cells and retinal ganglion cells are critical for maintaining retinal function. In a diabetic rat model, sustained hyperglycemia induces marked increase in apoptotic RPE cells. AS-IV treatment has been shown to attenuate apoptosis of RPE cells by stimulating the expression of microRNA-128 (miR-128), thereby preserving retinal cellular integrity [32]. Increased miR-128 expression is believed to modulate downstream apoptosis-related target genes, contributing to the maintenance of retinal structure. The protective effects of AS-IV in DR are also closely associated with its anti-inflammatory action. As a potent inhibitor of the NF-κB signaling cascade, AS-IV suppresses the expression of multiple inflammatory mediators in retinal tissues, thereby alleviating the chronic inflammatory milieu that drives retinal injury [27]. These observations are supported by network pharmacology studies which identify inflammation-related targets as central nodes in the therapeutic effects of AS-IV against DR [33].

Pathological neovascularization represents another hallmark of advanced DR and is primarily driven by vascular endothelial growth factor (VEGF). Hyperglycemia and hypoxia synergistically induce excess VEGF production, leading to the formation of fragile and hyperpermeable retinal vessels and subsequent development of macular edema and vitreous hemorrhage. Evidence indicates that AS-IV substantially suppresses the expression of VEGF and its receptor VEGFR2 in diabetic animal models [33, 34]. AS-IV is beneficial in vascular normalization and preservation of BRB integrity by inhibiting VEGF/VEGFR2 signaling. Collectively, the ability of AS-IV to simultaneously protect retinal cells and control inflammation and pathological angiogenesis underscores its therapeutic potential in DR.

Diabetic foot ulcer (DFU)

DFU is a critical complication arising from peripheral neuropathy and peripheral artery disease, characterized by chronic non-healing wounds, persistent inflammation, and frequent secondary infection, and represents a major cause of lower-limb amputation in patients with diabetes [35]. The therapeutic potential of AS-IV in DFU is largely attributable to its dual ability to promote angiogenesis and modulate the local inflammatory microenvironment, thereby facilitating tissue repair [36].

Diabetic wound milieu is characterized by impaired angiogenesis, in which chronic hyperglycemia induces endothelial dysfunction and insufficient neovascularization, resulting in inadequate oxygen and nutrient supply to the wound bed. AS-IV has demonstrated the ability to effectively overcome this deficit by activating pro-angiogenic signaling pathways. Topical AS-IV administration in streptozotocin (STZ)-induced diabetic rat models of DFU significantly enhanced the activation of hypoxia-inducible factor-1α (HIF-1α) along with upregulation of its downstream effector VEGF [35]. This stimulation promotes the endothelial cell proliferation, migration, and tube formation, thereby accelerating neovascularization and restoration of blood supply within the wound tissue. In addition, AS-IV stabilizes HIF-1α and augments its transcriptional activity through activation of the

PI3K/Akt signaling pathway, which is vital for the survival and functioning of endothelial cells in a diabetogenic environment [36].

Beyond angiogenesis, resolution of inflammation is critical for successful wound healing. DFU is characterized by a dysregulated inflammatory response, with predominance of pro-inflammatory M1 macrophages that produce high levels of cytokines (e.g., TNF-α and IL-1β), leading to collateral tissue damage and impaired repair. AS-IV promotes a phenotypic shift from the pro-inflammatory M1 state to the reparative M2 phenotype. Local administration of AS-IV in diabetic mice has been shown to accelerate wound healing along with a marked increase in the abundance of M2 macrophages, as indicated by elevated expression of arginase-1 and CD206 in wound tissues [37]. This immunomodulatory effect is associated with activation of the Nrf2/Heme oxygenase-1 (HO-1) signaling pathway, a key cytoprotective mechanism against oxidative stress and inflammation [38]. Through Nrf2/HO-1 activation, AS-IV enhances antioxidant enzyme expression, promotes M2 macrophage polarization, and stimulates the secretion of anti-inflammatory cytokines (e.g., IL-10) and growth factors, thereby supporting tissue remodeling and wound healing.

Atherosclerosis (AS) and vascular endothelial dysfunction

Endothelial dysfunction triggers atherosclerosis, a chronic inflammatory disease of the arterial wall and represents the major pathological basis of macrovascular complications, including coronary artery disease and stroke, in T2DM. AS-IV exerts a potent vasculoprotective effect by directly targeting the pathophysiological processes of AS, including endothelial cell death and persistent inflammatory signaling that drives plaque development and progression [39]. Critically, beyond its impact on established plaques, AS-IV effectively ameliorates the underlying vascular endothelial dysfunction, a pivotal early event in atherogenesis development. AS-IV enhances endothelial nitric oxide synthase (eNOS) activity and increases nitric oxide (NO) bioavailability, a key mediator of endothelium-dependent vasodilation and vascular homeostasis [40]. Furthermore, it mitigates endothelial oxidative stress by reducing reactive oxygen species (ROS) generation and upregulating antioxidant defenses via activation of the Nrf2 pathway, thereby improving endothelial function [41]. Experimental studies have demonstrated that AS-IV treatment significantly improves endothelium-dependent vasorelaxation in aortic rings from diabetic animals, confirming its direct beneficial effect on vascular endothelial function [42].

Vascular endothelial cells are highly vulnerable to hyperglycemic and dyslipidemic insults, which trigger regulated cell death pathways and compromise barrier integrity. AS-IV has been shown to protect human umbilical vein endothelial cells (HUVECs) against apoptosis induced by oxidized low-density lipoprotein (ox-LDL), a key pathogenic event in AS, primarily through activation of the Nrf2-mediated antioxidant response, thus preserving endothelial viability [39]. In addition, AS-IV potently suppresses pyroptosis, a highly inflammatory form of programmed cell death mediated by inflammasome activation. AS-IV inhibits endothelial pyroptosis by inhibiting activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and downstream cleavage of gasdermin D (GSDMD), the executor of pyroptotic cell death [43, 44]. This is particularly relevant, as endothelial pyroptosis not only disrupts vascular barrier integrity but also amplifies local inflammatory signaling.

Inhibition of the NF-LB/NLRP3 inflammasome axis is an essential part of the anti-atherosclerotic effects of AS-IV. Chronic activation of NF-κB, a master regulator of inflammatory gene expression, is a hallmark in diabetic pathophysiology. AS-IV suppresses NF-κB by inhibiting nuclear translocation of the NF-κB p65 subunit, an effect that is partially mediated through attenuation of Toll-like receptor 4 (TLR4) signaling [45]. Downregulation of NF-κB activity, in turn, inhibits the activation of the NLRP3 inflammasome. Moreover, AS-IV directly interferes with the assembly of the NLRP3 inflammasome complex (NLRP3, ASC, and pro-caspase-1) to prevent the maturation and release of the pro-inflammatory cytokines IL-18 and IL-18 [46]. This dual-level suppression of NLRP3 inflammasome signaling has been validated in both high glucose-treated endothelial cells and in animal models of AS, including ApoE-/- mice, in which AS-IV treatment significantly reduced

atherosclerotic plaque burden and vascular inflammation [47]. Through its coordinated actions on endothelial survival and inflammatory processes, AS-IV preserves vascular homeostasis and delays atherosclerosis progression in the diabetic environment (**Table 1**).

m6A RNA methylation in the pathogenesis of T2DM vascular complications

As a subset of epitranscriptomics, m6A RNA methylation provides a novel insight into post-transcriptional gene regulation that extends beyond conventional genetics and proteomics. m6A is the most common interior modification in eukaryotic mRNA. Its deposition, removal, and recognition are dynamically regulated by methyltransferases ("writers", mainly METTL3/METTL14), demethylases ("erasers", including FTO and ALKBH5), and m6A-binding proteins ("readers", predominantly the YTH domain family) [48, 49]. Increasing evidence indicates that dysregulation of this epitranscriptomic system contributes critically to the pathogenesis of T2DM-associatd vascular complications, including endothelial dysfunction, inflammation, and emerging forms of regulated cell death, highlighting m6A modification as an important yet previously underappreciated regulatory mechanism.

Expression and functional dysregulation of m6A modulators

Aberrant expression and activity of key m6A enzymes are frequently encountered in T2DM vascular complications and triggers a cascade of pathological processes. Among writers, METTL3 is most consistently dysregulated. For example, METTL3 expression is markedly elevated in podocytes in DN, where it promotes podocyte injury by augmenting m6A modification of diabetic transcripts such as TIMP2 and MDM2 [50, 51]. METL14 is upregulated in DR and acts as a well-known mediator of pathological retina neovascularization through m6A-dependent regulation of autophagy-related transcripts [52]. In addition, proteins such as BARD1 stabilize METTL14, thereby exacerbating retinal neovascularization via m6A modification of MXD1 mRNA in a YTHDF2-dependent manner [53].

Erasers that remove m6A alterations are also critically involved. The demethylase ALKBH5 has been identified as a regulatory of microglia polarization in DR by modulating the m6A level of the anti-inflammatory protein A20 [54]. Moreover, recent studies indicate that ferroptosis - an iron-dependent regulated cell death - can be suppressed in the diabetic retina via ALKBH5-mediated regulation of the m6A-YTHDF1-ACSL4 axis [55]. FTO, another important eraser, has been implicated in the development of DN, partly through modulation of NLRP3 inflammasome activity [56]. The pathological relevance of FTO is further reinforced by its established roles in adipogenesis and lipid metabolism, which are central to the overall metabolic dysregulation in T2DM [57, 58].

m6A reader proteins act as critical downstream effectors that translate m6A marks into functional outcomes. YTHDF2 has been shown to be involved in the pathogenesis of DR, by regulating the pyroptosis and autophagy of retinal pigment epithelial cells via the YTHDF2 protein [59]. Also, in the context of diabetic wound healing, YTHDF2 promotes ferroptosis in endothelial progenitor cells by recognizing m6A-modified ACSL4 transcripts, thus hindering tissue repair [60].

m6A-mediated regulation of key pathological processes

Dysregulation of m6A modulators orchestrates core pathological processes in diabetic vascular injury through post-transcriptional regulation of critical genes, focusing particularly on regulated cell death pathways such as pyroptosis and ferroptosis. In DN, METTL3 promotes podocyte pyroptosis via m6A modification of TRIM29 [61] and modulates autophagy through SIRT1-dependent mechanisms [62], while FTO-mediated demethylation of NLRP3 directly links m6A regulation to inflammatory progression [56]. Furthermore, ferroptosis in DN is enhanced via the METTL3/YTHDF3 axis by stabilizing transferrin receptor (TFR1) mRNA [63, 67]. In macrovascular complications, METTL3 facilitates atherosclerosis through the JAK2/STAT3 pathway [65] and is essential for smooth muscle cell function [66]. Simultaneously, m6A remodeling of the SLC7A11 transporter in macrophages promotes atherosclerotic progression [67], supported by FTO-mediated regulation of autophagy and macrophage polarization [68, 69]. Regarding DFU, bioinformatic

Table 1. Classic protective mechanisms of Astragaloside IV in T2DM-asssociated vascular complications

Complication	Target Cells/Tissues	Key Signaling Pathways	Main Protective Mechanisms	Ref.
DN	Podocytes, mesangial cells, tubular epithelial cells	SIRT1/NF-κB, TGF-β1/Smad, Nrf2, PINK1/Parkin, gut microbiota-ferroptosis axis	Inhibits apoptosis, EMT, inflammation, fibrosis, oxidative stress, and ferroptosis; enhances autophagy and mitochondrial homeostasis	[24-30]
DR	Retinal pigment epithelial cells, retinal ganglion cells, vascular endothelium	NF-κB, VEGF/VEGFR2, miR-128	Anti-apoptotic, anti-inflammatory, anti-angiogenic; preserves blood-retinal barrier	[31-34]
DFU	Endothelial cells, keratinocytes, macrophages	HIF-1α/VEGF, PI3K/Akt, Nrf2/HO-1	Promotes angiogenesis, endothelial cell survival, macrophage M2 polarization, and wound healing	[35-38]
AS & Endothelial Dysfunction	Endothelial cells, vascular smooth muscle cells, macrophages	Nrf2, NLRP3 inflammasome/NF-κB, TLR4	Antioxidant, anti-apoptotic, anti-inflammatory; inhibits pyroptosis and plaque progression	[39-47]

Notes: AS, Atherosclerosis; DFU, Diabetic Foot Ulcer; DN, Diabetic Nephropathy; DR, Diabetic Retinopathy; EMT, Epithelial-mesenchymal transition; HIF-1α, Hypoxia-inducible factor-1 alpha; HO-1, Heme oxygenase-1; miR-128, microRNA-128; NF-κB, Nuclear Factor-kappa B; NLRP3, NOD-like receptor family pyrin domain containing 3; Nrf2, Nuclear factor erythroid 2-related factor 2; PI3K/Akt, Phosphatidylinositol 3-kinase/Protein Kinase B; PINK1, PTEN-induced kinase 1; SIRT1, Sirtuin 1; T2DM, Type 2 Diabetes Mellitus; TGF-β1, Transforming Growth Factor-beta 1; TLR4, Toll-like receptor 4; VEGF, Vascular endothelial growth factor; VEGFR2, Vascular endothelial growth factor receptor 2.

Table 2. Dysregulation of m6A regulators in T2DM-associated vascular complications

m6A Regulator	Type	Alteration in Complications	Target Gene/Pathway	Complication	Ref.
METTL3	Writer	Upregulated in podocytes; promotes injury, pyroptosis, ferroptosis	TIMP2, MDM2, TRIM29, SIRT1, TfR1	DN	[50, 51, 61-64]
METTL3	Writer	Promotes angiogenesis and atherosclerosis via JAK2/STAT3; essential for VSMC function	JAK2/STAT3, SLC7A11	AS	[65-67]
METTL14	Writer	Upregulated; mediates pathological retinal neovascularization	Autophagy-related transcripts, MXD1	DR	[52, 53]
FTO	Eraser	Regulates NLRP3 inflammasome activation; influences lipid metabolism	NLRP3, Nrf2	DN, AS	[56-58, 62]
ALKBH5	Eraser	Modulates microglial polarization; inhibits ferroptosis	A20, ACSL4	DR	[54, 55]
YTHDF2	Reader	Mediates RPE cell pyroptosis and autophagy; regulates ferroptosis in endothelial cells	ACSL4	DR, DFU	[59, 60]

Notes: ACSL4, Acacyl-CoA synthetase long-chain family member 4; ALKBH5, AlkB homolog 5; AS, Atherosclerosis; DFU, Diabetic Foot Ulcer; DN, Diabetic Nephropathy; DR, Diabetic Retinopathy; FTO, Fat mass and obesity-associated protein; m6A, N6-methyladenosine; MDM2, Mouse double minute 2 homolog; METTL3/14, Methyltransferase-like 3/14; MXD1, MAX dimerization protein 1; NLRP3, NOD-like receptor family pyrin domain containing 3; Nrf2, Nuclear factor erythroid 2-related factor 2; RPE, Retinal pigment epithelial; SIRT1, Sirtuin 1; SLC7A11, Cystine/glutamate transporter; TfR1, Transferrin receptor 1; TIMP2, Tissue inhibitor of metalloproteinases 2; TRIM29, Tripartite motif-containing 29; VSMC, Vascular smooth muscle cell; YTHDF2, YTH domain family, member 2.

analyses have revealed significant changes in ferroptosis-related genes [70, 71], with YTHDF2 specifically regulating ACSL4-dependent ferroptosis in endothelial progenitor cells to hinder wound healing [63]. The interplay between these m6A-controlled ferroptosis and pyroptosis pathways constitutes a broader regulatory network across T2DM-associated vascular complications [72, 73], establishing m6A RNA methylation as a central hub for integrating pathological signals in diabetic vascular disease [54-59] (**Table 2**).

A novel perspective: m6A RNA methylation as a key mediator for the vascular protective effects of AS-IV

Given the central role of m6A RNA methylation in the pathogenesis of T2DM associated vascular complications, an emerging and critical issue is whether the vasculoprotective effects of AS-IV are mediated, at least in part, through modulation of this epitranscriptomic layer. Recent studies have started to reveal this previously unrecognized dimension of AS-IV pharmacology, indicating that AS-IV functions as a potent regulator of the m6a landscape (**Figure 2**).

AS-IV directly modulates the m6A regulatory machinery

Accumulating evidence suggests that AS-IV directly interacts with and regulates key components of the m6A machinery, contributing to its protective effects against diabetic vascular injury. Through this, AS-IV fine-tunes gene expression to counteract pathological processes underlying diabetic complications.

This mechanism is exemplified in DFU, where AS-IV accelerates wound healing through modulation of the METTL3-SIRT1 axis. A 2025 study demonstrated that AS-IV upregulates the expression of the m6A writer, METTL3, in glucose-challenged human keratinocytes, leading to increased m6A modification of SIRT1 mRNA. This modification enhances SIRT1 mRNA stability and elevates SIRT1 protein expression Notably, SIRT1 is a prime metabolic sensor previously identified as a target of AS-IV-mediated protection in podocytes [25]. In keratinocytes, elevated SIRT1 promotes keratinocyte proliferation and migration, eventually facilitating wound healing in a DFU animal model [74]. To further support this conclusion, a study on Astragalus polysaccharide (APS), another bioactive component of Astragalus, reported that APS alleviated DKD by inhibiting METTL3, thereby reducing m6A modification of SIRT1 mRNA and activating the SIRT1/FOXO3a signaling pathway, which enhanced podocyte autophagy and mitigated kidney damage [75].

In diabetic retinopathy (DR), AS-IV appears to exert its effects primarily through modulation of the m6A eraser FTO. A 2025 study showed that AS-IV inhibited FTO activity and expression in a model of RPE cell senescence. This inhibition altered the m6A methylation status of IL-1β mRNA, resulting in reduced mRNA stability and diminished IL-1β expression. By suppressing this potent pro-inflammatory cytokine, AS-IV effectively attenuated RPE cell senescence and retinal aging in vivo, pathological features closely relevant to DR development [76]. Collectively, these findings demonstrate that AS-IV can remodel the m6A epitranscriptome by targeting both writers and erasers in a situation-specific way.

Interplay with traditional pathways and future directions

Elucidation of the AS-IV-m6A regulatory axis represents a major conceptual advance; however, this rapidly evolving field still faces several unresolved questions. A primary limitation of the existing studies is its predominant focus on two m6A regulators, FTO and METTL3. Whether AS-IV is capable of modulating other critical components of the m6A machinery, particularly the demethylase ALKBH5 or members of the diverse m6A reader protein families, remains largely unexplored.

Additionally, a major knowledge gap concerns the role of the AS-IV-m6A axis in macrovascular complications, especially atherosclerosis. Although AS-IV is known to exert anti-atherosclerotic effects [39, 47], direct experimental evidence linking these protective actions to m6A-dependent mechanisms is currently lacking. Nevertheless, insights from related natural compounds provide a compelling rationale for this hypothesis. For example, leonurine has been shown to attenuate atherosclerosis by inhibiting METTL3-mediated m6A modification of AKT1S1 mRNA in macrophages [77]. Given the shared mechanisms of leonurine and AS-IV

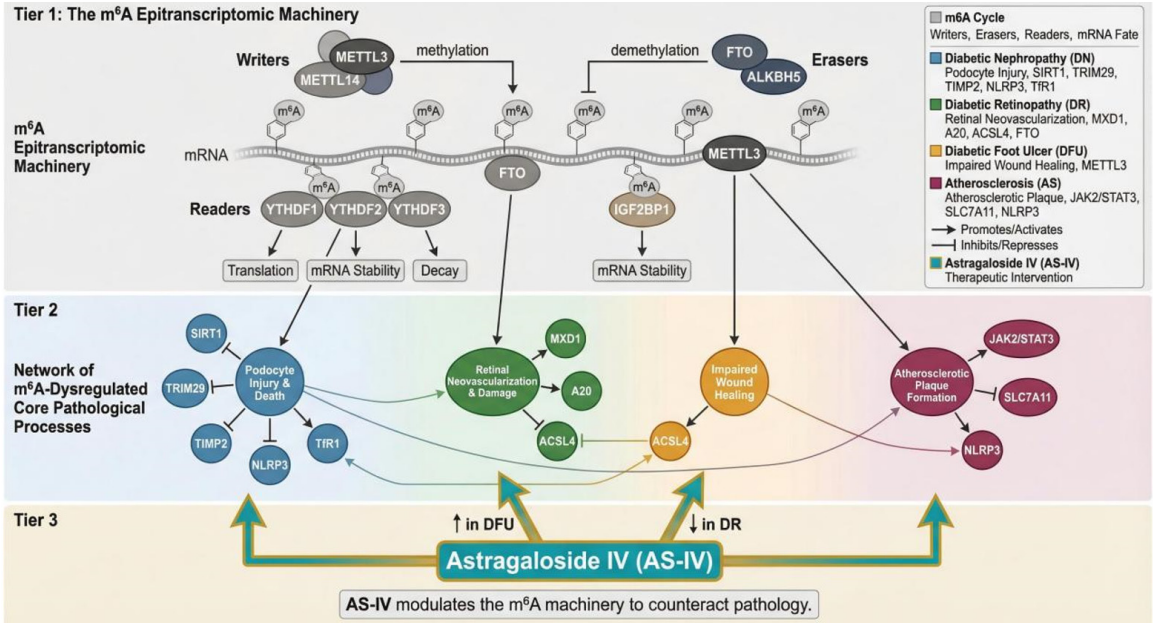

Figure 2. m6A epitranscriptomic regulation as a central hub linking vascular complications of T2DM and the therapeutic actions of AS-IV. Tier 1: The m6A epitranscriptomic machinery. The top panel demonstrates the dynamic and reversible regulation of m6A modification on mRNA. m6A "writers" catalyze methylation, "erasers" remove methylation, and "readers" recognize m6A-modified transcripts to regulate mRNA stability, translation, splicing, or decay. Tier 2: m6A-mediated regulation of core pathological processes in T2DM vascular complications. The middle panel summarizes representative m6A regulators and their downstream targets across four major complications. In DN, dysregulated m6A signaling-such as YTHDF2-mediated transcript regulation-contributes to podocyte injury. In DR, m6A-dependent regulation of angiogenesis involves factors such as MXD1 and is influenced by modulators including METTL14 and associated regulatory proteins. In DFU, METTL3-mediated m6A modification affects wound healing and ferroptosis, partly through regulation of ACSL4. In AS, METTL3 promotes plaque progression via pathways including JAK2/STAT3 signaling and NLRP3 inflammasome activation. Tier 3: Therapeutic modulation by AS-IV. The lower panel highlights AS-IV as an epitranscriptomic modulator capable of restoring m6A homeostasis in diabetic vascular disease. By regulating the expression or activity of specific m6A enzymes (e.g., upregulation of METTL3 in DFU or inhibition of FTO in DR), AS-IV counteracts pathological gene expression programs and mitigates vascular injury. Notes: m6A, N6-Methyladenosine; T2DM, Type 2 Diabetes Mellitus; DN, Diabetic Nephropathy; DR, Diabetic Retinopathy; DFU, Diabetic Foot Ulcer; AS, Atherosclerosis; m6A, N6-methyladenosine; YTHDF2, YTH Domain Family Protein 2; ACSL4, Acyl-CoA Synthetase Long-Chain Family Member 4; ALKBH5, AlkB Homolog 5; METTL3, Methyltransferase-Like 3; METTL14, Methyltransferase-Like 14; MXD1, MAX Dimerization Protein 1; JAK2, Janus Kinase 2; STAT3, Signal Transducer and Activator of Transcription 3; FTO, Fat Mass and Obesity-Associated Protein.

in modulating inflammatory and metabolic pathways, it is plausible that AS-IV may exert similar anti-atherosclerotic effects through an epitranscriptomic mechanism.

A particularly promising research direction lies in the interaction between m6A-mediated regulation and the classical signaling pathways already known to be targeted by AS-IV. Among these, the Nrf2 antioxidant signaling pathway represents a key intersection point. AS-IV is a well-established activator of Nrf2 signaling [38, 39]. Interestingly, m6A eraser FTO was reported to regulate Nrf2 expression through demethylating its mRNA [78]. Therefore, it is possible that AS-IV enhances its antioxidant efficacy through coordinated activation of Nrf2 at the protein level and stabilization of Nrf2 mRNA through inhibition of FTO-mediated demethylation. Confirmation of this crosstalk may offer a more integrated apprehension of the multi-target therapeutic efficacy of AS-IV [79].

Finally, the most challenging yet critical step is the clinical translation of these preclinical findings. Validation of the AS-IV-m6A regulatory mechanisms in more sophisticated disease models and ultimately in humans is essential. To sum up, despite substantial progress, further multidisciplinary research is needed to realize the therapeutic potential of targeting the AS-IV-m6A axis.

Conclusion and perspectives

This review integrates current evidence on AS-IV as a therapeutic agent for vascular complications of T2DM, bridging its conventional pharmacological activities and the emerging field of epitranscriptomics. Evidence suggests that the protective effects of AS-IV extend beyond its canonical actions and are closely associated with the modulation of m6A RNA methylation, which may represent a novel mechanism underlying its vascular protective effects. Directly targeting key m6A regulators, such as the writer METTL3 and the eraser FTO, AS-IV modulates the expression of critical genes such as SIRT1 or IL-1β, thereby attenuating diabetic vascular injury at the post-transcriptional level. This AS-IV-m6A regulatory axis represents an influential, yet previously underappreciated mechanism that combines the anti-inflammatory, anti-senescence, and pro-regenerative activities of AS-IV into a unified molecular framework. As a natural product-derived agonist of m6A methylation, AS-IV exhibits considerable translational potential and offers a novel pharmacological scaffold for the development of epitranscriptome-targeted therapies in metabolic diseases.

Nevertheless, this field remains in its preliminary stage, and several key issues warrant further investigation. First, the spectrum of m6A regulators influenced by AS-IV should be expanded beyond METTL3 and FTO to include more erasers, writers, and the functionally diverse reader proteins (such as ALKBH5 or the YTH family). Second, there is still a major knowledge gap in the role of AS-IV-m6A axis in macrovascular complications and macrovascular diseases, particularly atherosclerosis. Third, future studies should clarify the interactions between m6A-mediated regulation and the canonical signaling pathways modulated by AS-IV, including the Nrf2 antioxidant pathway, to establish an integrated mechanistic framework.

Furthermore, evaluating the therapeutic potential of combining AS-IV with traditional glucose-lowering drugs, such as metformin or sodium-glucose cotransporter-2 (SGLT2) inhibitors, represents a promising clinical direction. Such combination strategies may confer synergistic benefits by simultaneously addressing systemic metabolic dysregulation and local epitranscriptomic dysregulation. Addressing these questions will not only refine mechanistic understanding but also facilitate the development of new AS-IV derivatives or rational combination therapies tailored to modulate the m6A epitranscriptome. Continued investigation of this nexus contribute to the development of innovative therapies for T2DM-associated vascular complications.

Disclosure of conflict of interest

None.

Address correspondence to: Liping Yin, Department of Endocrinology, Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, No. 39, Shierqiao Road, Jinniu District, Chengdu 610075, Sichuan, China. Tel: +86-028-87783481; E-mail: as161708@163.com

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