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REVIEW

A Review of the Mechanisms of Astragaloside IV and Berberine in Vascular Dysfunction Associated with Obesity and Diabetes

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Abstract: The global epidemic of obesity and diabetes imposes a significant strain on healthcare systems, substantially elevating the risk of vascular dysfunction and its associated complications. Astragaloside IV (AS-IV) and berberine (BBR) have demonstrated considerable promise in addressing vascular issues linked to these conditions. This review examines the mechanisms driving their vascular protective effects, drawing on evidence from preclinical studies to compare and contrast their modes of action. It explores both the unique and overlapping pathways through which they mitigate the complications of obesity and diabetes. A thorough analysis of their therapeutic potential highlights promising preclinical data and its clinical implications. However, challenges remain, such as enhancing the bioavailability of AS-IV and BBR and translating preclinical findings into robust clinical trials. This synthesis provides critical insights for advancing research and practical approaches in managing vascular dysfunction associated with obesity and diabetes.

Keywords: astragaloside IV, berberine, vascular dysfunction, diabetes, obesity, complications

Introduction

The global prevalence of obesity and diabetes has reached epidemic levels, posing significant public health challenges and placing substantial strain on healthcare systems. According to The Lancet, nearly 880 million adults were classified as obese in 2022, marking a 4.5-fold increase since 1990.[1] Meanwhile, the International Diabetes Federation reported that approximately 537 million adults were living with diabetes in 2021, with this number expected to rise sharply in the coming years.[2] Both obesity and diabetes contribute to a range of severe health complications, including cardiovascular diseases, diabetic retinopathy, nephropathy, encephalopathy, and neuropathy, leading to significant increases in morbidity and mortality.

Vascular dysfunction, a key underlying factor in the pathogenesis of these complications, is common and often an early feature in both obesity and diabetes.[3–5] Characterized by impaired endothelial function, abnormal vascular remodeling, and chronic inflammation, vascular dysfunction disrupts the homeostatic balance between vasodilation and vasoconstriction, coagulation, and fibrinolysis, as well as pro-inflammatory and anti-inflammatory responses.[6,7] In obesity, excessive adipose tissue promotes vascular dysfunction through the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[8] These cytokines drive oxidative stress and endothelial damage while reducing the bioavailability of nitric oxide (NO), essential for vascular relaxation and homeostasis.[9,10] Insulin resistance, a hallmark of obesity, exacerbates endothelial dysfunction by impairing insulin-mediated NO

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production and promoting vasoconstriction.[11] Clinical evidence from a cross-sectional study (N = 8,823) reveals significant associations between abdominal obesity (quantified by the A Body Shape Index) and endothelial dysfunction, evidenced by inverse correlations with flow-mediated vasodilation (men: r = −0.23, P = 0.003; women: r = −0.32, P < 0.001).[12] Similarly, diabetes accelerates vascular damage via hyperglycemia-induced mechanisms, such as advanced glycation end-product (AGE) formation, increased oxidative stress, and the activation of inflammatory pathways.[13–15] Hyperglycemia also triggers endothelial cell apoptosis and impairs vascular repair processes, leading to progressive damage in both macrovascular and microvascular systems.[16,17] A population-level analysis (N = 1,384) highlights the vascular effects specific to diabetes, with diagnosed patients exhibiting a 42% prevalence of endothelial dysfunction and significantly lower reactive hyperemia index (RHI) values compared to 23% in normoglycemic controls.[18] The interplay between obesity and diabetes exacerbates vascular dysfunction. For instance, obesity-induced insulin resistance amplifies the harmful effects of hyperglycemia on endothelial cells, while diabetes-related vascular damage worsens the pro-inflammatory state triggered by obesity. This vicious cycle underscores the critical importance of targeting vascular dysfunction in the management of obesity and diabetes.

Current pharmacological therapies, including GLP-1 agonists, SGLT2 inhibitors, and metformin, have demonstrated clinical benefits in managing obesity- and diabetes-associated vascular complications through mechanisms such as glycemic control, anti-inflammatory actions, and oxidative stress reduction. However, challenges such as hypoglycemia risk (particularly with intensive insulin therapy), gastrointestinal side effects and variable cost-effectiveness in long-term use remain unresolved.[19–21] These limitations emphasize the urgent need for safer, cost-effective, and multi-target alternatives to address these complex vascular complications. Natural bioactive compounds, particularly astragaloside IV (AS-IV) and berberine (BBR), have emerged as promising candidates. Notably, emerging clinical evidence supports their translational potential: a randomized controlled trial showed that BBR supplementation (0.4 g, three times daily for one month) significantly improved endothelial function, as assessed by flow-mediated dilation (FMD).[22] Furthermore, an ongoing clinical trial (Registration number: ITMCTR2025000262) is investigating the efficacy of an AS-IV-containing herbal formulation in reducing carotid intima-media thickness in individuals with early-stage carotid plaque. Preclinical studies have demonstrated that AS-IV enhances insulin sensitivity, regulates lipid metabolism, and reduces oxidative stress.[23,24] In animal models of diabetic vasculopathy, BBR mitigated vascular inflammation and improved microvascular perfusion.[25] Despite the growing body of evidence supporting the benefits of AS-IV and BBR, a significant gap remains in the literature regarding a comprehensive analysis of their specific mechanisms in the context of obesity- and diabetes-induced vascular dysfunction. This review aims to address this gap by consolidating the latest research on the therapeutic potential of AS-IV and BBR in managing vascular complications associated with obesity and diabetes. By synthesizing current insights and exploring emerging therapeutic pathways, this study provides a robust foundation for future investigations, underscoring the promise of natural compounds in alleviating vascular dysfunction and improving health outcomes for affected populations.

Latest Findings on AS-IV and BBR in the Treatment of Vascular Dysfunction Associated with Obesity and Diabetes

Astragaloside IV

AS-IV, a bioactive saponin primarily extracted from *Astragalus membranaceus* ("Huangqi" in Chinese), with the molecular formula $C_{41}H_{68}O_{14}$,[26] exhibits considerable therapeutic potential in treating obesity- and diabetes-related vascular dysfunction. This is attributed to its anti-inflammatory, anti-apoptotic, antioxidant, and autophagy-enhancing properties, as well as its ability to promote vasodilation, enhance angiogenesis, inhibit cell proliferation, improve cytoskeletal remodeling, and regulate metabolic processes (Figure 1 and Table 1).

In streptozotocin (STZ)-induced diabetic rats, AS-IV improved endothelial function by upregulating endothelial nitric oxide synthase (eNOS) and NO levels, facilitating vasodilation, and reducing pro-inflammatory cytokines such as IL-6 and TNF-α. TLR4, a key member of the toll-like receptor family, activates the classical TLR4/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, leading to NF-κB p65 translocation into the nucleus and promoting the secretion of pro-inflammatory cytokines. This pathway also activates the NLR family pyrin domain

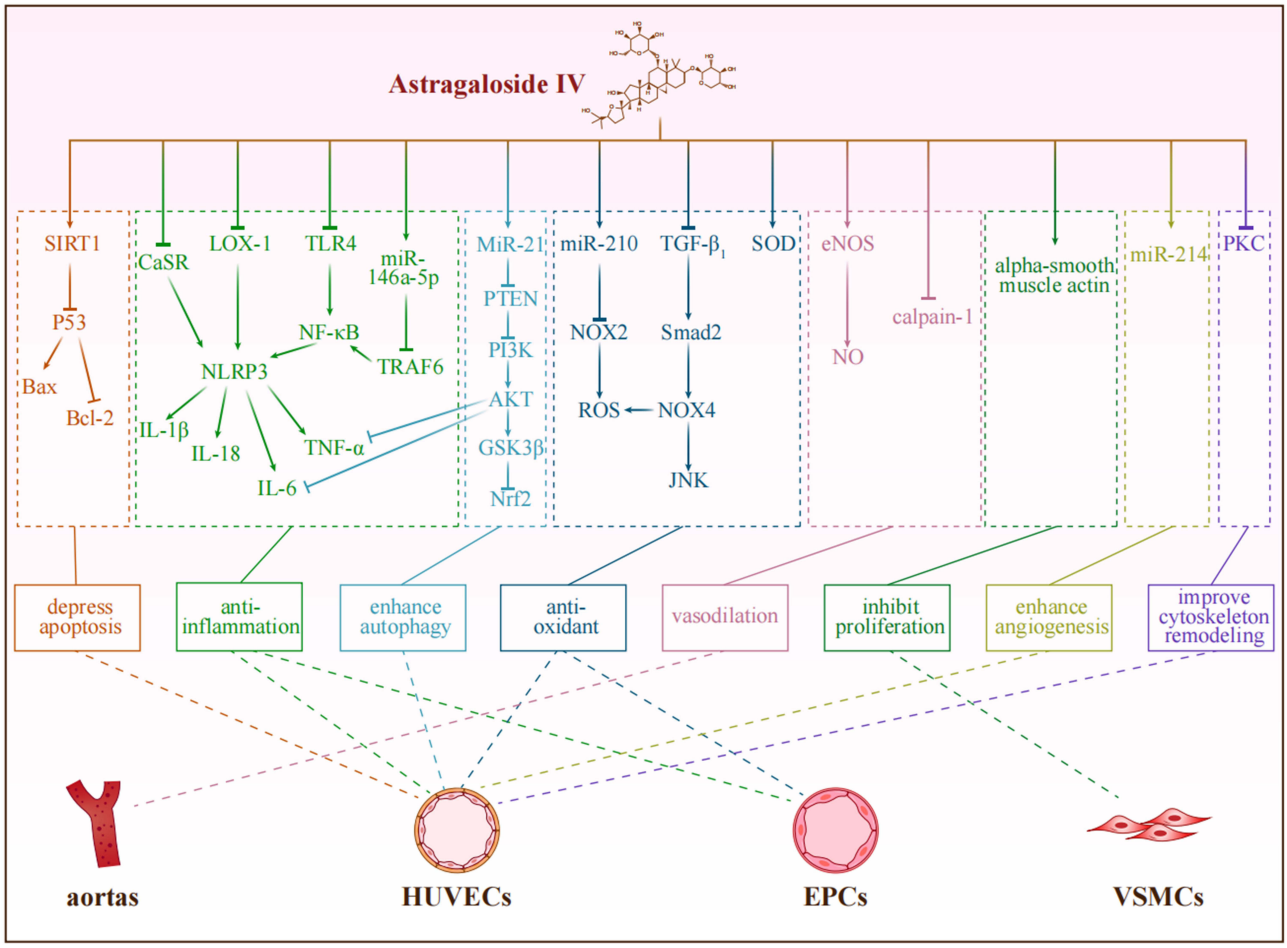

Figure 1 Summary of the biological effects of AS-IV in various vascular cell models. Previous studies have investigated the mechanisms of AS-IV in addressing vascular dysfunction using models such as aortas, human umbilical vein endothelial cells (HUVECs), Endothelial progenitor cells (EPCs), and vascular smooth muscle cells (VSMCs). AS-IV has been shown to suppress apoptosis, reduce inflammation, enhance autophagy, exhibit antioxidant properties, promote vasodilation, inhibit proliferation, support angiogenesis, and improve cytoskeletal remodeling. Symbol key: Activation is indicated by arrow lines (→), inhibition by blocker lines (—|).

Abbreviations: HUVECs, human umbilical vein endothelial cells; EPCs, Endothelial progenitor cells; VSMC, vascular smooth muscle cell; SIRT1, sirtuin 1; Bax, BCL2-associated X; Bcl-2, B-cell lymphoma-2; CaSR, calcium-sensing receptor; LOX-1, lectin-like oxidized LDL receptor; NLRP3, NLR family pyrin domain containing 3; TLR4, Toll-like receptor-4; NF-kB, Nuclear factor kappa-light-chain-enhancer of activated B cells; TRAF6,TNF receptor associated factor 6; IL-1β, interleukin 1β; TNF-α, tumor necrosis factor; PTEN, phosphatase and tensin homolog; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; GSK 3β, glycogen synthase kinase-3 β; Nrf2, nuclear factor E2-related factor 2; Nox2, NADPH oxidase 2; ROS, reactive oxygen species; TGF-β1, transforming growth factor-β1; Smad2, mothers against decapentaplegic homolog 2; JNK, c-Jun N-terminal kinase; SOD, superoxide dismutase; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PKC, protein kinase C.

containing 3 (NLRP3) inflammasome.[44] Similarly, the calcium-sensing receptor (CaSR), a G protein-coupled receptor, plays a significant role in regulating inflammation and activating the NLRP3 inflammasome.[45] AS-IV alleviated endothelial dysfunction by downregulating TLR4 expression, inhibiting NF-κB p65 translocation, and reducing adhesion molecules (ICAM-1, VCAM-1) levels.[27] Furthermore, AS-IV suppressed the NLRP3 inflammasome by downregulating

Table 1 Overview of Astragaloside IV on Vascular Dysfunction Related to Obesity and Diabetes

References	Model	Inducer	Experimental Model	Molecular mechanism
Leng, Bin et al (2018)[27]	Diabetes	STZ/HG	Thoracic aortas of rats	Inhibit TLR4/NF-κB signaling pathway
		HG	HUVECs	

(*Continued*)

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Table 1 (Continued).

References	Model	Inducer	Experimental Model	Molecular mechanism
Nie, Qu et al (2019)[28]	Diabetes	STZ	Thoracic aortas of rats	Reduce oxidative stress, downregulate calpain-1 and improve eNOS/NO signaling.
		HG	HUVECs	
Yuan, Wei et al (2008)[29]	Diabetes	HG	VSMCs	Inhibit proliferation
Leng, Bin et al (2019) [30]	Diabetes	STZ	rats	Inhibit TLR4/NF-κB signaling pathway and CaSR
		HG	HUVECs	
Qian, Weibin et al (2019)[31]	Diabetes	ox-LDL	EPCs	Inhibit lox-1/nlrp3 pathway
Zou, Xiaoling et al (2020)[32]	Diabetes	HG	HUVECs	Promote the expression of miR-214
Xiong, Wu et al (2022)[33]	Diabetes	HG	HUVECs	Enhance autophagy and depress apoptosis; miR-21/PTEN axis
Chen, Jiye et al (2024)[34]	Diabetes	HG	HUVECs	Increase miR-146a-5p; inhibit TRAF6/NF-κB pathway
Xiong, Wu et al (2024)[35]	Diabetes	HG	HUVECs	miR-210/Nox2/ROS pathway
Li, Han-Bing et al (2006)[36]	Diabetes	HG	HUVECs	Inhibit PKC activation; stabilize the endothelial cell cytoskeleton
Wu, Hui et al (2016)[37]	Obesity	HFD	C57BL/6 mice	Improve lipid metabolism; enhance leptin sensitivity and modulate thermogenic network
		/	The leptin receptor deficient db/db mice	
		/	Neuronal cell line SH-SY5Y cells	
Jiang, Boren et al (2008)[38]	Obesity	TNF-α	3T3-L1 adipocytes	Decrease FFA levels; increase insulin sensitivity
You, Liangzhen et al (2019)[39]	diabetes	HG	HUVECs	Reduce cell apoptosis and inflammation; inhibit the JNK signaling pathway and mitochondria-mediated apoptosis pathway
Ma, Yuhong et al (2015)[40]	Diabetes	H2O2	HUVECs	Decrease Nox4 expression through the TGF-β1/Smad2 signaling pathway
Guo, Xuxi et al (2023)[41]	Obesity	PA + glucose + BSA	Adipocytes	Reduce IR and inflammation; through the miR- 21/PTEN/PI3K/Akt signaling pathway
Zhang, Yue et al (2022)[42]	Diabetes	PA + glucose + BSA	Adipocytes	Attenuate IR and inflammation via targeting CTRP3/PI3K/Akt signaling pathway
Lin, Yuqiong et al (2022)[43]	Diabetes	STZ	Pancreatic β-cell line INS-1	Alleviate oxidative stress, apoptosis and cell dysfunction; through the SIRT1/p53 and Akt/GSK3β/Nrf2 signaling pathways.

Abbreviations: STZ, streptozotocin; HG, high-glucose; HUVECs, human umbilical vein endothelial cells; TLR4, Toll-like receptor-4; NF-kB, Nuclear factor kappa-light-chain -enhancer of activated B cells; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; VSMC, vascular smooth muscle cell; CaSR, calcium-sensing receptor; ox-LDL, oxidized low-density lipoprotein; LOX-1, lectin-like oxidized LDL receptor; NLRP3, NLR family pyrin domain containing 3; PTEN, phosphatase and tensin homolog; TRAF6, TNF receptor associated factor 6; Nox2, NADPH oxidase 2; ROS, reactive oxygen species; PKC, protein kinase C; HFD, high-fat diet; TNF-α, tumor necrosis factor; FFA, free fatty acid; JNK; c-Jun N-terminal kinase; TGF-β1; transforming growth factor-β1; Smad2, mothers against decapentaplegic homolog 2; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; PA, palmitic acid; IR, insulin resistance; BSA, bovine serum albumin; CTRP3, C1q tumor necrosis factor-related protein 3; GSK 3β, glycogen synthase kinase-3 β; Nrf2, nuclear factor E2-related factor 2.

cytokines (IL-1β, IL-18) through inhibition of both the TLR4/NF-κB pathway and CaSR.[30] In high-glucose (HG)-treated endothelial cells, AS-IV reduced pro-inflammatory cytokine secretion and enhanced mesenchymal stem cell (MSC)-derived exosomal miR-146a-5p expression, improving cell viability and reducing inflammation by targeting TNF receptor-associated factor 6 (TRAF6) and NF-κB phosphorylation.[34]

Beyond its anti-inflammatory effects, AS-IV exhibited significant anti-apoptotic benefits in HG-treated human umbilical vein endothelial cells (HUVECs) by reducing the Bax/Bcl-2 ratio and suppressing mitochondrial apoptotic markers, including Cyt-c, cleaved-caspase-9, and cleaved-caspase-3.[39] AS-IV also protected pancreatic β-cells from STZ-induced apoptosis by modulating the SIRT1/p53 pathway, essential for regulating apoptosis under stress. SIRT1, a NAD +-dependent deacetylase, deacetylates p53, preventing p53-mediated apoptosis and promoting cell survival.[46] AS-IV activated SIRT1, which suppressed p53-mediated apoptosis by increasing the expression of the anti-apoptotic protein Bcl-2 and decreasing the levels of pro-apoptotic proteins such as Bax and caspase-3.[43] AS-IV further promoted autophagy, a critical process for cellular survival under stress, by upregulating autophagic markers LC3II/I and ATG5. LC3II/I facilitates autophagosome formation, while ATG5 plays a pivotal role in autophagosome maturation, together supporting the clearance of damaged cellular components.[33] Additionally, AS-IV exerted potent antioxidant effects by modulating the protein kinase B (Akt)/GSK3β/Nuclear factor erythroid 2–related factor 2(Nrf2) signaling axis. The Akt/GSK3β pathway is involved in cell survival and metabolic regulation, while Nrf2, a key transcription factor, regulates the expression of antioxidant enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px).[43]

AS-IV also promoted angiogenesis and reinforced endothelial barrier function through multiple mechanisms. Endothelial progenitor cells (EPCs), essential for vascular repair and regeneration, play a critical role in angiogenesis.[47] In HG-treated EPCs, exosomes derived from AS-IV-treated cells enhanced tube formation and upregulated miR-214, a microRNA known to activate angiogenic signaling by modulating the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and increasing the expression of angiopoietin-1, a protein vital for endothelial cell maturation and vascular integrity.[32] AS-IV regulated the miR-210/Nox2/reactive oxygen species (ROS) axis in EPCs, where miR-210, involved in hypoxic responses, reduced oxidative stress by modulating Nox2 and ROS production. This action further promoted angiogenesis and vascular regeneration.[35] Additionally, AS-IV stabilized the endothelial barrier by modulating the dynamics of filamentous actin (F-actin), which is essential for maintaining cell structure and integrity. It inhibited protein kinase C (PKC) translocation, a process that can disrupt endothelial function and barrier permeability, thereby enhancing vascular stability.[36] In STZ-induced diabetic models and HG-treated endothelial cells, AS-IV restored endothelial function by increasing eNOS levels and reducing calpain-1, an enzyme associated with endothelial dysfunction.[28]

In metabolic regulation, AS-IV improved glucose and lipid metabolism in high-fat diet (HFD)-fed models by reducing triglyceride and cholesterol levels and enhancing thermogenesis. This was achieved through upregulation of genes such as peroxisome proliferator-activated receptor alpha (PPARα) and uncoupling protein 1 (UCP1), which are involved in fat oxidation and energy expenditure.[37] AS-IV alleviated leptin resistance and regulated adipocyte lipolysis, stabilizing lipid storage and mitigating TNF-α-induced disruptions.[38] Phosphatase and tensin homolog (PTEN) plays a pivotal role in regulating cellular metabolism and autophagy by modulating the PI3K/Akt signaling pathway.[48] In insulin-resistant adipocytes, AS-IV enhanced glucose consumption, increased glucose transporter type 4 (GLUT-4) expression, and improved insulin sensitivity through PTEN inhibition and PI3K/Akt activation.[41]

Berberine

BBR, a quaternary ammonium alkaloid primarily extracted from *Coptis chinensis Franch*. ("Huanglian" in Chinese), with the molecular formula $[C_{20}H_{18}NO_4]^+$,[49] exhibits a broad spectrum of beneficial biological activities in treating vascular dysfunction associated with obesity and diabetes. These include inhibiting AGE formation, promoting vasodilation, anti-apoptosis, anti-inflammation, antioxidant effects, enhancing autophagy, improving glucose and lipid metabolism, and enhancing insulin sensitivity (Figure 2 and Table 2).

BBR improved vascular function in HFD- and STZ-induced diabetic rats by enhancing NO bioavailability, crucial for maintaining endothelial function and vascular tone. It increased serum NO levels and promoted endothelium-dependent relaxation, primarily through upregulation of eNOS expression.[51] BBR also reduced oxidative stress by downregulating

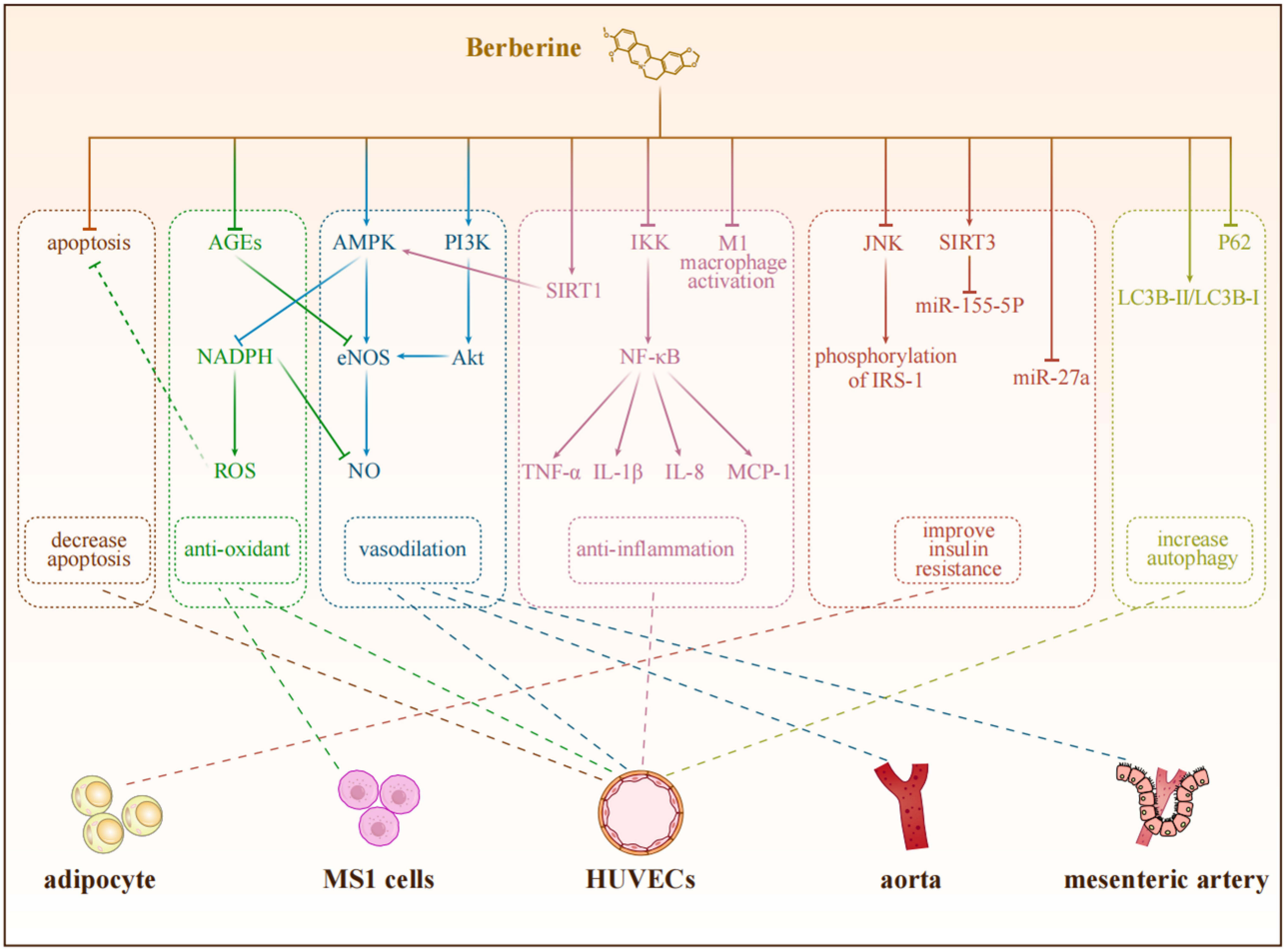

Figure 2 Summary of the biological effects of BBR in various vascular cell models. Previous studies have investigated the mechanisms of BBR in alleviating vascular dysfunction using models such as adipocytes, MS1 cells, HUVECs, aortas, and mesenteric arteries. BBR has been shown to suppress apoptosis, exhibit antioxidant and anti-inflammatory effects, promote vasodilation, improve insulin resistance, and enhance autophagy. Symbol key: Activation is indicated by arrow lines (→), inhibition by blocker lines (—|).

Abbreviations: AGEs, advanced glycation end products; AMPK, AMP-activated protein kinase; IKK, IκB kinase; MCP-1, monocyte chemotactic protein-1; JNK, c-Jun N-terminal kinase.

Nox4, a subunit of NADPH oxidase, which contributes to the production of ROS and endothelial dysfunction in diabetes.[54] Furthermore, BBR significantly inhibited AGE formation, improving HG-induced endothelial cell injury in microvascular models.[50] In palmitate or HG-treated HUVECs, BBR similarly enhanced eNOS activation and NO production through the AMP-activated protein kinase (AMPK) pathway.[52,54] AMPK, a critical regulator of cellular energy balance, when activated, increases eNOS activity, thereby contributing to NO production and improving endothelial function.[61] In diabetic rats, BBR also enhanced acetylcholine-induced vasodilation in mesenteric arteries

Table 2 Overview of berberine on Vascular Dysfunction Related to Obesity and Diabetes

References	Model	Inducer	Experimental Model	Molecular Mechanism
Hao, Min et al (2011)[50]	Diabetes	HG+ AGEs	MS1 cells	Increase NO release, NOS and thrombomodulin production; inhibit the formation of AGEs
Wang, Chunmei et al (2009)[51]	Diabetes	HFD+STZ	Rats	Improve glucose and lipid metabolism; enhance NO bioavailability

(*Continued*)

Table 2 (Continued).

References	Model	Inducer	Experimental Model	Molecular Mechanism
Wang, Yiqun et al (2009)[52]	Diabetes	HG	HUVECs	AMPK/eNOS activation
		Gently rubbing the luminal surface	Thoracic aortas of rats	
Geng, Feng-Hao et al (2016)[53]	Diabetes	HFD+STZ	Mesenteric artery of rats	Up-regulating insulin receptor-mediated signalling
		HG+HFD	HUVECs	
Zhang, Ming et al (2013)[54]	Diabetes	Palmitate	HUVECs	Upregulate eNOS expression and downregulate expression of Nox4; activation of AMPK
Ye, Liang et al (2016)[55]	Obesity	HFD	Mice	Improve IR by inhibiting M1 macrophage activation
		TNF-α	3T3-L1 preadipocytes	
Zhou, Jiyin, and Shiwen Zhou (2010)[56]	Diabetes	STZ+high-carbohydrate +HFD	rats	Regulate the PPARs/P-TEFb signal transduction pathway
Shan, Yun et al (2020)[57]	Obesity	/	3T3-L1 preadipocytes	Upregulate SIRT1 expression; activate the AMPK pathway
		HFD	C57BL/6J mice and Sirt1+/−mice	
Li, Dan et al (2022)[58]	Obesity	HFD	Mice	Activate SIRT3 expression;
		/	Adipocytes	
Yi, Ping et al (2008)[59]	IR	PA	3T3-L1 adipocytes	Inhibit phosphorylation of IKKβ Ser
Du, Junda et al (2024)[60]	Obesity	HFD	Mice	Inhibit miR-27a levels; improve IR
		PA	Adipocytes	

Abbreviations: AGEs, advanced glycation end products; AMPK, AMP-activated protein kinase; PPARs, peroxisome proliferator-activated receptors; P-TEFb, positive transcription elongation factor b; SIRT1, sirtuin 1; IKK, IκB kinase.

and improved insulin-induced vasodilation via the PI3K/Akt signaling pathway, a key mechanism for endothelial function and insulin sensitivity.[53]

Beyond its vascular benefits, BBR exerts significant anti-inflammatory effects and improves insulin resistance, both of which are key factors in obesity and diabetic vascular dysfunction. In HG-treated HUVECs, BBR activated AMPK, promoting NO production and inhibiting monocyte adhesion by suppressing NF-κB activation and reducing the expression of adhesion molecules such as VCAM-1 and ICAM-1, thereby mitigating inflammation.[52] In HFD-induced mice, BBR improved insulin sensitivity and reduced macrophage infiltration, particularly M1 macrophages, into adipose tissue. M1 macrophages, being pro-inflammatory, play a pivotal role in the development of insulin resistance.[62] BBR also reduced levels of inflammatory cytokines, including MCP-1, IL-6, and TNF-α. This anti-inflammatory effect is associated with the inhibition of key inflammatory kinases, such as c-Jun N-terminal kinase (JNK) and IκB kinase β (IKKβ), which are involved in NF-κB activation and inflammatory responses.[63] Furthermore, BBR reduced p65 expression, further alleviating inflammation and macrophage chemotaxis.[55]

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In both HFD-fed C57BL/6J and Sirt1+/− mice, BBR upregulated SIRT1 expression, activating AMPK and reducing both local and systemic inflammation, thereby improving insulin resistance.[57] Additionally, BBR modulated macrophage polarization in adipose tissue, shifting them towards an anti-inflammatory phenotype, and activated SIRT3, a mitochondrial deacetylase that mitigates adipose tissue remodeling and miR-155-5p secretion, providing further protection against insulin resistance.[58] In palmitic acid-treated 3T3-L1 adipocytes, BBR increased the expression of insulin receptor substrate-1 (IRS-1) and PI3K p85 while inhibiting IRS-1 and IKKβ phosphorylation, thereby preventing NF-κB activation.[59] Co-treatment with BBR and insulin in HG/HF-treated HUVECs enhanced phosphorylation of the insulin receptor (InsR), Akt, and eNOS, suggesting that BBR enhances insulin receptor-mediated signaling.[53] In HFD-induced mice, BBR also reduced miR-27a levels in both serum and adipocyte supernatants, significantly alleviating insulin resistance linked to elevated miR-27a.[60] These findings further support BBR's anti-inflammatory effects and its capacity to improve insulin signaling.

BBR also promotes improvements in glucose and lipid metabolism. In HFD and STZ-induced diabetic rats, BBR reduced fasting blood glucose (FBG), triglycerides, and 2-hour glucose levels in the oral glucose tolerance test (OGTT), indicating metabolic improvements.[53] Furthermore, BBR promoted adipocyte differentiation and decreased lipid accumulation in 3T3-L1 adipocytes by modulating key regulators such as peroxisome proliferator-activated receptors (PPARs) and positive transcription elongation factor b (P-TEFb).[56] PPARs are nuclear hormone receptors that regulate lipid metabolism, adipogenesis, and insulin sensitivity,[64] while P-TEFb regulates gene transcription related to adipocyte function and lipid metabolism.[65] BBR also reduced body weight and fat percentage, improving serum parameters, including FBG, total cholesterol, triglycerides, and LDL-C in palmitic acid-treated adipocytes.[60] Additionally, BBR enhanced autophagy and promoted cell viability in HG/HF-treated HUVECs, as evidenced by an increased LC3B-II /LC3B-I ratio, a key marker of autophagy, and a reduction in p62 expression, a substrate of autophagic degradation and indicator of impaired autophagic flux.[53]

Complications of Obesity and Diabetes

Cardiovascular Disease Related to Obesity and Diabetes

Cardiovascular disease (CVD) is an increasingly prevalent public health issue, particularly in the context of rising global rates of obesity and diabetes.[66] These metabolic disorders are strongly associated with key CVD risk factors, including hyperglycemia, insulin resistance, dyslipidemia, hypertension, and systemic inflammation.[67] In diabetic individuals, chronic hyperglycemia and metabolic dysregulation contribute to vascular damage through mechanisms such as oxidative stress, AGE formation, endothelial dysfunction, and persistent low-grade inflammation.[68] These pathological processes collectively lead to a range of cardiovascular complications, including atherosclerosis, hypertension, myocardial infarction, stroke, and heart failure. Moreover, obesity exacerbates these risks by promoting adipose tissue expansion and remodeling, which increases the secretion of pro-inflammatory cytokines and places additional strain on the cardiovascular system.[69,70]

Astragaloside IV

AS-IV offers multiple therapeutic benefits in CVDs associated with obesity and diabetes through the modulation of several signaling pathways that regulate lipid metabolism, oxidative stress, cardiac energy metabolism, inflammation, autophagy, and endothelial function. It regulates lipid metabolism by lowering total cholesterol, triglycerides, and LDL-C levels while increasing HDL-C,[71,72] thus promoting vascular health. AS-IV also alleviates oxidative stress by inhibiting Nox4 and modulating the TGF-β1/Smad2 signaling pathway.[40] The TGF-β1/Smad2 pathway plays a critical role in fibrosis and endothelial dysfunction,[73] and its regulation by AS-IV helps protect against vascular damage. In diabetic cardiomyopathy, AS-IV enhances cardiac energy metabolism by upregulating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and nuclear respiratory factor 1 (NRF1),[74] both of which are key regulators of mitochondrial biogenesis and oxidative metabolism.[75] Additionally, AS-IV prevents ferroptosis by downregulating CD36 expression,[76] a fatty acid transporter involved in lipid peroxidation.[77] AS-IV further modulates mitogen-activated protein kinase (MAPK) signaling by inhibiting JNK and p38 pathways while promoting extracellular signal-regulated kinase

(ERK) activation.[78,79] JNK and p38 are associated with stress and inflammation,[80] while ERK activation promotes cell survival and proliferation,[81] thus improving cardiac function and protecting against apoptosis.

AS-IV also enhances endothelial function by promoting NO signaling and cyclic guanosine monophosphate (cGMP) production.[26,82] Additionally, it improves hypothalamic leptin sensitivity by increasing leptin receptor mRNA and pro-opiomelanocortin (POMC) expression, while downregulating inhibitory factors such as suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B).[83] POMC plays a role in energy homeostasis, and the downregulation of SOCS3 and PTP1B (both negative regulators of leptin signaling) aids in metabolic balance.[84] Moreover, AS-IV exerts anti-inflammatory effects through upregulation of the α7 nicotinic acetylcholine receptor (α7nAChR) and inhibition of the IKKβ/NF-κB pathway, mechanisms that help prevent obesity-associated hypertension.[83] The α7nAChR is a key component of the cholinergic anti-inflammatory pathway,[85] while the IKKβ/NF-κB pathway is central to inflammation, making its inhibition essential for reducing inflammatory responses. Additionally, AS-IV enhances autophagy in vascular smooth muscle cells,[86] reduces inflammation via the PI3K/Akt/mTOR pathway, and modulates gut microbiota to promote beneficial bacterial populations[87] (Table 3).

Table 3 Overview of Astragaloside IV and berberine on Cardiovascular Disease of Related to Obesity and Diabetes

References	Model	Inducer	Experimental Model	Molecular Mechanism
Astragaloside IV				
Wang, Zhongyuan et al (2020)[71]	DCM	HF+STZ	Rats	Improve lipid metabolism
Song, Zhenhua et al (2019)[86]	AS	ox-LDL+β-Glycerophosphate	VSMC	H19 overexpression and DUSP5 inhibition
		HF	Thoracic aorta of mice	
Sun, Dongwen et al (2024)[87]	AS	The Western diet	Rats	Anti-inflammatory and modulate intestinal flora; PI3K/Akt/mTOR pathway
Zhang, Zhen et al (2019)[74]	DCM	STZ	Rats	Regulate the release of PGC-1α and NRF1
		HG	H9c2 cardiomyocytes	
Li, Xin et al (2023)[76]	DCM	HF+STZ	rats	Decrease cardiomyocyte injury and myocardial dysfunction
		PA	H9c2 cardiomyocytes	
Sun, Chuang et al (2021)[78]	MI	HG+HF	H9c2 cardiomyocytes	Prevent apoptosis and restored cardiac function; MAPK signaling pathway
Zhang, Yifan et al (2022)[79]	AS	HF	LDLR-/-mice	Via MAPK/NF-κB signaling pathway
Lin, Xin et al (2020)[26]	Metabolic syndrome	High-fructose+hf	Rats	Alleviate oxidative stress and activate the endothelial NOS/NO/cGMP pathway
Zhang, Ning et al (2011)[82]	Metabolic syndrome	Fructose	Rats	Regulate lipid metabolism, endothelium-dependent vasorelaxation and the NO-cGMP-related pathway
Jiang, Ping et al (2018)[83]	Obesity-associated Hypertension	HFD	Obese rats	Inhibit inflammatory reaction and improve leptin resistance; increase α7nachr expression
Zhu, Yaobin et al (2019) [88]	DCM	HG	H9C2 cardiomyocytes	Inhibit oxidative stress and autophagy via the miR-34a/Bcl2/(LC3II/LC3I) and pAKT/Bcl2/(LC3II/LC3I) pathways
Zhu, Zhongsheng et al (2019)[89]	AS	ox-LDL	HUVECs	Reduce apoptosis, oxidative stress, and inflammatory response

(*Continued*)

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Table 3 (Continued).

References	Model	Inducer	Experimental Model	Molecular Mechanism
Berberine				
Man, Bin et al (2022)[90]	AS	HF+STZ	Mice	Enhance the interplay between KLF16 and PPARα
		HG	HUVECs	
Wu, Min et al (2020)[91]	AS	HF	mice	Modulate gut microbiota
Zhu, Lin et al (2018)[92]	AS	HF	Apoe-/- mice	Modulate gut microbiota
Ma, Yu-Guang et al (2017)[93]	Diabetes-associated hypertension	HF+STZ	Rats	BK_{Ca} channel
		HG	VSMCs	
Zhong, Changsheng et al (2024)[94]	DCM	/	Male db/db mice	Regulate the mTOR/mtROS axis to inhibit pyroptosis
		HG	H9C2 cardiomyocytes	
Li, Guohua et al (2018)[95]	DCM	HF+STZ	Rats	Downregulate IGF-1 receptor expression and MMP2/9 levels
Wang, Mingfeng et al (2013)[96]	DCM	HG+insulin	Cardiomyocytes	PPAR α /NO signaling pathway
Paul, Manoj et al (2019)[97]	AS	HG	Human platelet	Inhibit AR and Nox

Abbreviations: DCM, diabetic cardiomyopathy; AS, atherosclerosis; H19, long non-coding (lncRNA) H19; DUSP5, dual-specificity phosphatase 5; mTOR, mammalian target of rapamycin; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-α; NRF1, nuclear respiratory factor 1; MI, myocardial infarction; MAPK, mitogen-activated protein kinase; α7nAChRα7, nicotinic acetylcholine receptor; KLF16, Krüppel-like factor 16; PPARα, peroxisome proliferator-activated receptor alpha; BKCa, large-conductance Ca2+-activated K+ channel; mtROS, mitochondrial reactive oxygen species; MMP2/9, matrix metalloproteinase-2/9; AR, aldose reductase.

Berberine

BBR exerts therapeutic effects through a network of pathways that regulate lipid metabolism, vascular inflammation, gut health, cardiac function, and oxidative stress, underscoring its potential in managing complications associated with obesity and diabetes. It improves lipid and glucose metabolism, reduces vascular inflammation, and attenuates atherogenesis in diabetic apoE-/- mice by enhancing interactions between Krüppel-like factor 16 (KLF16) and PPARα.[90] KLF16, a transcription factor involved in lipid metabolism and endothelial function,[98] and PPARα, which regulates fatty acid oxidation and inflammation,[99] play pivotal roles in BBR's vascular protective effects through their interaction. BBR also promotes gut health by enriching beneficial microbiota, such as Akkermansia spp., helping to mitigate metabolic endotoxemia and inflammation.[91,92] In diabetic rat models, BBR reduced blood glucose and blood pressure, improved vascular function, and activated large conductance calcium-activated potassium (BK_{Ca}) channels.[93] BK_{Ca} channels, critical for regulating vascular tone and endothelial function,[100] contribute to enhanced vascular health when activated by BBR.

Additionally, BBR improved cardiac function and reduced fibrosis in db/db mice by modulating the mTOR/mitochondrial reactive oxygen species (mtROS) axis and inhibiting pyroptosis.[94] The mTOR/mtROS pathway is involved in cellular energy metabolism and oxidative stress regulation, with dysregulation contributing to cardiac dysfunction and fibrosis.[101] Pyroptosis, a form of programmed cell death associated with inflammation,[102] was mitigated by BBR, providing further protection to cardiac tissue. In diabetic cardiomyopathy, BBR reduced cardiac fibrosis and dysfunction via insulin-like growth factor 1 receptor (IGF-1R) signaling in cardiac fibroblasts.[95] IGF-1R signaling is essential for cell growth, survival, and tissue repair, making it a crucial target in preventing cardiac fibrosis.[103] BBR also alleviated cardiomyocyte hypertrophy by activating PPARα and modulating NO signaling.[96] Furthermore, BBR protected against HG-induced platelet hyper-reactivity and apoptosis by modulating oxidative stress pathways.[97] These effects contribute to reducing thrombosis and vascular injury, common complications in diabetes (Table 3).

Diabetic Retinopathy

Diabetic retinopathy (DR) is a prevalent and severe microvascular complication of diabetes mellitus (DM), representing the leading cause of vision impairment and blindness among working-age adults globally.[104] Its pathogenesis is closely associated with chronic hyperglycemia, which induces progressive damage to the retinal microvasculature, including endothelial dysfunction, capillary basement membrane thickening, pericyte loss, and increased vascular permeability.[105] These cellular and molecular alterations lead to ischemia, hypoxia, and inflammation in the retina, triggering a cascade of events that culminate in the hallmark features of DR: microaneurysms, retinal hemorrhages, hard exudates, and, ultimately, proliferative retinopathy.[106] Additionally, oxidative stress,[107,108] chronic low-grade inflammation,[109,110] and an upregulated renin-angiotensin system (RAS)[111] exacerbate these vascular changes, promoting pathological neovascularization and fibrovascular proliferation, which significantly heighten the risk of vision loss.

Astragaloside IV

AS-IV exerts protective effects against DR through a combination of antioxidant, anti-inflammatory, and anti-apoptotic mechanisms, targeting multiple signaling pathways and molecular mediators. In vitro studies on retinal capillary endothelial cells (RCECs) demonstrated that AS-IV enhanced cell viability, reduced glucose transporter-1 (GLUT-1) expression, and decreased oxidative stress markers such as hydrogen peroxide (H_2O_2) and malondialdehyde (MDA). It also boosted antioxidant enzyme activity, increased glutathione levels, and lowered Nox4 expression,[112] thus reducing oxidative damage in retinal cells. In retinal ganglion cells (RGCs), AS-IV improved cell viability, reduced oxidative stress, and promoted retinal layer thickness. Network pharmacology identified additional potential targets for AS-IV, including hypoxia-inducible factor 1-alpha (HIF-1α) and Akt1.[113] HIF-1α is critical for cellular adaptation to hypoxia,[114] while Akt1 plays a pivotal role in cell survival, growth, and metabolism.[115]

In diabetic rats, AS-IV prevented ferroptosis in retinal pigment epithelial (RPE) cells by promoting the expression of SIRT1 and Nrf2, along with increasing miR-138-5p levels.[116] SIRT1 is involved in mitochondrial function and cellular stress responses, while Nrf2 regulates antioxidant defenses, both crucial for cell survival under oxidative stress conditions. miR-138-5p is linked to ferroptosis regulation,[117] further enhancing AS-IV's protective effect on RPE cells. Moreover, AS-IV functioned as an aldose reductase inhibitor, reducing ERK1/2 phosphorylation and NF-κB activation, both critical in inflammatory and apoptotic pathways in retinal cells.[118] It also protected RPE cells from apoptosis by modulating pro-apoptotic proteins (eg, Bax and active caspases) and anti-apoptotic proteins (eg, Bcl-2 and FasL). AS-IV upregulated miR-128 expression, which regulates apoptosis and cell survival in retinal cells[119] (Table 4).

Berberine

BBR also demonstrates significant therapeutic potential for DR by reducing hyperglycemic damage, inhibiting angiogenesis and inflammation, and modulating immune responses while promoting cellular survival and autophagy in retinal cells. It effectively lowered FBG and triglyceride levels, thereby mitigating hyperglycemic damage to retinal tissue.[120] BBR inhibited the expression of HIF-1α and vascular endothelial growth factor (VEGF), key factors involved in

Table 4 Overview of Astragaloside IV and berberine on Diabetic Retinopathy

References	Model	Inducer	Experimental Model	Molecular Mechanism
Astragaloside IV				
Qiao, Yuan et al (2017)[112]	DR	HG	RCECs	Antioxidative function
Wang, Tao et al (2020)[119]	DR	STZ	RCECs	Upregulate miR-128 expression
Li, Jun-Qi et al (2024)[113]	DR	STZ	Rats	Regulate the AGE-RAGE signaling pathway and the Th17 cell differentiation signaling pathway
		HG	RGCs	
Ding, Yuzhi et al (2014)[118]	DR	/	db/db mice	Prevent the activation of ERK1/2 phosphorylation and NF-κB

(*Continued*)

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Table 4 (Continued).

References	Model	Inducer	Experimental Model	Molecular Mechanism
Berberine				
Yin, Zhujun et al (2021)[120]	DR	/	*db*/*db* transgenic mice	Modulate the glucolipid metabolism and inhibit the HIF-1α /VEGF/ NF-κB pathway
Ai, Xiaopeng et al (2022)[121]	DR	/	db/db mice	Alleviate angiogenesis and apoptosis by suppressing the HIF-1α/ VEGF/DLL-4/Notch-1 pathway
Wang, Ning et al (2021)[122]	DR	STZ	Mice	Akt/mTOR/HIF-1α/VEGF pathway
		insulin	RPECs	
Yang, Yi et al (2024)[123]	DR	STZ+HF	Mice	Regulate T cell subpopulation differentiation, reduce the Th17/ Treg ratio
		HG	CD4+T cells and DC2.4 cell lines	
Chen, Han et al (2018)[124]	DR	HG	Primary retinal Müller cells	Enhance autophagy and activate the AMPK/mTOR signaling pathway

Abbreviations: DR, diabetic retinopathy; RCECs, retinal capillary endothelial cells; RPECs, retinal pigment epithelial cells; RGCs, retinal ganglion cells; RAGE, receptors of AGEs; ERK1/2, extracellular signal-regulated kinase 1/2; HIF-1α, hypoxia-inducible factor-1α; VEGF, vascular endothelial growth factor; DLL-4, delta-like ligand 4.

angiogenesis and vascular permeability, via the AKT/mTOR signaling pathway.[121,122] Additionally, BBR modulated immune responses by increasing regulatory T cells (Tregs) and decreasing pro-inflammatory Th17 cells, fostering a balanced immune environment.[123] This immune modulation helped reduce the inflammatory responses that contribute to retinal damage in DR. BBR also protected retinal Müller cells from apoptosis, a process often aggravated by hyperglycemia, and promoted autophagy, further preserving retinal health under diabetic conditions.[124] (Table 4)

Diabetic Nephropathy

Diabetic nephropathy (DN) is a severe microvascular complication of DM, characterized by progressive kidney damage that often progresses to end-stage renal disease (ESRD).[125] DN is a leading cause of chronic kidney disease globally, with patients facing significant morbidity and mortality due to the gradual decline in renal function,[126] as well as an increased risk of CVD and other comorbidities.[127] Pathologically, DN is marked by glomerular hypertrophy, basement membrane thickening, mesangial matrix expansion, and tubulointerstitial fibrosis, all of which contribute to proteinuria and a reduction in glomerular filtration rate (GFR).[128,129] The pathogenesis of DN is multifactorial, involving hyperglycemia-induced oxidative stress, inflammation, accumulation of AGEs, and dysregulation of various signaling pathways.[130,131] These processes result in cellular injury within the renal microvasculature and impair the function of podocytes, mesangial cells, and endothelial cells.

Astragaloside IV

AS-IV has demonstrated significant renoprotective effects in DN by targeting multiple pathways involved in oxidative stress, inflammation, apoptosis, and fibrosis.[132–137] In various DN models, AS-IV reduced albuminuria, serum creatinine levels, and mesangial expansion by inhibiting key signaling pathways such as MEK1/2-ERK1/2-RSK2, TUG1/TRAF5, and Akt/mTOR.[138–140] The MEK1/2-ERK1/2-RSK2 pathway is critical for cell survival, inflammation, and fibrosis, while the TUG1/TRAF5 axis regulates inflammation and immune responses in kidney cells. The Akt/mTOR pathway is involved in cell growth and metabolism, and AS-IV's inhibition of these pathways helped mitigate renal damage in DN.

In podocytes exposed to high glucose, AS-IV enhanced the expression of klotho, a protein that suppresses oxidative stress and pyroptosis by inhibiting the NF-κB and NLRP3 inflammasome pathways.[141] In palmitic acid-bound BSA-treated NRK-52E cells, AS-IV inhibited mitochondrial dysfunction and inflammation, further supporting its protective

effects on renal cells under diabetic conditions.[142] Additionally, AS-IV promoted autophagy and reduced apoptosis by activating AMP-activated protein kinase alpha (AMPKα) and sarco/endoplasmic reticulum calcium ATPase 2b (SERCA2b).[143] AMPKα is a critical regulator of cellular energy balance, while SERCA2b plays a role in maintaining intracellular calcium homeostasis,[144] both contributing to cellular protection in the kidney.

AS-IV also enhanced gut-renal interactions by restoring intestinal barrier function and promoting beneficial gut microbiota while reducing renal and intestinal ferroptosis in db/db mice.[145] Ferroptosis, an iron-dependent form of cell death, plays a role in both renal and intestinal damage in DN.[146] By modulating histone modifications and reducing markers of endoplasmic reticulum (ER) stress, including eukaryotic initiation factor-2α (eIF2α), Protein Kinase RNA-like Endoplasmic Reticulum Kinase (PERK), JNK, Glucose Regulated Protein 78 (GRP78), and cleaved Activating Transcription Factor 6 (ATF6),[147,148] AS-IV upregulated anti-apoptotic factors and downregulated pro-inflammatory cytokines such as TNF-α and MCP-1.[149,150] In endothelial cells, AS-IV preserved barrier integrity by activating the AKT-GSK3 pathway,[151] crucial for regulating cell survival, migration, and vascular integrity. Additionally, AS-IV enhanced NO synthesis via modulation of eNOS,[152] vital for maintaining endothelial function and vasodilation (Table 5).

Table 5 Overview of Astragaloside IV and berberine on Diabetic Nephropathy

References	Model	Inducer	Experimental Model	Molecular Mechanism
Astragaloside IV				
He, Ke-Qiang et al (2018)[133]	DN	STZ	Rats	Anti-oxidative stress, anti-inflammation, downregulate ERK1/2 activation, and upregulate TRPC6 expression
Su, Yong et al (2019)[134]	DN	HF+STZ	Rats	Downregulate CD36 expression, mediate FFA uptake and lipid accumulation
		PA	HMCs	
Zhang, Mingyu et al (2023)[153]	DN	STZ	Rats	Regulate SIRT6/HIF-1α pathway
Zhang, Yudi et al (2020)[136]	DN	HF+STZ	Rats	Inhibit inflammation-related gene expression
Chen, Qingqing et al (2018)[137]	DN	PA	HK-2 cell	Inhibit ROS generation and apoptotic protein expression
Wang, Xiaolei et al (2019)[132]	DN	HG	Mouse podocytes	Modulate the SIRT1-NF-κB pathway and autophagy activation
		/	Diabetic KK-Ay mice	
Song, Gaofeng et al (2018)[139]	DN	STZ	Mice	Inhibit the MEK1/2-ERK1/2-RSK2 signaling pathway
Lei, Xiao et al (2018)[140]	DN	STZ	Rats	lncRNA-TUG1/TRAF5 pathway
		HG	MPC5	
Sun, Huili et al (2016)[138]	DN	/	db/db mice	Inhibit Akt/mTOR, NFκB and Erk1/2 signaling pathways.
He, Jiaxin et al (2023)[141]	DN	HF+STZ	Rats	Inhibit NLRP3-mediated pyroptosis via the NF-κB signaling pathway
		HG	Mouse podocytes	
Wang, Jing et al (2024)[142]	DN	HF+STZ	Rats	Inhibit FATP2-mediated fatty acid transport
		FFA-deleted BSA or PA-bound BSA	NRK-52E cells	

(*Continued*)

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Table 5 (Continued).

References	Model	Inducer	Experimental Model	Molecular Mechanism
Guo, Hengjiang et al (2017)[143]	DN	STZ	Mice	By SERCA2-dependent ER stress attenuation and AMPKα-promoted autophagy induction
		HG	Podocytes	
Lyu, Xin et al (2024)[145]	DN	/	db/db mice	Intestinal microbiome alterations and ferroptosis modulation
Guo, Hengjiang et al (2016)[147]	DN	/	*db*/*db* mice	Restore SERCA activity and SERCA2 expression;
		Palmitate	Mouse podocytes	
Wang, Zeng Si et al (2015)[148]	DN	STZ	Rats	Decrease ER stress
		TM	Human podocytes	
Fan, Yuyan et al (2022)[149]	DN	HG	NRK-52E cells	Downregulate MAP4K3 expression by regulating H3K4me1 binding and further reducing apoptosis
		HF	Polygenic diabetic KK-Ay mice	
Gui, Dingkun et al (2013)[150]	DN	STZ	Rats	Inhibit NF-κB mediated inflammatory genes expression
Berberine				
Tang, Li-Qin et al (2016)[154]	DN	HF+HG+STZ	Rats	Regulate of β-arrestin expression, ICAM-1 and VCAM-1 levels
Xie, Xi et al (2013)[155]	DN	STZ	Rats	RhoA/ROCK inhibition
		HG	GMCs	
Liu, Weihua et al (2009)[156]	DN	HG	GMCs	Inhibit fibronectin and collagen synthesis partly via p38 MAPK signal pathway
Wang, Ying-Ying et al (2018)[157]	DN	HG	GMCs +podocyte	Inhibit the transfer of TGFβ1 from the glomerular mesangial cells to the podocytes
Ma, Zejun et al (2022)[158]	DN	HF+STZ	Rats	Suppress the NLRP3 inflammasome.
		HG	HK-2 cell	
Wang, Feng Ling et al (2013)[159]	DN	HF+STZ	Rats	Modulate the proteins expression of GRKs in G protein-AC-cAMP signaling pathway
Liu, Weihua et al (2008)[160]	DN	STZ	Rats	Inhibit AR in mesangium, reduce oxidative stress, and ameliorate extracellular matrix synthesis and cell proliferation
		HG	Rat mesangial cells	

Abbreviations: TRPC6, transient receptor potential cation channel 6; HMCs, human glomerular mesangial cells; HK-2, proximal renal tubular epithelial cells; MEK1/2, mitogen-activated protein kinase 1/2; RSK2, ribosomal S6 kinase 2; MPC5, Conditionally immortalized mouse podocytes; TUG1, taurine upregulated gene 1; FATP2, Fatty acid transport protein 2; SERCA, sarcoplasmic reticulum Ca2+-ATPase; TM, tunicamycin; H3K4me1, H3 lysine 4 monomethylation; Rock, Rho kinase; GMCs, glomerular mesangial cells; GRKs, G protein-coupled receptor kinases.

Berberine

BBR exhibits therapeutic efficacy in DN by reducing inflammation and oxidative stress and alleviating histopathological changes. It lowered levels of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), markers of endothelial activation and inflammation.[154] Furthermore, BBR inhibited the RhoA/ROCK

signaling pathway and NF-κB activity, both critical for regulating fibronectin accumulation and renal inflammation.[155] The RhoA/ROCK pathway governs cell contraction, motility, and fibrosis,[161] while NF-κB serves as a central mediator of inflammatory responses. Modulating these pathways, BBR reduced fibrosis and inflammation in DN. Additionally, BBR mitigated tubulointerstitial fibrosis and epithelial-to-mesenchymal transition (EMT) in kidney cells. EMT involves renal epithelial cells losing their characteristics and acquiring a mesenchymal phenotype, contributing to fibrosis and tissue remodeling in DN.[162] BBR downregulated NLRP3 inflammasome activation, a key factor in inflammation, and inhibited TGF-β1 transfer from mesangial cells, further protecting against fibrosis and EMT.[156–158]

Moreover, BBR reduced collagen synthesis by inhibiting the p38 mitogen-activated protein kinase (p38MAPK) pathway and modulated G protein-coupled receptor kinases (GRKs) to increase cyclic adenosine monophosphate (cAMP) levels, further contributing to its renoprotective effects.[159] Additionally, BBR decreased aldose reductase activity, lowering oxidative stress and extracellular matrix synthesis.[160] Aldose reductase, an enzyme involved in the polyol pathway, is activated under hyperglycemic conditions and contributes to oxidative damage.[163] Inhibiting this enzyme helped reduce oxidative stress, a major contributor to kidney injury in DN (Table 5).

Discussion

The increasing global prevalence of obesity and diabetes, alongside their associated vascular complications, highlights the urgent need for effective therapeutic strategies to manage vascular dysfunction in these conditions. As endothelial dysfunction plays a central role in the pathogenesis of diabetic vascular complications, targeting the underlying mechanisms of vascular injury is essential to prevent the further progression of diseases such as CVD, DR, and DN. In this context, AS-IV and BBR, two bioactive compounds with distinct mechanisms of action, present promising therapeutic potential for mitigating vascular dysfunction associated with obesity and diabetes.

Mechanistic Insights and Therapeutic Potentials

The therapeutic potential of AS-IV and BBR in treating vascular dysfunction and associated complications in obesity and diabetes is evident through their complementary mechanisms. Both compounds target inflammation, oxidative stress, endothelial dysfunction, and insulin resistance, providing promising treatment options for CVDs, DR, and nephropathy (Supplementary Table 1).

Vascular Dysfunction

AS-IV and BBR enhance endothelial function by promoting NO production and reducing oxidative stress. They achieve this by upregulating eNOS and inhibiting NADPH oxidase. Both compounds also improve insulin sensitivity; AS-IV activates the PI3K/Akt pathway, while BBR activates AMPK, leading to enhanced glucose uptake. AS-IV reduces pro-inflammatory cytokines and adhesion molecules via TLR4/NF-κB inhibition, while BBR modulates macrophage polarization through SIRT1 and AMPK activation. Both compounds promote autophagy, with AS-IV utilizing the PI3K/Akt/mTOR pathway and BBR relying on AMPK signaling. While AS-IV focuses on angiogenesis and anti-apoptotic effects, BBR targets inhibiting AGEs formation and macrophage polarization, highlighting their complementary roles in vascular repair and metabolic regulation.

Cardiovascular Protection

AS-IV and BBR both improve lipid metabolism and reduce vascular inflammation. AS-IV increases HDL-C and reduces LDL-C, whereas BBR modulates KLF16 and PPARα interactions to enhance lipid metabolism. AS-IV acts through the PI3K/Akt/mTOR and α7nAChR pathways, while BBR reduces metabolic endotoxemia by modulating gut microbiota. In terms of cardiac protection, AS-IV promotes energy metabolism and reduces oxidative stress through Nox4 and TGF-β1/Smad2 pathways, whereas BBR protects against cardiac fibrosis via the mTOR/mtROS axis. AS-IV also prevents ferroptosis, while BBR modulates PPARα and NO signaling to reduce cardiomyocyte hypertrophy.

Retinal and Renal Protection

In DR, AS-IV protects retinal cells through enhanced antioxidant enzyme activity and inhibition of apoptosis, particularly through modulation of pro-apoptotic proteins. BBR also improves retinal health by reducing oxidative damage,

promoting autophagy, and modulating the immune response by increasing regulatory T cells. Both compounds inhibit angiogenesis, with BBR acting through the Akt/mTOR pathway. AS-IV targets ferroptosis resistance, while BBR inhibits aldose reductase and reduces inflammation. In DN, both compounds reduce inflammation and oxidative stress. AS-IV enhances klotho expression and modulates the Akt/mTOR pathway to alleviate fibrosis, while BBR inhibits TGF-β1 and NLRP3 inflammasome activation to prevent fibrosis.

Challenges and Future Directions

Despite promising preclinical findings, several obstacles must be overcome before AS-IV and BBR can be widely incorporated into clinical practice, particularly their limited bioavailability. The absolute bioavailability of AS-IV is only 3.66% in rats and 7.4% in beagle dogs,[164] while BBR's bioavailability in rats is even lower, at 0.68%.[165] Another significant challenge lies in the standardization of dosing regimens. Both clinical and preclinical studies have utilized varying doses and formulations, leaving the optimal therapeutic dose undetermined. For instance, a study on AS-IV's protective effects against endothelial dysfunction assessed doses of 40 mg/kg/day and 80 mg/kg/day.[166] Conversely, research on podocyte apoptosis in DN models administered a substantially lower dose of 5 mg/kg/day,[140] demonstrating considerable variability in dosing strategies. In BBR research, experiments with HFD and STZ-induced diabetic rats used doses of 50, 100, and 150 mg/kg/day.[167] Studies examining BBR's lipid-lowering efficacy, particularly in combination with resveratrol, utilized as low as 30 mg/kg/day.[168] This wide dosage range emphasizes the need for further investigations to determine the most effective and safe doses for both AS-IV and BBR.

To address bioavailability limitations, innovative drug delivery systems such as nanoparticle-based formulations and absorption enhancers are under exploration. A water-soluble AS-IV derivative, astragalosidic acid (LS-102), demonstrated nearly 500-fold greater transepithelial permeability compared to AS-IV.[169] Hyaluronate-based liposomes encapsulating BBR have also enhanced its lipophilicity and bioavailability.[170] Additionally, chitosan-alginate nanoparticles loaded with BBR increased oral bioavailability by 4.1-fold in rats relative to a standard BBR suspension.[171] Absorption enhancers like sodium caprate and sodium deoxycholate significantly boosted BBR absorption, elevating plasma concentrations by 41.1-fold and 35.3-fold, respectively.[172] While these approaches show potential, further research is necessary to refine these strategies for clinical application.

While both AS-IV and BBR exhibit complementary mechanisms, their potential synergism remains underexplored. Three critical questions warrant immediate attention: (1) Do AS-IV and BBR interact pharmacokinetically or pharmacodynamically when co-administered? (2) Can optimize combined dosing ratios enhance efficacy without increasing toxicity in multifactorial vascular dysfunction models? (3) Can advance delivery systems mitigate the bioavailability limitations of dual therapy? In parallel with these mechanistic inquiries, the establishment of standardized dosing regimens is essential, which requires rigorous pharmacodynamic studies, particularly considering interactions with conventional antidiabetic medications. Furthermore, large-scale randomized trials are necessary to assess the long-term safety profiles of this combination in comorbid populations. Addressing these gaps will bridge the gap between mechanistic insights and clinically applicable combination strategies.

Conclusion

AS-IV and BBR represent two promising natural compounds with substantial potential for managing vascular dysfunction in obesity and diabetes. While preclinical data are promising, clinical evidence remains limited. The combination of these compounds may offer a comprehensive approach to addressing both the metabolic and vascular aspects of these diseases. However, challenges such as bioavailability, optimal dosing, combinatorial efficacy, and long-term safety must be resolved. Overcoming these hurdles could position AS-IV and BBR as integral components in clinical strategies aimed at combating the growing global burden of obesity, diabetes, and their vascular complications.

Abbreviations

A list of abbreviations used in this study is provided in Supplementary Table 2.

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Disclosure

The authors report no conflicts of interest in this work.

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