

Cellular and Molecular Mechanisms of Hyperglycemia-Induced Atherosclerosis and Intervention Strategies of Chinese Herbal Medicine

Shengping Luo^{1,2}, Jiayu Zhu³, Qianru Zeng⁴, Le Yang^{1,2}, Jing Liu^{1,2}, Yihui Deng⁴

¹School of Integrated Chinese and Western Medicine, Hunan University of Chinese Medicine, Changsha, People's Republic of China; ²Hunan Province Key Laboratory of Cerebrovascular Disease Prevention and Treatment of Integrated Traditional Chinese and Western Medicine, Hunan University of Chinese Medicine, Changsha, People's Republic of China; ³The First Clinical College of Chinese Medicine, Hunan University of Chinese Medicine, Changsha, People's Republic of China; ⁴School of Traditional Chinese Medicine, Hunan University of Chinese Medicine, Changsha, People's Republic of China

Correspondence: Yihui Deng, School of Traditional Chinese Medicine, Hunan University of Chinese Medicine, Changsha, People's Republic of China, Email dengyihui@hnuucm.edu.cn

Abstract: Diabetes is a significant global public health issue, and atherosclerosis serves as the primary pathological basis for the occurrence and progression of cardiovascular and cerebrovascular events. Studies have shown that hyperglycemia can promote the occurrence and progression of atherosclerosis by damaging vascular endothelial cells, macrophages, and vascular smooth muscle cells. In recent years, Chinese herbal medicines and their active ingredients have demonstrated unique advantages in preventing and treating high-glucose-induced vascular cell damage. Their mechanisms of action primarily encompass two aspects: firstly, regulating blood glucose through multiple pathways such as modulating the insulin signaling pathway, enhancing peripheral glucose uptake and utilization, and delaying intestinal carbohydrate absorption; secondly, intervening in key pathological processes such as high-glucose-induced vascular cell inflammation, cell death, phenotypic transformation, and metabolic reprogramming. This, in turn, slows down the progression of diabetes-related atherosclerosis. This article systematically elucidates the molecular mechanisms underlying hyperglycemia-induced damage to vascular endothelial cells, macrophages, and vascular smooth muscle cells. It also summarizes the protective mechanisms of Chinese herbal medicine active ingredients (albiflorin, salvianolic acid B, scutellarin, vitexin, hydroxysafflor yellow A, ginsenoside Rb1, maslinic acid, paeonol, citronellal, matrine, Panax notoginseng saponins, astragalus polysaccharides, 6-gingerol, and sodium tanshinone IIA sulfonate) and traditional Chinese medicine compounds (buyang huanwu decoction, guanxining tablets, and fufang zhenzhu tiaozhi) against vascular endothelial cells, macrophages, and vascular smooth muscle cells. The aim is to provide a theoretical basis for the prevention and treatment of diabetes-related atherosclerosis, as well as the development of related therapeutic drugs.

Keywords: hyperglycemia, atherosclerosis, Chinese herbal medicine, endothelial cells, macrophages, vascular smooth muscle cells, molecular mechanisms, protective effect

Introduction

Diabetes mellitus is a metabolic disease characterized by chronic hyperglycemia, caused by defects in insulin secretion or action. Global disease burden data show that there were 536 million people with diabetes in 2021, and this is expected to rise to 783 million by 2045.^{1,2} Due to long-term hyperglycemic states and chronic inflammation, diabetes can lead to numerous complications. Among these, diabetic cardiovascular and cerebrovascular complications are the leading cause of death in patients with type 2 diabetes, and about 90% of patients with diabetic cardiovascular and cerebrovascular diseases suffer from atherosclerotic cardiovascular disease.³ Atherosclerosis is a chronic inflammatory disease characterized by local lipid deposition, fibrous tissue proliferation, and calcium deposition, forming plaques, reducing

vascular elasticity, and leading to vascular wall hardening.⁴ Research has found that compared to the general population, patients with diabetes exhibit earlier and more rapid progression of atherosclerosis; furthermore, plaques in diabetic patients often possess larger necrotic cores and more pronounced inflammation, leading to plaque instability and an increased risk of plaque rupture, which in turn can trigger acute clinical complications of atherosclerosis.^{5,6}

The mechanism by which hyperglycemia exacerbates atherosclerosis is relatively complex, encompassing inflammatory response, oxidative stress, vascular proliferation, stromal changes, and vascular cell damage.^{7–10} The clinical efficacy of Chinese herbal medicines in treating diabetes-associated atherosclerosis has been confirmed.¹¹ Animal and cell experiments further reveal that its effects are attributed to a dual mechanism: on the one hand, it regulates glucose metabolism by modulating the insulin signaling pathway, enhancing peripheral glucose uptake and utilization, and delaying intestinal carbohydrate absorption, thereby eliminating hyperglycemia as the fundamental cause;¹² on the other hand, it intervenes in the core pathological process of hyperglycemia-induced vascular cell damage, blocking the cascade reaction of “hyperglycemia-vascular damage atherosclerosis progression”.¹³ For example, albiflorin, an active ingredient extracted from white Baishao (*Paeonia lactiflora* Pall), can promote glucose uptake in skeletal muscle cells and regulate insulin signaling, thereby reducing blood glucose levels and eliminating the damaging factor of hyperglycemia. Additionally, it can inhibit the release of inflammatory factors induced by hyperglycemia, reduce endothelial cell apoptosis, and thus mitigate hyperglycemia-induced damage to human umbilical vein endothelial cells, thereby delaying the progression of diabetes-associated atherosclerosis.^{13,14} Therefore, this article focuses on the damage to three types of vascular cells: endothelial cells, macrophages, and smooth muscle cells, summarizing the molecular mechanisms by which hyperglycemia exacerbates atherosclerosis. Furthermore, this article systematically reviews the mechanisms by which Chinese herbal medicine and its active ingredients regulate blood glucose and hyperglycemia-induced vascular cell damage, thereby improving diabetes-associated atherosclerosis. This may provide new directions for future research and aid in the further development of candidate drugs.

Review Methodology

We employed a systematic literature search methodology to identify high-quality studies, with coverage spanning authoritative academic platforms such as PubMed and Web of Science, to track research progress in this field comprehensively. The specific retrieval formula as follows: literature search strategy=(“Hyperglycemia” OR “Diabetes Mellitus” OR “High glucose”) AND (“Atherosclerosis” OR “Arteriosclerosis” OR “Plaque, Atherosclerotic” OR “vascular plaque”) AND (“Endothelial Cell*” OR “Vascular Endothelial Cell*” OR “Macrophage*” OR “Muscle, Smooth, Vascular” OR “vascular smooth muscle cell*”) AND (“Medicine, Chinese Traditional” OR “Chinese Traditional Medicine*” OR “Traditional Chinese Medicine*” OR “Chinese herbal medicine*” OR “active compound*” OR “metabolite*” OR “active component*” OR “Natural product*”). This search strategy focused on mechanistic studies investigating Chinese herbal medicines and their active components in intervening against high-glucose-induced injury to endothelial cells, macrophages, and vascular smooth muscle cells to prevent and treat diabetes-associated atherosclerosis. No time restrictions were applied to publication selection, and publications with low relevance and non-English-language publications were excluded. To strictly control selection bias and ensure objectivity in screening results, two authors independently conducted the initial literature screening following systematic review protocols, with cross-checking and verification performed upon completion. Any disagreements were resolved through third-party adjudication to reach a consensus. The search strategy was implemented across multiple databases in accordance with PRISMA guidelines (PRISMA 2020 citation). The detailed literature screening and inclusion process is illustrated in Figure 1.

Mechanism of Hyperglycemia-Induced Damage to Vascular Cells Accelerating Atherosclerosis

Mechanism of Hyperglycemia-Induced Endothelial Cell Damage

Endothelial cells (ECs) are a monolayer lining the inner surface of blood vessels. They play a central role in maintaining cardiovascular homeostasis by forming a selective barrier, regulating vascular tone, and inhibiting coagulation and inflammation.^{15–17} Studies have demonstrated that hyperglycemia is an independent risk factor for atherosclerosis, with

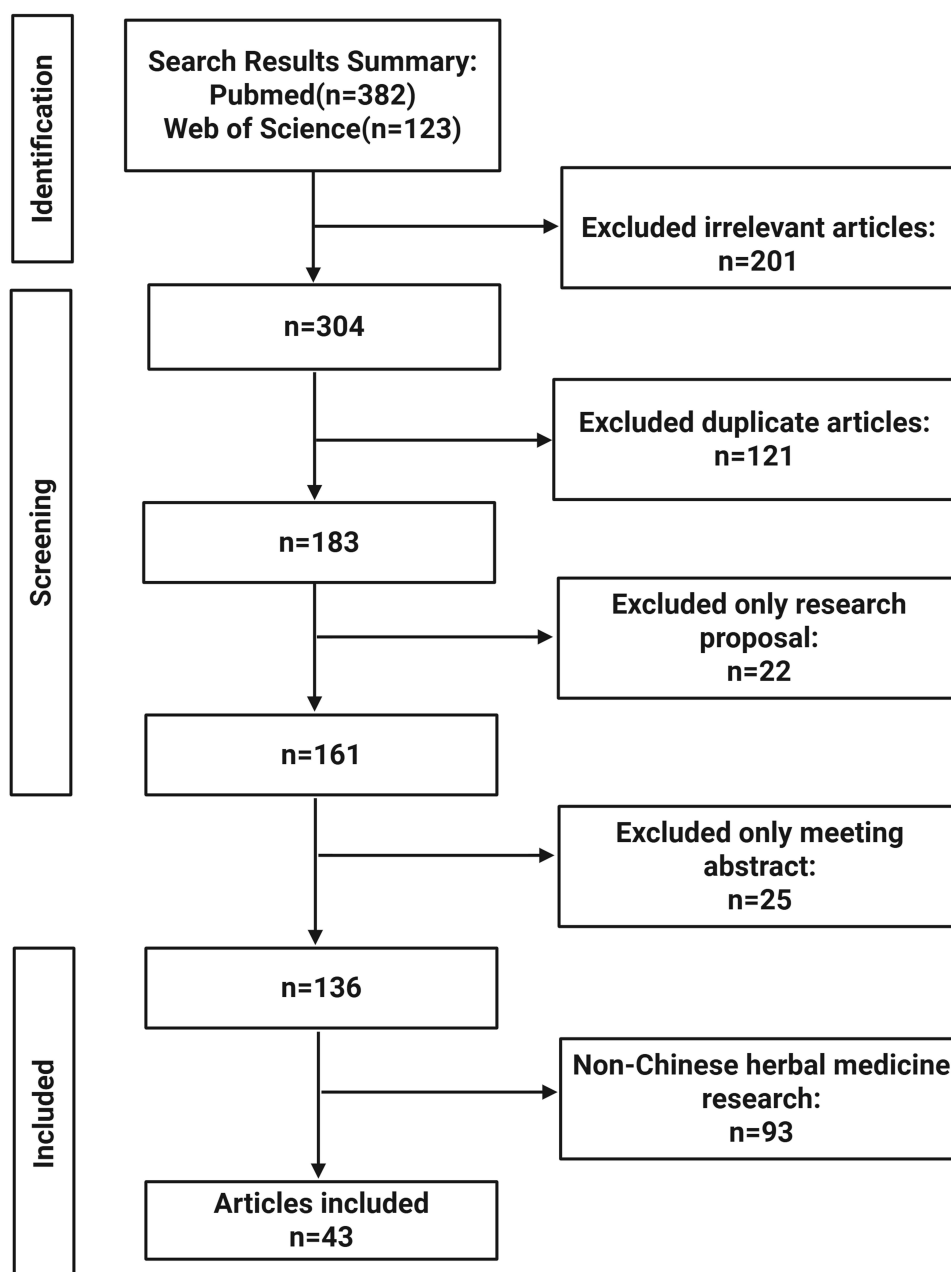


Figure 1 The detailed process of literature screening. Conduct a literature search using search strategy in the PubMed and Web of Science, remove duplicates and irrelevant literature to the research topic, and conduct an in-depth study of the included literature.

its pathogenic effects originating from the functional disturbances of vascular endothelial cells.¹⁸ In the presence of persistent elevated glucose levels, endothelial cells exhibit a series of pathological alterations, including the upregulation of pro-inflammatory adhesion molecules, the uncoupling of endothelial nitric oxide synthase (eNOS), resulting in diminished bioavailability of nitric oxide (NO), augmented oxidative stress, as well as cell death and senescence.^{19–22} The combined consequences of these changes are disruption of endothelial barrier integrity and a significant increase in permeability, creating the initial conditions for the deposition of low-density lipoprotein (LDL) beneath the endothelium and the infiltration of macrophages. Consequently, hyperglycemia-induced endothelial dysfunction is recognized as the “initiator” of the atherosclerotic process, signifying the pivotal initial connection between metabolic disorders and vascular pathology. The mechanism of hyperglycemia-induced endothelial cell injury is illustrated in Figure 2.

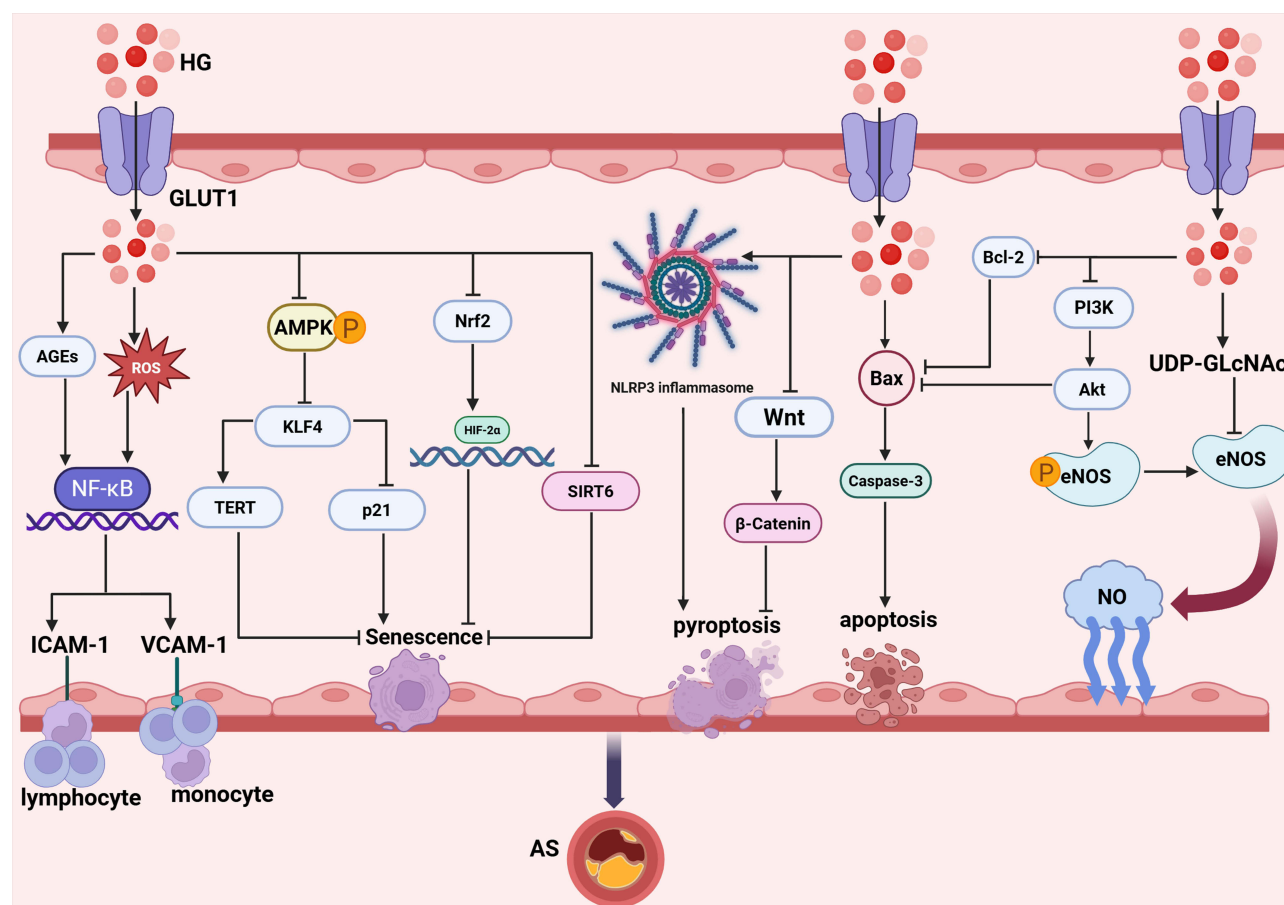


Figure 2 Molecular mechanisms of hyperglycemia-driven endothelial dysfunction promoting atherosclerosis. Hyperglycemia (HG) enters endothelial cells via GLUT1 and activates multiple pathological signaling pathways. On the one hand, HG promotes the generation of ROS and AGEs, activating the NF- κ B signaling pathway and upregulating the expression of ICAM-1 and VCAM-1, thereby facilitating the adhesion of monocytes and lymphocytes. Additionally, HG activates the hexosamine pathway to produce UDP-GlcNAc, which inhibits eNOS activity and significantly reduces NO production. Moreover, HG suppresses the PI3K/Akt/eNOS pathway, decreasing eNOS phosphorylation levels and reducing both eNOS activity and NO generation. Moreover, HG can directly upregulate Bax expression and downregulate Bcl-2 protein, thereby promoting apoptosis. Simultaneously, HG can inhibit the Wnt/ β -catenin pathway, thereby inducing pyroptosis. In addition, HG can also activate the NLRP3 inflammasome to induce pyroptosis. On the other hand, HG inhibits AMPK phosphorylation, thereby relieving the suppression of KLF4. The activation of KLF4 can relieve the inhibition of p21 and suppress TERT activity, ultimately inducing cellular senescence. Furthermore, HG can disrupt the interaction between Nrf2 and HIF-2 α , thereby inducing endothelial senescence. Meanwhile, HG can also directly downregulate SIRT6 expression, promoting cellular senescence. Under the combined effects of these multiple mechanisms of high glucose on endothelial cells, vascular endothelial integrity is compromised, accelerating the formation and progression of diabetes-associated atherosclerosis.

eNOS Activity Decline

eNOS is a calcium-dependent enzyme predominantly located in vascular endothelial cells. Under normal physiological conditions, eNOS catalyzes the conversion of L-arginine to NO, which subsequently exerts multiple physiological functions, including regulating vascular tone and maintaining vascular dilation.²³ In addition to these effects, NO has been shown to inhibit platelet aggregation, suppress inflammatory responses, and promote angiogenesis.^{24,25} However, under certain pathological conditions, eNOS may alter its activity and leading to a significant reduction in NO production. Research has demonstrated that under conditions of hyperglycemia, the hexosamine pathway is overactivated, which inhibits the activity of eNOS, thereby reducing the production of NO.²⁶ Furthermore, the hyperglycemia environment has been shown to reduce the phosphorylation levels of protein kinase B (AKT) and phosphatidylinositol 3-kinase (PI3K), thereby inhibiting the activity of the PI3K/AKT signaling pathway. This phenomenon also results in a decrease in eNOS phosphorylation, which, in turn, leads to the suppression of eNOS activity and, consequently, a further reduction in NO production.²⁷

The reduction in NO production can trigger a cascade of adverse consequences. On the one hand, the anti-inflammatory capacity of endothelial cells is diminished, resulting in the infiltration of inflammatory cells into the

vascular wall. Conversely, a reduction in NO production has been shown to impair endothelial cell repair, resulting in a decrease in their number and, consequently, a compromise in the integrity of the vascular endothelium and a weakening of the vascular barrier.^{28,29} The synergistic effect of these factors can lead to a heightened rate of atherosclerosis progression.

Upregulation of Adhesion Molecule Expression

Chronic inflammation is a hallmark of hyperglycemia. Hyperglycemia has been demonstrated to induce the production of substantial quantities of reactive oxygen species (ROS) and advanced glycation end products (AGEs) within the body. These phenomena have been observed to activate the NF- κ B pathway.^{30,31} Upon activation, NF- κ B initiates the transcription of a series of pro-inflammatory genes, including those encoding intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). ICAM-1 and VCAM-1 are both expressed at high levels on the surface of endothelial cells. These adhesion molecules function as “hooks” on the rails, enabling circulating monocytes and lymphocytes to firmly adhere to the typically smooth vascular endothelium by binding to ICAM-1 and VCAM-1.³² Subsequent to adhesion, leukocytes undergo further activation, resulting in the release of additional inflammatory cytokines. These cytokines have been shown to recruit additional immune cells to the site, thereby exacerbating the local inflammatory response and promoting plaque progression.³³

Endothelial Cell Death and Senescence

Cell death is a significant phenomenon in life processes, playing a pivotal role in the development and maintenance of physiological homeostasis and health in organisms. The phenomenon of cell death can be broadly categorized into two distinct classifications: programmed cell death and non-programmed cell death. Programmed cell death, otherwise known as apoptosis and pyroptosis, contrasts with non-programmed cell death, which is primarily characterized by necrosis.³⁴ During the progression of atherosclerotic lesions, a hyperglycemic microenvironment induces aberrant endothelial cell death, which impairs endothelial integrity. Consequently, a substantial amount of LDL in the bloodstream infiltrates the subendothelial space through these defective sites, undergoes oxidation to form oxidized low-density lipoprotein (ox-LDL), and accumulates as lipid streaks—the pathological core of atherosclerosis—thereby accelerating disease progression.³⁵ Research has demonstrated that hyperglycemia treatment significantly inhibits the activity of the PI3K/Akt signaling pathway in human umbilical vein endothelial cells (HUVECs). Concurrently, the study found that hyperglycemia treatment upregulates the expression of caspase 3 and Bcl-2-associated X protein (Bax) proteins and downregulates the level of the B cell lymphoma-2 (Bcl-2) protein. The result of these changes is the promotion of apoptosis in HUVECs.²⁷ Additionally, hyperglycemia has been reported to further increase apoptosis in HUVECs by inhibiting the Wnt/ β -catenin pathway.³⁶ Moreover, hyperglycemia has also been found to activate the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, thereby inducing pyroptosis in endothelial cells.³⁷

Cellular senescence is an inevitable natural process in organisms. It serves as a self-protective mechanism of cells in response to external stimuli and is also closely associated with organismal aging and the development of various chronic diseases.¹⁹

It has been reported that high glucose induced cellular senescence exerts a direct pro-atherosclerotic effect.³⁸ Endothelial cell senescence is characterized by permanent arrest of cell growth and proliferation. Pathological studies have demonstrated that senescent endothelial cells accumulate in the subendothelial space at the onset of AS, driving disease pathogenesis by upregulating the expression of key pro-atherosclerotic inflammatory cytokines and chemokines, thereby acquiring a phenotype termed the senescence-associated secretory phenotype.^{39,40} Furthermore, due to impaired cell proliferation, permeability, and motility, endothelial cell senescence compromises endothelial barrier function, which may lead to endothelial erosion and intraplaque hemorrhage.^{41,42} Research has demonstrated that a hyperglycemia environment has the capacity to impede AMP-activated kinase (AMPK) phosphorylation, consequently diminishing its inhibitory effect on Krüppel-like factor 4 (KLF4) and resulting in augmented KLF4 expression. As a transcription factor, KLF4 has been observed to exert dual regulatory functions, namely the activation of the pro-senescence gene p21 and the repression of telomerase reverse transcriptase (TERT). This phenomenon ultimately leads to the senescence of HUVECs and the expansion of the area occupied by atherosclerotic plaques.⁴³ Additionally, it has been reported that

hyperglycemia can downregulate Sirtuin type-6 (SIRT6) expression, thereby inducing endothelial cell senescence.⁴⁴ Furthermore, the available evidence suggests that elevated glucose levels can interfere with the interaction between nuclear factor erythroid-2 related factor 2 (Nrf2) and hypoxia-inducible factor-2 α (HIF-2 α), consequently weakening the inhibition of HIF-2 α 's pro-oxidative effects. Consequently, this results in the activation of senescence pathways, which in turn triggers endothelial cell senescence and promotes the development and progression of diabetic vascular complications.⁴⁵

Mechanism of Hyperglycemia-Induced Damage to Macrophages

Foam cells represent the hallmark pathological feature of atherosclerosis. These macrophage-derived cells, characterized by abundant cytoplasmic lipid droplets, constitute the lipid core of atherosclerotic plaques. Previous studies have established that the excessive uptake of LDL by macrophages via scavenger receptors is the central mechanism underlying foam cell formation.⁴⁶ Emerging evidence indicates that hyperglycemia can further promote lipid accumulation and foam cell transformation in macrophages on this basis, thereby accelerating the progression of atherosclerotic lesions.⁴⁷ Elucidating the mechanisms by which hyperglycemia drives macrophage foam cell formation will provide novel targets for atherosclerosis intervention strategies targeting the metabolism-immunity interface. The mechanism of hyperglycemia-induced Macrophages injury is illustrated in Figure 3.

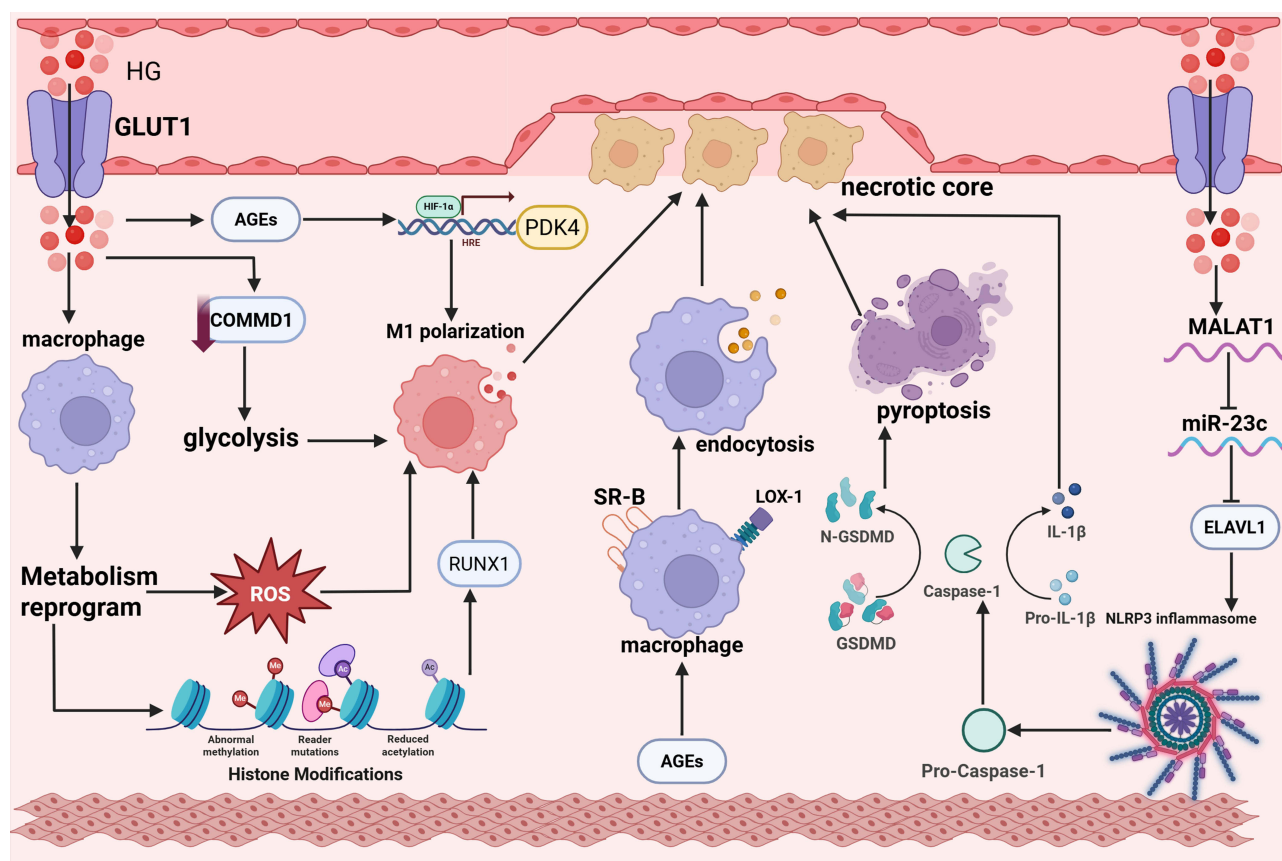


Figure 3 Molecular mechanisms of hyperglycemia-driven macrophage dysfunction promoting atherosclerosis. Upon entering the vascular wall via GLUT1, HG induces macrophage metabolic reprogramming: On one hand, HG promotes ROS generation, inducing macrophage M1 polarization; on the other hand, through histone modification-mediated epigenetic reprogramming, HG activates the RUNX1 transcription factor, driving macrophage polarization toward the pro-inflammatory M1 phenotype. Additionally, HG induces COMMD1 deficiency, enhances the glycolytic pathway, and thereby promotes macrophage M1 polarization. Meanwhile, HG also promotes AGE formation; AGEs further enhance M1 polarization via the HIF-1 α /PDK4 pathway, and can bind to macrophage surface receptors such as SR-B and LOX-1, enhancing macrophage endocytosis and promoting lipid uptake. Simultaneously, HG can also upregulate MALAT1 expression, inhibit miR-23c expression, relieve the suppression of ELAVL1, thereby promoting NLRP3 inflammasome activation, activating Caspase-1-dependent GSDMD cleavage, inducing pyroptosis, and the release of inflammatory factors such as IL-1 β . Ultimately, these pathological processes promote the development and progression of necrotic cores in diabetes-associated atherosclerosis.

Metabolic Reprogramming

Macrophage polarization is defined as the process by which macrophages acquire distinct functional phenotypes and stably express corresponding marker molecules in response to signals from the microenvironment.⁴⁸ The categorisation of this condition is primarily into M1 and M2 subtypes. M1-type macrophages have the capacity to secrete substantial quantities of proinflammatory cytokines, thereby exacerbating inflammatory responses. Furthermore, M1 macrophages have also been shown to produce matrix metalloproteinases. These enzymes have the capacity to degrade the fibrous cap of atherosclerotic plaques, thereby impairing plaque stability and increasing the risk of plaque rupture.⁴⁹ Upon uptake of ox-LDL, M1-type macrophages undergo a transformation into foam cells. These foam cells accumulate within the arterial wall, forming the core of atherosclerotic plaques. The accumulation of foam cells has been demonstrated to augment plaque volume, thereby amplifying the inflammatory response.⁵⁰ Conversely, M2-type macrophages have been shown to exhibit anti-inflammatory properties, thereby facilitating tissue repair and angiogenesis.⁵¹ Furthermore, M2-type macrophages exhibit robust phagocytic activity, enabling them to clear apoptotic cells and cellular debris, which in turn contributes to atherosclerotic plaque stabilisation.⁵²

In recent years, the field of immunometabolism has undergone rapid development, leading to a significant increase in research activity. This has included research into metabolic reprogramming in the context of cardiovascular diseases. Glucose metabolic reprogramming, in particular, has attracted considerable attention due to its role as a regulatory node. Studies have confirmed that the atherosclerotic plaque microenvironment is characterized by hyperglycemia, hypoxia, and lipid enrichment. Macrophages infiltrating this microenvironment undergo an irreversible metabolic pattern switch—specifically, shifting from mitochondrial-dependent oxidative phosphorylation to aerobic glycolysis.^{53,54} This metabolic reprogramming event has been confirmed to be a crucial driver regulating the polarization of macrophages toward a proinflammatory phenotype, thereby accelerating the formation and unstable progression of atherosclerosis plaques.⁵⁵

Previous studies have demonstrated that hyperglycemia can significantly enhance cellular glucose uptake capacity by upregulating the expression level of glucose transporter 1 (GLUT1) on the macrophage surface, ultimately inducing glucose metabolic reprogramming in macrophages.^{56,57} This process is accompanied by increased ROS production, which in turn drives the activation of macrophages toward a proinflammatory phenotype. In addition, deficiency of copper metabolism domain-containing protein 1 (COMMD1) is also a critical predisposing factor for diabetes-associated atherosclerosis. The underlying mechanism involves the direct promotion of glycolysis pathway activation in macrophages, which in turn enhances the pro-inflammatory activation of macrophages and foam cell formation. Notably, 2-deoxy-D-glucose (2-DG), a glycolysis-specific inhibitor, can effectively reverse the aforementioned pathological effects, further corroborating the central role of glucose metabolic reprogramming in this pathological process.⁵⁸ A study by Edgar⁵⁹ et al further expands this understanding, demonstrating that hyperglycemia can not only induce a shift in aerobic glycolysis-mediated metabolic reprogramming in mature macrophages but also in their precursor hematopoietic stem cells. This metabolic switch triggers histone modification-mediated epigenetic reprogramming, which activates the transcription factor Runt-related transcription factor 1 (RUNX1) to regulate the sustained expression of downstream pro-inflammatory genes, ultimately leading to macrophages maintaining a pro-atherosclerotic phenotype. Furthermore, when the research team transplanted bone marrow from diabetic mice into atherosclerosis-susceptible mice with normoglycemia, they found that this transplantation exacerbated the severity of atherosclerotic lesions at the aortic root in recipient mice. Additionally, they validated the conservation of the aforementioned metabolic and epigenetic regulatory patterns in human peripheral blood mononuclear cells and macrophages derived from atherosclerotic plaques. This finding suggests that hyperglycemia can induce trained immunity in macrophages and their progenitor hematopoietic stem cells via a glycolysis-dependent mechanism. This provides a crucial mechanistic explanation for the observation that clinical hypoglycemic therapy is challenging to effectively reduce the risk of macrovascular complications in diabetic patients.

Accumulation of Advanced Glycation End Products

AGEs are heterogeneous, irreversible adducts generated by the non-enzymatic glycation and oxidation of proteins, lipids, and nucleic acids.⁶⁰ In diabetic patients, chronic hyperglycemia promotes the formation and accumulation of AGEs, thereby facilitating the development and progression of diabetic vascular complications.⁶¹ Studies have demonstrated that

AGEs enhance M1 polarization of macrophages via hypoxia-inducible factor-1 α (HIF-1 α)/Pyruvate dehydrogenase kinase 4 (PDK4) pathway, thereby accelerating the progression of diabetes-associated atherosclerosis. Notably, this inductive effect exhibits concentration- and time-dependent characteristics.⁶² Furthermore, AGEs can enhance the endocytosis of macrophages, thereby increasing lipid uptake. This effect is attributed to the interaction of AGEs with macrophage surface receptors (eg, scavenger receptors class B (SR-B) and lectin-like oxidized low-density lipoprotein receptor 1 [LOX-1]), which upregulates the expression of these receptors.⁶³

Macrophage Death

Accumulating research evidence indicates that the aberrant death of macrophages contributes to the progression of atherosclerosis. This is primarily attributed to the massive release of pro-inflammatory cytokines from dying macrophages, which exacerbates the instability of atherosclerotic plaques.^{64,65} It has been reported that high glucose can regulate macrophage death. Hyperglycemia upregulates the expression of the long non-coding Ribonucleic Acid (RNA) metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). MALAT1 specifically binds to and inhibits the function of miR-23c, which normally targets and suppresses the expression of ELAV like RNA binding protein 1 (ELAVL1) by direct binding. The sequestration of miR-23c by MALAT1 impairs its inhibitory activity, thereby relieving the repression of ELAVL1 and leading to a marked elevation in ELAVL1 protein levels. As a positive regulator of the NLRP3 inflammasome, the upregulated ELAVL1 directly activates the NLRP3 inflammasome complex. Once activated, the inflammasome cleaves pro-caspase-1 into its biologically active form, caspase-1. On the one hand, active caspase-1 induces macrophage pyroptosis; on the other hand, it promotes the maturation and secretion of the pro-inflammatory cytokine Interleukin-1 β (IL-1 β). These processes further amplify the inflammatory response and accelerate the progression of diabetes-associated atherosclerosis.⁶⁶ The persistent inflammatory microenvironment and cell pyroptosis accelerate the formation of atherosclerotic plaques, thereby enhancing the progression of diabetes-related atherosclerosis.⁶⁷

Mechanism of Hyperglycemia-Induced Damage to Vascular Smooth Muscle Cells

Vascular smooth muscle cells (VSMCs) play a pivotal role in determining vascular caliber, regulating blood pressure, and mediating local tissue perfusion.⁶⁸ Dysfunction of VSMCs constitutes a fundamental mechanism underlying the pathogenesis of vascular diseases. Moreover, hyperglycemia can induce VSMCs dysfunction, thereby contributing to the development of vascular atherosclerosis. The mechanism of hyperglycemia-induced VSMCs injury is illustrated in Figure 4.

Migration, proliferation, and inflammation represent the major hallmarks of phenotypic changes in VSMCs. Under physiological conditions, VSMCs exist in a contractile phenotype, whose primary function is to maintain vascular tone and hemodynamic homeostasis.⁶⁹ However, under hyperglycemic conditions, VSMCs rapidly initiate a dedifferentiation program and transdifferentiate into a synthetic/inflammatory phenotype. This phenotypic shift is characterized by a marked downregulation of contractile proteins, coupled with enhanced synthetic, secretory, and migratory capacities. Consequently, VSMCs become the major cellular source of the fibrous cap and neointima in atherosclerosis plaques.^{70,71}

Activation of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway represents one of the critical mechanisms underlying hyperglycemia-induced phenotypic switching of VSMCs. Under hyperglycemic conditions, angiotensin II (AngII) exerts a direct interaction with Janus kinase 2 (JAK2) via the angiotensin type 1 receptor (AT1), which promotes the tyrosine phosphorylation of JAK2 and inhibits the activity of Src homology region 2 domain-containing phosphatase-1 (SHP-1)-its negative regulator—thereby prolonging the phosphorylated state of JAK2.^{72,73} Subsequently, signal transducer and activator of transcription 3 (STAT3) is phosphorylated and translocates into the nucleus, where it acts as a transcription factor to regulate the expression of downstream target genes. Specifically, phosphorylated STAT3 suppresses myocardin-mediated expression of contractile proteins, while upregulating the expression of proliferative genes.⁷⁴ These regulatory effects collectively induce the phenotypic transition of VSMCs from a contractile to a synthetic phenotype, and further enhance VSMCs proliferation and migration.

Krüppel-like factors (KLFs) also play a crucial role in hyperglycemia-induced phenotypic switching of VSMCs. VSMCs isolated from diabetic patients and murine models treated with hyperglycemia exhibit enhanced Krüppel-like factor 5 (KLF5) expression.⁷⁵ Specifically, nitration modification occurs at the tyrosine residues of KLF5, which

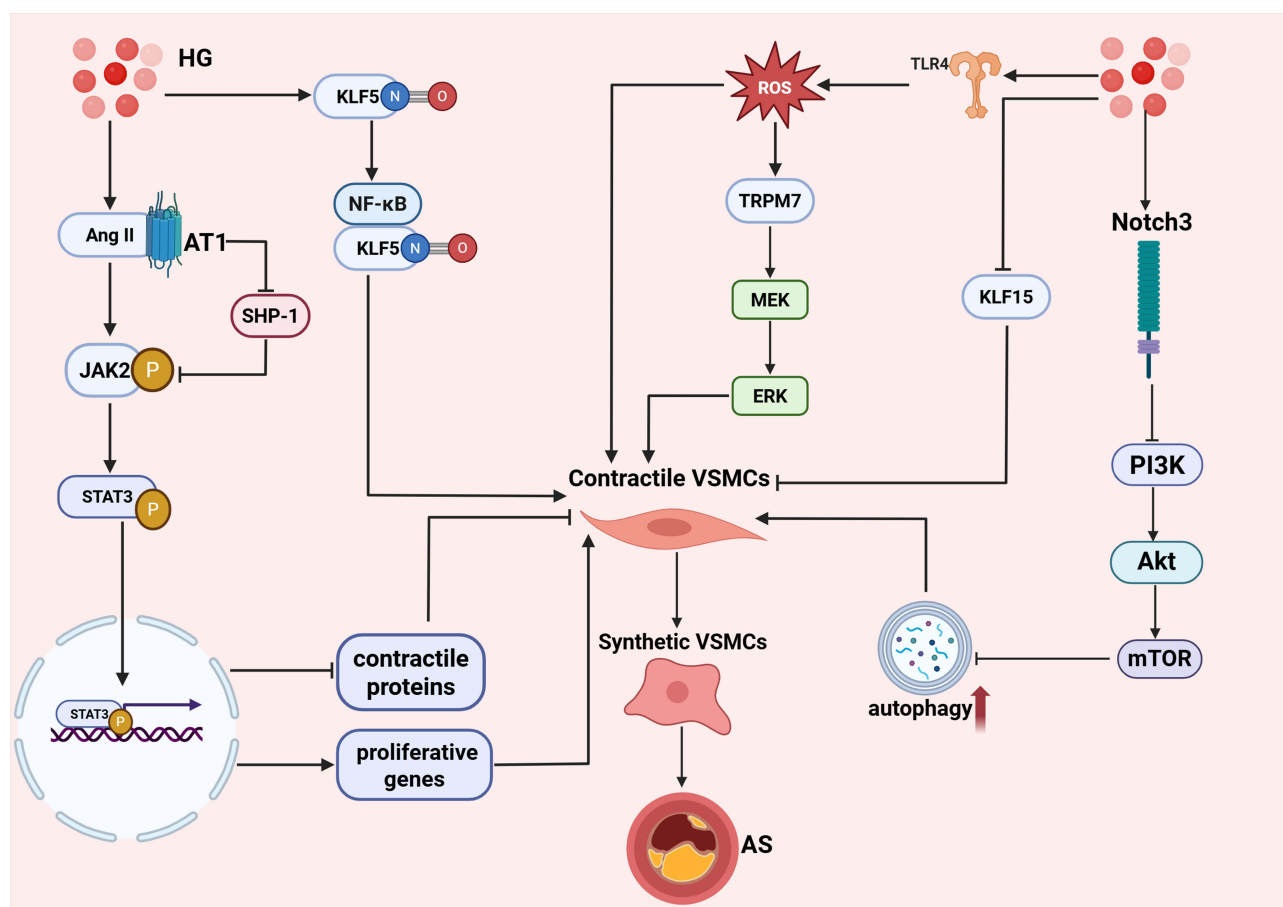


Figure 4 Molecular mechanisms of hyperglycemia-driven VSMCs dysfunction promoting atherosclerosis. On one hand, HG promotes Ang II binding to the AT1 receptor, activating the JAK2/STAT3 signaling pathway; phosphorylated STAT3 translocates into the nucleus to suppress contractile protein expression while upregulating proliferation genes, driving VSMCs phenotypic switching. On the other hand, HG induces tyrosine nitration of KLF5, promoting its interaction with NF- κ B and increasing pro-inflammatory cytokine expression; meanwhile, HG downregulates KLF15 expression, relieving its negative regulation of phenotypic switching. Additionally, HG activates the TLR4 signaling pathway to promote excessive ROS generation; ROS upregulates TRPM7 expression and activates the MEK/ERK signaling pathway to facilitate VSMCs phenotypic switching, while accumulated ROS can also directly promote phenotypic transformation. Furthermore, HG upregulates Notch3 expression, inhibiting the PI3K/Akt/mTOR pathway and causing excessive autophagy activation, which further promotes VSMCs switching toward the synthetic phenotype. Ultimately, phenotypically transformed VSMCs exhibit enhanced proliferation, migration, and secretion capabilities, accelerating diabetes-associated atherosclerotic plaque progression.

facilitates its interaction with NF- κ B and thereby increases the expression of pro-inflammatory cytokines. Furthermore, studies⁷⁶ have demonstrated that the aortas of mice treated with hyperglycemia exhibit decreased KLF15 mRNA expression, elevated levels of pro-inflammatory cytokines, and enhanced cellular proliferation. Notably, overexpression of KLF15 can reverse these aforementioned effects, suggesting that KLF15 may serve as a negative regulator of VSMCs phenotypic switching under hyperglycemic conditions.

Hyperglycemia also modulates the generation of ROS. Specifically, it promotes excessive ROS production by activating Toll-like receptor 4 (TLR4) signaling in VSMCs. Conversely, inhibition of TLR4 leads to a significant reduction in ROS levels in hyperglycemia-treated VSMCs.⁷⁷ Excessive ROS accumulation can drive the proliferation, migration, and apoptosis of VSMCs, thereby facilitating the completion of phenotypic switching. Accumulating evidence has demonstrated that hyperglycemia induces oxidative stress, which in turn upregulates the mRNA and protein expression of transient receptor potential melastatin 7 (TRPM7) and activates the mitogen-Activated protein kinase-(MEK)/extracellular signal-regulated kinase(ERK)signaling pathway. Collectively, these events promote the phenotypic switching of aortic VSMCs from the contractile to the synthetic phenotype and enhance cellular proliferation in rats. Notably, silencing of TRPM7, inhibition of MEK1/2, or scavenging of ROS can significantly abrogate the aforementioned effects, thus confirming that the ROS-TRPM7-ERK1/2 axis serves as a critical mechanism underlying hyperglycemia-induced abnormal proliferation and phenotypic switching of VSMCs.⁷⁸ Notably, autophagy, a catabolic process

responsible for the clearance and recycling of damaged cells and organelles, is also involved in the phenotypic switching of VSMCs. Accumulating evidence suggests that autophagy is crucial for maintaining the contractile phenotype of VSMCs, whereas excessive autophagy promotes the phenotypic transition of VSMCs toward a synthetic phenotype. Furthermore, studies have demonstrated that hyperglycemia upregulates Notch receptor 3 (Notch3) expression, which in turn inhibits PI3K/Akt/mechanistic target of rapamycin (mTOR) signaling pathway, thereby exacerbating the excessive activation of autophagy.⁷⁹

Ultimately, VSMCs that have undergone phenotypic switching exhibit robust proliferative, migratory, and secretory capacities. Studies have revealed that hyperglycemia treatment leads to an elevated rate of DNA synthesis and an increased migratory rate of VSMCs. Moreover, this treatment results in enhanced activities of matrix metalloproteinase-2 and -9, which further potentiates the migratory capacity of these cells.^{80,81} Furthermore, dedifferentiated VSMCs secrete substantial amounts of OPN, type I collagen, and fibronectin, which contribute to the formation of the fibrous cap. Concomitantly, these cells release pro-inflammatory cytokines including interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and granulocyte-macrophage colony-stimulating factor, thereby recruiting monocytes/macrophages and amplifying local vascular inflammation.⁸² Single-cell sequencing studies have further revealed that VSMCs under hyperglycemic conditions can undergo further multidirectional phenotypic differentiation into diverse subpopulations, including osteogenic-like, chondrogenic-like, macrophage-like, and even stem cell-like subsets, thereby providing a cellular basis for plaque calcification and neovascularization.^{83,84}

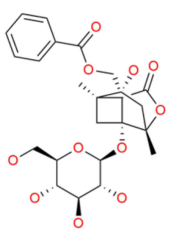
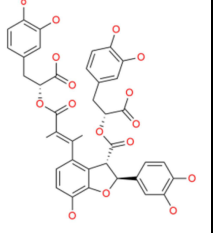
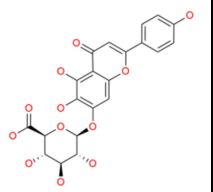
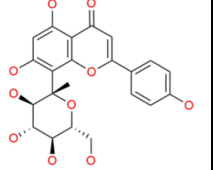
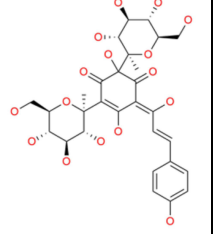
Mechanisms of Chinese Herbal Medicines in Intervening with Diabetes-Associated Atherosclerosis

The pathogenic mechanisms underlying hyperglycemia-driven atherosclerosis are highly intricate, with macrophages, endothelial cells, and VSMCs playing pivotal roles. Recent investigations have revealed that traditional Chinese herbal medicines exhibit a “multi-component–multi-target–multi-pathway” pattern of synergistic regulation. Contemporary pharmacological investigations have further confirmed that traditional Chinese herbal medicines and their bioactive constituents possess anti-apoptotic, antioxidant, anti-inflammatory, and hypoglycemic properties.^{85,86} These attributes endow traditional Chinese herbal medicines with unique advantages in the prevention and treatment of hyperglycemia-associated atherosclerosis. Moreover, traditional Chinese herbal remedies have been formally incorporated into China’s clinical management pathway for hyperglycemia-associated atherosclerosis, and their efficacy has been substantiated by a growing body of evidence-based investigations.^{87,88} Building on these foundations, the precise delineation of molecular targets and the mechanistic underpinnings of bioactive constituents derived from traditional Chinese herbal medicines is expected to furnish novel strategies for the precision management of hyperglycemia-driven atherosclerosis. Consequently, a systematic dissection of the molecular networks through which these phytochemicals modulate hyperglycemia-associated atherosclerosis will provide innovative translational avenues for subsequent drug discovery and clinical application. The table summarizes the protective effects of Chinese herbal medicines decoctions and active components against hyperglycemia-associated atherosclerosis (Table 1).

Protection Mechanisms of Chinese Herbal Medicines Intervention on Endothelial Cells in Hyperglycemia Environments

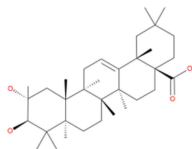
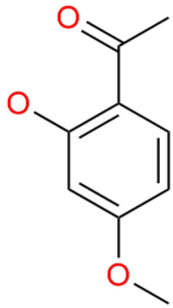
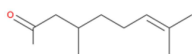
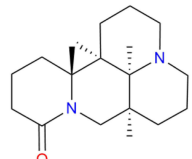
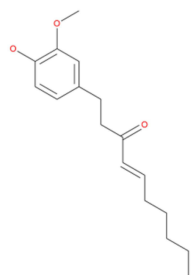
Albiflorin, a monoterpene glycoside, is the principal bioactive constituent isolated from the traditional Chinese herb Baishao (*Paeonia lactiflora* Pall). Studies have found that Albiflorin can enhance the sensitivity of peripheral tissues to insulin and improve insulin-stimulated glucose clearance. Additionally, it can promote the translocation of glucose transporter 4 (GLUT4) to the cell membrane, accelerate glucose uptake by cells, and reduce blood glucose levels. Furthermore, Albiflorin can regulate systemic energy metabolism, thereby maintaining blood glucose homeostasis.^{14,103} Recent research has revealed that Albiflorin also exhibits a protective effect on blood vessels. In an in vitro model, Yang et al demonstrated that albiflorin can reverse the loss of viability in HUVECs induced by hyperglycemia. They also found that albiflorin can promote the proliferation and migration of HUVECs, as well as suppress the release of pro-inflammatory cytokines, such as tumour necrosis factor- α (TNF- α), IL-6 and IL-1 β . Finally, they observed that

Table 1 Active Components and Decoctions Protective Effects on Diabetes-Associated Atherosclerosis

Active Components and Decoctions	Source	Relevant Cellular Targets	Molecular Target	Molecular Weight (g/mol)	Chemical Structure	References
Albiflorin	Baishao (<i>Paeonia lactiflora</i> Pall.)	HUVECs,	PARP1, TNF- α , IL-6, IL-1 β	480.5		[13]
Salvianolic acid B	Danshen (<i>Salvia miltiorrhiza</i> Bunge)	HUVECs,	ROCK1	718.6		[89]
Scutellarin	Deng Zhanhua (<i>Erigeron breviscapus</i> (Vaniot) Hand.-Mazz.)	HUVECs	Nrf2, FBXL2, NLRP3	462.4		[90]
Vitexin	Shanzha (<i>Crataegus pinnatifida</i> Bunge)	HUVECs	wnt/ β -catenin, bax/bcl-2, TCF/LEF	432.4		[36]
Hydroxysafflor yellow A	Honghua (<i>Carthamus tinctorius</i> L.)	HUVECs	MDA, GPX4, SLC7A11, ACSL4, miR-429	612.5		[91]
Ginsenoside Rb1	Renshen (<i>Panax ginseng</i> C. A. Mey.)	HUVECs	Nrf2/PGC-1 α , Keap1, p47phox,	1109.3	-	[18]

(Continued)

Table 1 (Continued).

Active Components and Decoctions	Source	Relevant Cellular Targets	Molecular Target	Molecular Weight (g/mol)	Chemical Structure	References
Maslinic acid	Shanzha (<i>Crataegus pinnatifida</i> Bunge)	HUVECs	TNF- α , IL-6, IL-1 β , ALKBH5, TXNIP	472.7		[92]
Paeonol	Mu Danpi (<i>Paeonia suffruticosa</i> Andr.)	HUVECs	SIRT1, FOXO3a, NF- κ B	166.17		[93]
Citronellal	Xiangmao (<i>Cymbopogon citratus</i> (DC). Stapf)	HUVECs	MDA, SIP/SIPI	154.25		[94]
Matrine	Ku Douzi (<i>Sophora alopecuroides</i> L.)	Macrophage	DNMT3a/b, GPX1, TLR4/STAT1, RAGE	248.36		[95]
Panax notoginseng saponins	Sanqi (<i>Panax notoginseng</i> (Burkill) F. H.Chen)	Macrophage	I κ B- α , NF- κ B	-	-	[96]
Astragalus polysaccharide	Huangqi (<i>Astragalus membranaceus</i> (Fisch). Bunge)	Macrophage	IL-6, TNF- α , MCP-1 Nrf2/HO-1	-	-	[97]
6-shogaol	Ganjiang (<i>Zingiber officinale</i> Rosc.)	VSMCs	Akt, NLRP3, OCN, ALP	276.4		[98]
Sodium Tanshinone IIA Silate	Danshen (<i>Salvia miltiorrhiza</i> Bunge)	VSMCs	p53, cyclinD1, MMP-2, NF- κ B, AMPK	-	-	[99]

(Continued)

Table 1 (Continued).

Active Components and Decoctions	Source	Relevant Cellular Targets	Molecular Target	Molecular Weight (g/mol)	Chemical Structure	References
Buyang Huanwu Decoction (BYHWD)	Huangqi (<i>Astragalus membranaceus</i> (Fisch.) Bunge), Danggui (<i>Angelica sinensis</i> (Oliv.) Diels), Chishao (<i>Paeoniae Radix Rubra</i>), Dilong (<i>Pheretima aspergillum</i>), Chuanxiong (<i>Ligusticum wallichii</i> Franch.), Taoren (<i>Prunus persica</i> (L.) Batsch), Honghua (<i>Carthamus tinctorius</i> L.)	HUVECs	AMPK, Drp1, Fis1	-	-	[100]
Guanxining tablets (GXN)	Danshen (<i>Salvia miltiorrhiza</i> Bunge), Chuanxiong (<i>Ligusticum wallichii</i> Franch.)	HUVECs	IRE1, XBPI	-	-	[101]
Fufang Zhenzhu Tiaozhi capsules (FTZ)	Huanglian (<i>Coptis chinensis</i> Franch.), Danshen (<i>Salvia miltiorrhizae</i> Radix), Sanqi (<i>Panax notoginseng</i> (Burkill) F.H.Chen), Nü Zhenzi (<i>Ligustri Lucidi Fructus</i>), Daoji (<i>Cirsii Japonici Herba</i>), Duzhong (<i>Eucommia ulmoides</i> Oliv), Fuoshou (<i>Citri Sarcodactylis Fructus</i>), and Baizhu (<i>Atractylodis Macrocephalae Radix</i>)	HUVECs	YTHDF2, SIRT3, bax, caspase-3	-	-	[102]

albiflorin can attenuate endothelial apoptosis. Molecular-docking simulations in combination with plasmid transfection assays, performed by the same research group, identified poly (ADP-ribose) polymerase-1 (PARP1) as the critical molecular target through which albiflorin exerts its protective actions.¹³

Salvianolic acid B, a polyphenolic compound extracted from the traditional Chinese medicinal herb Danshen (*Salvia miltiorrhiza* Bunge), has attracted extensive scholarly attention because of its comprehensive cardiovascular protective effects.¹⁰⁴ Studies have shown that salvianolic acid B lowers blood glucose levels. Salvianolic acid B upregulates the expression of GLUT4 and glycogen synthase in skeletal muscle, promoting the uptake and utilization of glucose by peripheral tissues.¹⁰⁵ At the same time, salvianolic acid B can also inhibit hepatic gluconeogenic gene expression, reduce fasting blood glucose levels, and improve abnormal glucose tolerance. In addition, salvianolic acid B alleviates insulin resistance by inhibiting endoplasmic reticulum stress in the liver.^{106,107} Recent studies have found that salvianolic acid B can reduce vascular inflammation and inhibit the progression of atherosclerosis. Ko⁸⁹ et al used a hyperglycemia combined with oxLDL-induced human endothelial cell injury model to confirm that salvianolic acid B dose-dependently inhibits mitochondrial reactive oxygen species generation, thereby reducing oxidative stress. Specifically blocking Rho-associated coiled-coil-containing protein kinase 1 (ROCK1) pathway inhibits endothelial cell apoptosis and mitochondrial fission abnormalities, ultimately improving endothelial cell injury, alleviating endothelial dysfunction, and ameliorating hyperglycemia-induced endothelial cell injury.

Scutellarin, a flavonoid isolated from the traditional Chinese medicinal herb Deng Zhanhua (*Erigeron breviscapus* (Vaniot) Hand.-Mazz), exhibits potent anti-inflammatory, antioxidant, and vasorelaxant properties.^{108,109} Currently, it is primarily employed in the clinical management of stroke and myocardial infarction.^{108,110} Studies have found that Scutellarin can activate the AMPK pathway, thereby improving insulin resistance; in addition, Scutellarin can accelerate glucose uptake and utilization by cells, thereby reducing blood glucose levels.^{111,112} Recent research has shown that Scutellarin can alleviate hyperglycemia-induced endothelial cell damage. Meng⁹⁰ et al utilized HUVECs to establish an in vitro model of diabetes-associated atherosclerosis induced by hyperglycemia. They found that scutellarin up-regulates Nrf2. Acting as a transcription factor, Nrf2 binds to the F-box and leucine-rich repeat protein 2 (FBXL2) promoter and enhances its transcription. FBXL2, in turn, targets the inflammasome core component NLRP3 for ubiquitin-dependent degradation. This process has been demonstrated to suppress endothelial pyroptosis and inflammatory responses, thereby ultimately ameliorating hyperglycemia-induced endothelial injury. Moreover, the team employed shRNA-mediated knockdown and demonstrated that silencing Nrf2 down-regulated FBXL2 and abolished the protective effect of

scutellarin. FBXL2 knockdown attenuated NLRP3 degradation and exacerbated cellular injury, whereas NLRP3 knockdown alleviated hyperglycemia-induced damage. These findings indicate that scutellarin confers protection against diabetic AS via the Nrf2-FBXL2–NLRP3 signaling axis.

Vitexin is a flavonoid compound extracted from traditional Chinese medicinal herbs such as Shanzha (*Crataegus pinnatifida* Bunge).¹¹³ Studies have shown that Vitexin can regulate insulin signaling pathways and improve insulin resistance. Additionally, it can inhibit α -glucosidase activity, delay the digestion and absorption of carbohydrates in the intestine, and thereby reduce postprandial blood glucose spikes.^{114,115} In vitro experiments conducted by Zhang et al revealed that vitexin facilitates the nuclear translocation of β -catenin and its subsequent interaction with T-cell factor (TCF)/lymphoid enhancer-binding factor (LEF) transcription factors, thereby suppressing the pro-apoptotic protein Bax while enhancing the expression of the anti-apoptotic protein Bcl-2, ultimately attenuating apoptosis in HUVECs.³⁶

Hydroxysafflor yellow A is a monomeric chalcone glycoside principally isolated from the traditional Chinese medicinal herb Honghua (*Carthamus tinctorius* L).¹¹⁶ Studies have found that Hydroxysafflor yellow A can reduce pancreatic β -cell apoptosis and maintain insulin secretion function; additionally, Hydroxysafflor yellow A can inhibit α -glucosidase activity, delay intestinal carbohydrate absorption, and lower postprandial blood glucose levels.^{117,118} It has been reported that hydroxysafflor yellow A exerts vascular-protective effects.¹¹⁹ Additionally, Xie et al demonstrated that hydroxysafflor yellow A effectively ameliorates H₂O₂-induced oxidative injury in human umbilical vein endothelial cells.¹²⁰ Rong⁹¹ et al constructed a diabetes AS model using ApoE^{−/−} mice and found that hydroxysafflor yellow A can improve glucose and lipid metabolism disorders, reduce the production of Malondialdehyde (MDA) and ROS, upregulate the expression of anti-ferroptosis-related proteins Glutathione Peroxidase 4 (GPX4) and Solute Carrier Family 7 Member 11 (SLC7A11), inhibit the pro-ferroptosis protein ACSL4, and downregulate the expression of miR-429. Moreover, the team also constructed a high-glucose and high-fat injury model using HUVEC, and further explored the mechanism through cell transfection technology. It was found that after transfection with miR-429 mimics (overexpressing miR-429) or SLC7A11 siRNA, the antioxidant stress and anti-ferroptosis effects of hydroxysafflor yellow A were weakened, and the protective effect on endothelial cells was significantly reduced. This indicates that hydroxysafflor yellow A exerts a protective effect on diabetes-associated atherosclerosis mice through the miR-429/SLC7A11 axis.

Ginsenoside Rb1 is a pivotal constituent of the ginsenoside family. Reports indicate that ginsenoside Rb1 can modulate central feeding mechanisms, suppress appetite, and reduce carbohydrate intake. Additionally, ginsenoside Rb1 can activate the AMPK pathway to promote glucose uptake, improve insulin resistance, and enhance insulin sensitivity, thereby achieving blood glucose regulation.¹²¹ Recent studies have shown that ginsenoside Rb1 also possesses cardiovascular and cerebrovascular protective effects.^{122,123} Wang¹⁸ et al established a murine model of diabetes-associated atherosclerosis in ApoE^{−/−} mice and demonstrated that ginsenoside Rb1 markedly attenuated oxidative stress and inflammatory responses while reducing aortic atherosclerotic plaque burden. Notably, tail-vein delivery of AAV9-Tie2 vectors to silence endothelial Nrf2 or Peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α) completely abolished these protective actions, unequivocally establishing that the anti-atherogenic efficacy of Ginsenoside Rb1 in vivo is contingent upon activation of Nrf2/PGC-1 α axis. To pinpoint the direct molecular targets of ginsenoside Rb1, Wang et al integrated molecular docking, surface plasmon resonance, and microscale thermophoresis analyses, revealing that ginsenoside Rb1 physically engages both Kelch-like ECH-associated protein 1 (Keap1) and p47phox. Ginsenoside Rb1–Keap1 interaction facilitated Keap1 ubiquitination and proteasomal degradation, liberating Nrf2 for nuclear translocation and subsequent heterodimerization with PGC-1 α . Concurrently, ginsenoside Rb1-bound p47phox exhibited diminished phosphorylation and membrane translocation, preventing NOX2 holoenzyme assembly. This dual-target engagement coordinately ignites the Nrf2/PGC-1 α transcriptional program. Collectively, Keap1 and p47phox are validated as the bona fide direct targets of Ginsenoside Rb1, and the Nrf2/PGC-1 α signaling axis constitutes the central pathway underpinning its anti-diabetic atheroprotective activity.

Maslinic acid is a pentacyclic triterpenoid principally enriched in the medicinal herb Shan zha (*Crataegus pinnatifida* Bunge) and related botanicals.¹²⁴ It has been reported that maslinic acid can inhibit glycogen phosphorylase activity, reduce hepatic glycogenolysis, and decrease hepatic glucose output; it can also inhibit α -glucosidase activity, thereby delaying carbohydrate digestion and absorption in the intestine and lowering postprandial blood glucose.^{125,126} Furthermore, studies have demonstrated that maslinic acid attenuates hyperglycemia-induced endothelial cell injury.

Wang⁹² et al demonstrated that maslinic acid lowers the levels of TNF- α , IL-6, and IL-1 β , attenuates ROS generation, and diminishes apoptosis in HUVECs. Mechanistically, maslinic acid facilitates the recruitment of the RNA demethylase alpha-ketoglutarate-dependent dioxygenase alkB homolog 5 (ALKBH5) to thioredoxin-interacting protein (TXNIP) mRNA, augmenting m⁶A demethylation of TXNIP transcripts and thereby reducing their stability. The consequent down-regulation of TXNIP—a glucose-sensing adaptor protein—suppresses hyperglycemia-induced ROS production and pro-inflammatory cytokine release, ultimately mitigating endothelial inflammation and apoptosis.

Paeonol is a phenolic acid compound derived from chinese herbal medicines such as Mu Danpi (*Paeonia suffruticosa* Andr).¹²⁷ Previous studies have found that Paeonol possesses anti-inflammatory and antioxidant properties, capable of mitigating oxidative and inflammatory damage to endothelial cells.^{128,129} Research has demonstrated that Paeonol can enhance insulin sensitivity, promote glycogen synthesis, and inhibit gluconeogenesis, thereby achieving blood glucose-lowering effects.^{130,131} Furthermore, Paeonol exhibits anti-inflammatory and antioxidant properties, capable of alleviating oxidative and inflammatory damage in endothelial cells. Tang⁹³ et al further demonstrated that paeonol mitigates hyperglycemia plus palmitic acid-induced HUVEC injury by up-regulating Sirtuin 1 (SIRT1) expression. Activated SIRT1 deacetylates Forkhead box protein O3 a (FOXO3a), thereby repressing its pro-apoptotic and pro-oxidative activities, while concurrently suppressing NF- κ B signaling to curtail transcription and release of inflammatory mediators. These complementary actions collectively ameliorate endothelial apoptosis, oxidative stress, and inflammatory damage.

Citronellal, a monoterpenoid aldehyde, is principally isolated from the essential oils of Xiangmao (*Cymbopogon citratus* (DC). Stapf).¹³² It has been reported that citronellal can inhibit α -glucosidase and α -amylase activities in the intestine, delay the digestion and decomposition of carbohydrates and the absorption rate of glucose, and reduce postprandial blood glucose peaks. Additionally, it can regulate insulin signaling pathways and enhance insulin sensitivity.¹³³ Previous investigations have demonstrated that citronellal attenuates atherosclerotic plaque formation and arterial stenosis by suppressing oxidative stress and promoting endothelial cell migration.¹³⁴ Qiu⁹⁴ et al employed a diabetic rat model induced by a high-fat diet plus streptozotocin (STZ) and cultured HUVECs under hyperglycemia to recapitulate the vascular injury elicited by hyperglycemia. It was observed that citronellal significantly reduced vascular lipid deposition, restored endothelial alignment, and enhanced endothelium-dependent vasodilation. Concurrently, citronellal lowered malondialdehyde and ROS production, thereby conferring protection against diabetes-associated endothelial damage. The beneficial effects of citronellal appear to be mediated by the activation of the sphingosine-1-phosphate (S1P)/Sphingosine 1-phosphate (S1P1) axis, which is induced by citronellal. This activation promotes the phosphorylation-dependent dimerisation of endothelial nitric-oxide synthase and augments nitric-oxide generation.

Buyang Huanwu Decoction (BYHWD), a classical formulation in traditional Chinese medicine, is renowned for its therapeutic efficacy against cardio-cerebrovascular disorders, including ischemic stroke and atherosclerosis.^{135,136} It is composed of 7 chinese medicinal herbs: Huangqi (*Astragalus membranaceus* (Fisch). Bunge), Danggui (*Angelica sinensis* (Oliv). Diels), Chishao (*Paeoniae Radix Rubra*), Dilong (*Pheretima aspergillum*), Chuanxiong (*Ligusticum wallichii* Franch), Taoren (*Prunus persica* (L). Batsch), and Honghua (*Carthamus tinctorius* L).¹³⁷ Research has found that BYHWD protects pancreatic β -cell function and improves insulin secretion capacity; moreover, BYHWD can also promote glucose uptake in skeletal muscle and adipose tissue, ultimately achieving blood glucose regulation.¹³⁸ Recent studies have shown that BYHWD also has protective effects against hyperglycemia-induced vascular cell injury. Tong¹⁰⁰ et al utilised STZ-induced ApoE^{-/-} mice to establish a diabetes-associated atherosclerosis model and ascertained that BYHWD activates AMPK pathway, down-regulates the expression of Dynamin-related protein 1 (Drp1) and Mitochondrial fission 1 (Fis1) proteins, suppresses aberrant mitochondrial fission, and reduces ROS generation, thereby improving endothelial function and inhibiting hyperglycemia-accelerated atherosclerosis. In order to provide further validation of the key molecular component of this pathway, the team silenced the AMPK gene in HUVECs via siRNA transfection. The results demonstrated that following AMPK knockdown, the protective effect of BYHWD against hyperglycemia-induced endothelial injury was significantly diminished, thereby confirming that AMPK is a critical mediator of BYHWD's protective action. Furthermore, molecular docking with AutoDock Vina revealed that BYHWD's core active constituents – ferulic acid and calycosin-7-glucoside – directly bind to the GTPase domain of Drp1. Subsequent GTPase activity assays further verified that both compounds effectively inhibit Drp1 GTPase activity, cooperatively blocking the mitochondrial fission signal. These findings not only clarify the therapeutic targets and active

ingredients of BYHWD, but also exemplify the multi-component, multi-target synergistic advantage of traditional Chinese medicine.

Guanxining tablets (GXN) are composed of two well-known Chinese herbal medicines—Danshen (*Salvia miltiorrhiza* Bunge) and Chuanxiong (*Ligusticum wallichii* Franch).—that are renowned for promoting blood circulation.¹³⁹ Studies have shown that GXN can decrease levels of Endothelin-1, von Willebrand factor, SOD, and TNF- α , thereby alleviating vascular inflammation and oxidative stress and protecting vascular endothelium.¹⁴⁰ Furthermore, Li¹⁴¹ et al reported that GXN effectively modulates glucose and lipid metabolism in Zucker diabetic fatty rats, lowering fasting and postprandial blood glucose, glycated hemoglobin, and total cholesterol levels. Wang¹⁰¹ et al further demonstrated in vitro that GXN modulates the interplay between endoplasmic-reticulum stress and autophagy: it up-regulates Endoplasmic reticulum stress proteins to potentiate the unfolded-protein response, while simultaneously promoting protective autophagy and suppressing endothelial-cell apoptosis, thereby attenuating hyperglycemia-induced injury to vascular endothelium.

Fufang Zhenzhu Tiaozhi capsules (FTZ) is composed of eight Chinese medicinal herbs: Huanglian (*Coptis chinensis* Franch), Danshen (*Salviae Miltiorrhizae* Radix), Sanqi (*Panax notoginseng* (Burkill) F.H.Chen), Nü Zhenzi (*Ligustri Lucidi* Fructus), Daji (*Cirsii Japonici* Herba), Duzhong (*Eucommia ulmoides* Oliv), Fuoshou (*Citri Sarcodactylis* Fructus), and Baizhu (*Atractylodis Macrocephalae* Radix).¹⁴² Studies have shown that FTZ can improve glucose and lipid metabolism, lower fasting blood glucose, ameliorate oxidative stress, and protect vascular endothelium.¹⁴³ Zhang¹⁰² et al first conducted a clinical trial, finding that FTZ lowers fasting plasma glucose, total cholesterol, and triglycerides, and reduces carotid intima-media thickness and plaque area in diabetic patients with atherosclerosis. They next generated a diabetes-associated atherosclerosis model by inducing streptozotocin in ApoE^{-/-} mice and showed that FTZ ameliorates glucose- and lipid-metabolic disorders, decreasing aortic lipid deposition and plaque area. To clarify the molecular mechanism, the same team established an in vitro model by stimulating HUVECs with hyperglycemia plus ox-LDL and demonstrated that FTZ suppresses YTH N6-methyladenosine RNA binding protein 2 (YTHDF2)-mediated m⁶A modification of SIRT3 mRNA, diminishes sirtuin 3 (SIRT3) mRNA degradation, up-regulates SIRT3 expression, lowers the levels of the pro-apoptotic proteins Bax and cleaved caspase-3, inhibits endothelial cell apoptosis, and alleviates atherosclerosis.

Protection Mechanisms of Chinese Herbal Medicines Intervention on Macrophages in Hyperglycemia Environments

Matrine is an alkaloid extracted from the Chinese herb Ku Douzi (*Sophora alopecuroides* L).¹⁴⁴ It has been shown to promote the secretion of glucagon-like peptide-1 from intestinal L cells, thereby improving insulin resistance and glucose metabolism. Additionally, it enhances glucose uptake in skeletal muscle and adipose tissue, ameliorating disorders of glucose metabolism.¹⁴⁵ Evidence indicates that matrine exerts cardiovascular protective effects, primarily attributed to its antioxidant, anti-apoptotic, and anti-atherosclerotic properties.^{146,147} Cui⁹⁵ et al stimulated primary mouse macrophages with AGEs to establish a model that mimics vascular injury caused by AGEs accumulation under diabetic conditions. They found that matrine down-regulates the expression of Deoxyribonucleic Acid methyltransferases 3a/b (DNMT3a/b), thereby reducing promoter methylation of glutathione peroxidase 1 (GPX1) and restoring GPX1 expression. As a key antioxidant molecule, GPX1 suppresses oxidative stress mediated by AGEs binding to their receptor, consequently inhibiting aberrant activation of TLR4/signal transducer and activator of transcription 1 (STAT1) signaling pathway and ultimately blocking macrophage polarization toward the pro-inflammatory M1 phenotype. To further elucidate the molecular mechanism, the team employed plasmid-mediated gene overexpression. The results showed that RAGE overexpression markedly attenuated matrine's inhibitory effects on oxidative stress, TLR4/STAT1 signaling activation, and M1 polarization, whereas TLR4 overexpression only weakened matrine's suppression of TLR4/STAT1 signaling and M1 polarization without appreciably affecting oxidative stress. These findings establish RAGE as the critical upstream target for matrine's antioxidant action and TLR4 as the core molecule governing the downstream signaling cascade, ultimately confirming that matrine's protection against diabetes-associated vascular injury depends on precise modulation of the RAGE/TLR4/STAT1 pathway.

Panax notoginseng saponins are the bioactive constituents extracted from Santi (*Panax notoginseng* (Burkill) F.H. Chen). According to reports, Panax notoginseng saponins can regulate insulin secretion, improve pancreatic β -cell function, and consequently ameliorate insulin resistance.^{148,149} Additionally, Panax notoginseng saponins possess anti-inflammatory and anti-atherosclerotic properties.¹⁵⁰ Zhao⁹⁶ et al found that Panax notoginseng saponins dose-dependently regulate macrophage polarization toward the anti-inflammatory M2 phenotype while suppressing the pro-inflammatory M1 phenotype. The underlying mechanism is primarily associated with the inhibition of I κ B- α phosphorylation and the activation of NF- κ B p50 and p65 subunits by Panax notoginseng saponins, thereby blocking NF- κ B signaling and improving diabetes-associated atherosclerosis.

Astragalus polysaccharide is the principal bioactive component extracted from the root of the traditional Chinese herb Huangqi (*Astragalus membranaceus* (Fisch.) Bunge).¹⁵¹ Modern pharmacological studies have found that astragalus polysaccharide can exert hypoglycemic effects by regulating intestinal flora structure and improving intestinal mucosal barrier function. In addition, astragalus polysaccharide can also improve insulin resistance, increase insulin sensitivity, and ameliorate glucose metabolism disorders.^{152,153} Recent studies have also shown that astragalus polysaccharide possesses cardiovascular-protective and anti-inflammatory properties. Sha⁹⁷ et al reported that Astragalus polysaccharide reduced the thickness of the thickened thoracic aortic wall in diabetic rats, whilst concomitantly reducing the expression of inflammatory mediators, including IL-6, TNF- α , and MCP-1, in thoracic aortic tissue. Furthermore, astragalus polysaccharide has been demonstrated to skew macrophage polarization towards the anti-inflammatory M2 phenotype whilst suppressing the pro-inflammatory M1 phenotype. In order to elucidate the underlying molecular mechanism, the group performed in vitro experiments in which macrophages were stimulated with lipopolysaccharide plus hyperglycemia. It was found that astragalus polysaccharide up-regulated Nrf2 and heme oxygenase-1 (HO-1) expression within the Nrf2/HO-1 signalling axis, thereby exerting the aforementioned protective effects. When Nrf2 was silenced, the protective actions of astragalus polysaccharide were largely abolished, indicating that Nrf2 is a critical target through which astragalus polysaccharide modulates macrophage polarization and ameliorates diabetes-associated vascular inflammation and injury.

Protection Mechanisms of Chinese Herbal Medicines Intervention on Vascular Smooth Muscle Cells in Hyperglycemia Environments

6-Shogaol, the principal bioactive constituent of the herbal medicine Ganjiang (*Zingiber officinale* Rosc), exerts anti-inflammatory and antioxidant effects.^{154,155} In addition, Studies have also found that 6-shogaol can improve insulin sensitivity in peripheral tissues, protect pancreatic β -cell morphology, reduce apoptosis, maintain islet function, and lower blood glucose levels.^{156,157} Recent research has demonstrated that 6-shogaol can delay the progression of diabetes-associated atherosclerosis. Chen⁹⁸ et al demonstrated that 6-shogaol mitigates hyperglycemia-induced injury in Human artery smooth muscle cells. Mechanistically, 6-shogaol blocks Akt phosphorylation, attenuates ROS generation, and consequently suppresses NLRP3 inflammasome activation. This cascade down-regulates osteogenic proteins—including osteopontin (OPN), osteocalcin (OCN), and alkaline phosphatase (ALP)—markedly inhibiting hyperglycemia-triggered vascular calcification and thereby protecting arterial smooth muscle cells.

Sodium Tanshinone IIA Silate is a water-soluble derivative of Tanshinone IIA. Previous studies have shown that Tanshinone IIA lowers blood glucose and improves glucose tolerance; it also suppresses vascular smooth muscle cell proliferation.¹⁵⁸ Wu⁹⁹ et al reported that, under hyperglycemia conditions, Sodium Tanshinone IIA Silate arrests VSMCs in G0/G1, markedly shrinking S and G2/M fractions. This is achieved by up-regulating p53 and the CDK inhibitor p21 while down-regulating cyclin D1 expression and promoter activity in an AMPK-dependent manner. Transwell assays further showed that Sodium Tanshinone IIA Silate dose-dependently blunts hyperglycemia-stimulated VSMCs migration, suppresses MMP-2, and blocks both NF- κ B nuclear translocation and cytosolic NF- κ B activation. Crucially, siRNA knockdown of AMPK abolished Sodium Tanshinone IIA Silate-mediated inhibition of proliferation and migration, confirming that the vascular protection conferred by Sodium Tanshinone IIA Silate requires AMPK activation.

Conclusions

With the continued rise in global diabetes prevalence, the incidence of diabetes-related vascular complications is also showing a significant upward trend.¹⁵⁹ Current clinical management primarily relies on glucose-lowering medications, dietary interventions, and exercise regimens to control blood glucose levels.^{160,161} However, these conventional interventions have limited efficacy in delaying or reversing the progression of diabetic vasculopathy and fail to effectively curb the onset and advancement of vascular complications such as atherosclerosis.¹⁶² Therefore, there is an urgent need to develop novel therapeutic strategies that can directly target the mechanisms of diabetic vascular injury. Hence, there is an urgent need to develop innovative therapeutic strategies capable of directly intervening in the pathogenic mechanisms underlying diabetic vascular injury.

Atherosclerosis, the most prevalent pathological basis for a variety of cardiovascular and cerebrovascular diseases, involves the functional disruption of multiple cell types. Vascular endothelial cells, vascular smooth-muscle cells, and macrophages play pivotal roles throughout the progression of atherosclerosis.¹⁶³ Recent studies have shown that hyperglycemia can act on these three types of cells through various molecular mechanisms, inducing their functional abnormalities and thereby promoting the initiation and progression of atherosclerosis.¹⁶⁴ Therefore, elucidating the specific mechanisms by which hyperglycemia affects vascular endothelial cells, smooth muscle cells, and macrophages not only helps to uncover the pathogenesis of diabetic vascular complications but also provides a theoretical basis for developing novel intervention strategies that target the functions of vascular cells. Therefore, elucidating the specific molecular mechanisms by which hyperglycemia disrupts the functions of vascular endothelial cells, smooth muscle cells, and macrophages not only deepens our understanding of the pathogenesis of diabetic vascular complications, but also provides a theoretical foundation for developing novel interventions that target vascular-cell function. This review systematically summarizes the molecular pathways through which hyperglycemia induces vascular-cell dysfunction, examining—through the three perspectives of endothelial cells, vascular smooth muscle cells, and macrophages—the mechanisms by which hyperglycemia acts on vascular cells, with the aim of offering a comprehensive theoretical framework for understanding how hyperglycemia promotes atherosclerosis.

In China, Chinese herbal medicines have demonstrated promising clinical prospects as an important therapeutic approach for diabetic atherosclerosis. Studies have shown that Chinese herbal medicines can slow the progression of diabetes-associated atherosclerosis.¹⁶⁵ Clinical retrospective analyses have also demonstrated that, when combined with conventional Western therapies, Chinese herbal medicines can further reduce carotid intima-media thickness and coronary artery calcification scores, with a favorable safety profile.¹⁶⁶ Moreover, relevant randomized controlled trials are currently underway and are expected to furnish robust evidence supporting the use of traditional Chinese herbal medicine in the treatment of diabetes-associated atherosclerosis.^{87,88} In recent years, research on the metabolically active components of Chinese herbal medicines has been gradually deepening. Therefore, this article systematically reviews the mechanisms by which Chinese herbal medicines and their active metabolic components improve diabetic atherosclerosis by regulating the functions of vascular endothelial cells, vascular smooth muscle cells, and macrophages. Furthermore, it summarizes the sources of acquisition for the relevant active components of Chinese herbal medicines (Table 2) and the Latin names and main efficacy of the major Chinese herbal medicines (Table 3) to demonstrate the reliability and rationality of the metabolically active components of Chinese herbal medicines. The aim is to provide new insights for diabetes-associated atherosclerosis.

Despite the growing body of research on Chinese herbal medicines for diabetes-associated atherosclerosis, several critical challenges continue to impede their translation into clinical practice. Firstly, limitations inherent to current animal and cell models. The most widely used diabetes-associated atherosclerosis model—the ApoE^{-/-} mouse—exhibits a lipoprotein profile dominated by VLDL and abnormally elevated HDL, markedly different from the LDL-driven pathology seen in humans. In vitro studies, meanwhile, typically rely on static single-cell cultures that lack crucial micro-environmental cues present in vivo—such as hemodynamic shear stress and inter-cellular crosstalk—resulting in systems that poorly recapitulate physiological or pathological conditions. These disparities can skew assessments of both the efficacy and the molecular targets of herbal constituents, and may overlook bioactive mechanisms that emerge only through multi-cellular cooperation, ultimately compromising the accuracy of downstream translational investigations.

Table 2 Sources of Active Components from Chinese Herbal Medicines

Active Ingredients	Source Acquisition	Supplier Information
Albiflorin	Commercial acquisition of standard products	This product was purchased as a standard from Bio-technology Co., LTD (Chengdu, China), with purity $\geq 98\%$.
Salvianolic acid B	Commercial acquisition of standard products	This product was purchased as a standard from Sigma-Aldrich.
Paeonol	Commercial acquisition of standard products	This product was purchased as a standard from Solarbio Life Sciences (China), with purity $\geq 98\%$.
Scutellarin	Commercial acquisition of standard products	This product was purchased as a standard from Sigma-Aldrich, with purity $\geq 98\%$.
Vitexin	Commercial acquisition of standard products	This product was purchased as a standard from MCE, with purity $\geq 98\%$.
Hydroxysafflor yellow A	Commercial acquisition of standard products	This product was purchased as a standard from Bio-technology Co., LTD (Chengdu, China), with purity $\geq 98\%$.
Ginsenoside Rb1	Commercial acquisition of standard products	This product was purchased as a standard from MedChemExpress (Princeton, NJ, USA).
Maslinic acid	Commercial acquisition of standard products	This product was purchased as a standard from Moqi (China), with purity $\geq 98\%$.
Citronellal	Commercial acquisition of standard products	This product was purchased as a standard from Yuke (China), with purity $\geq 98\%$.
6-shogaol	Commercial acquisition of standard products	This product was purchased as a standard from National Institute for the Control of Pharmaceutical and Biological Products (China), with purity $\geq 98\%$.
Sodium tanshinone IIA silate	/	/
Astragalus polysaccharide	/	/
Matrine	Commercial acquisition of standard products	This product was purchased as a standard from Sigma-Aldrich.
Panax notoginseng saponins	Commercial acquisition of standard products	This product was purchased as a standard from Kunming Pharmaceutical Company (China).

Table 3 Sources, supplies and purity of Active Components from Chinese Herbal Medicines

Chinese Herbal Medicines Names	Latin Name	Modern Pharmacological Efficacy	References
Baishao	<i>Paeonia lactiflora</i> Pall.	Glucose regulation, Antitumor, Immune regulation, Antiviral, Anti-inflammatory	[167]
Danshen	<i>Salvia miltiorrhiza</i> Bunge	Glucose regulation, Endothelial protection, Enhanced circulation, Anticoagulation, Vasodilation	[168,169]
Deng Zhanhua	<i>Erigeron breviscapus</i> (Vaniot) Hand.-Mazz.	Vasodilation, Anticoagulation, Anticoagulation, Reduced smooth muscle cell migration and proliferation, Anti-inflammatory	[170,171]
Shanzha	<i>Crataegus pinnatifida</i> Bunge	Endothelial protection, Vasodilation, Anti-inflammatory, Glucose regulation, Anti-atherosclerotic	[172,173]
Honghua	<i>Carthamus tinctorius</i> L.	Endothelial protection, Anti-inflammatory, Antitumor, Immune regulation, Anticoagulation	[174,175]

(Continued)

Table 3 (Continued).

Chinese Herbal Medicines Names	Latin Name	Modern Pharmacological Efficacy	References
Mu Danpi	<i>Paeonia suffruticosa</i> Andr.	Anti-inflammatory, Anticoagulation, Anti-atherosclerotic, Glucose regulation, Vasodilation	[176]
Xiangmao	<i>Cymbopogon citratus</i> (DC). Stapf	Anti-inflammatory, Glucose regulation, Blood pressure regulation, Antitumor, Antioxidant	[177,178]
Huangqi	<i>Astragalus membranaceus</i> (Fisch). Bunge	Glucose regulation, Anti-inflammatory, Blood pressure regulation, Immune regulation, Antiviral	[179]
Danggui	<i>Angelica sinensis</i> (Oliv). Diels	Glucose regulation, Anti-inflammatory, Immune regulation, Antitumor, Antioxidant	[180,181]
Dilong	<i>Pheretima aspergillum</i>	Anticoagulation, Anti-inflammatory, Glucose regulation, Analgesic, Antiviral	[182,183]
Chuanxiong	<i>Ligusticum wallichii</i> Franch.	Anti-inflammatory, Anticoagulation, Blood pressure regulation, Anti-atherosclerotic, Analgesic	[184]
Taoren	<i>Prunus persica</i> (L). Batsch	Anticoagulation, Anti-atherosclerotic, Anti-inflammatory, Immune regulation, Blood pressure regulation	[185]
Huanglian	<i>Coptis chinensis</i> Franch.	Anti-atherosclerotic, Blood pressure regulation, Glucose regulation, Antiviral, Antibacterial	[186]
Sanqi	<i>Panax notoginseng</i> (Burkill) F.H. Chen	Anti-inflammatory, Immune regulation, Anticoagulation, Glucose regulation, Reduced vascular permeability	[187]
Nü Zhenzi	<i>Ligustri Lucidi</i> Fructus	Antitumor, Immune regulation, Glucose regulation, Antiviral, Anti-osteoporotic	[188]
Daji	<i>Cirsii Japonici</i> Herba	Anti-inflammatory, Glucose regulation, Immune regulation, Analgesic, Antitumor	[189,190]
Duzhong	<i>Eucommia ulmoides</i> Oliv.	Blood Pressure Regulation, Glucose regulation, Anti-inflammatory, Immune regulation, Anti-osteoporotic	[191,192]
Fuoshou	<i>Citri Sarcodactylis</i> Fructus	Glucose regulation, Anti-inflammatory, Analgesic, Immune regulation, Antitumor	[193,194]
Baizhu	<i>Atractylodis Macrocephalae</i> Radix	Anti-inflammatory, Gastrointestinal Regulation, Antitumor, Glucose regulation, Immune regulation,	[195]
Kushen	<i>Sophora flavescens</i> Ait.	Antitumor, Anti-inflammatory, Analgesic, Glucose regulation, Immune regulation,	[196]
Ganjiang	<i>Zingiber officinale</i> Rosc.	Blood Pressure Regulation, Anti-inflammatory, Glucose regulation, Antitumor, Immune regulation	[197,198]

Secondly, inadequate safety evaluation. The chemical complexity of herbal medicines means that current studies rarely provide systematic data on hepatotoxicity, nephrotoxicity, chronic toxicity, or reproductive toxicity; moreover, information on herb–drug interactions with commonly prescribed hypoglycaemic or anti-atherosclerotic agents is scarce. The absence of a standardized safety-assessment framework makes it impossible to quantify the clinical risks associated with either whole herbs or their bioactive metabolites. Finally, insufficient clinical evidence. Most existing work centres on single purified constituents tested in cellular or animal models, whereas well-designed clinical trials lag far behind and are methodologically weak. Studies rarely stratify participants by diabetes subtype or stage of atherosclerotic lesion, further limiting the external validity and therapeutic guidance that can be derived from the data.

Future research should therefore focus on three priorities. First, model refinement: adopt systems that more faithfully replicate human LDL-driven atherosclerotic metabolism to enhance both scientific rigor and translational relevance. Second, establish a comprehensive pharmacological safety platform specifically tailored to herbal medicines, systematically evaluating hepatorenal toxicity, chronic toxicology, and herb–drug interactions. Third, launch large-scale, multicentre, long-term clinical trials that generate high-level evidence. Such efforts will not only foster wider acceptance of herbal therapies among patients with diabetes-associated atherosclerosis, but also provide safer, more effective therapeutic options grounded in robust evidence-based medicine.

Abbreviations

ECs, Endothelial cells; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; LDL, low-density lipoprotein; AKT, protein kinase B; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; AGEs, advanced glycation end products; NF- κ B, Nuclear factor- κ B; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; ox-LDL, oxidized low-density lipoprotein; HUVECs, human umbilical vein endothelial cells; Bcl-2, B cell lymphoma-2; Bax, Bcl-2-associated X protein; NLRP3, NOD-like receptor family pyrin domain-containing 3; AMPK, AMP-activated kinase; KLF4, Krüppel-like factor 4; TERT, telomerase reverse transcriptase; SIRT6, Sirtuin type-6; Nrf2, nuclear factor erythroid-2 related factor 2; HIF-2 α , hypoxia-inducible factor-2 α ; GLUT1, glucose transporter 1; COMMD1, copper metabolism domain-containing protein 1; 2-DG, 2-deoxy-D-glucose; RUNX1, Runt-related transcription factor 1; HIF-1 α , hypoxia-inducible factor-1 α ; PDK4, Pyruvate dehydrogenase kinase 4; SR-B, scavenger receptors class B; LOX-1, low-density lipoprotein receptor 1; RNA, Ribonucleic Acid; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; ELAVL1, ELAV like RNA binding protein 1; IL-1 β , Interleukin-1 β , VSMCs, Vascular smooth muscle cells; JAK, Janus kinase; STAT, signal transducer and activator of transcription; JAK2, Janus kinase 2; AngII, angiotensin II; AT1, angiotensin type 1 receptor; SHP-1, Src homology region 2 domain-containing phosphatase-1; KLF5, Krüppel-like factor 5; TLR4, Toll-like receptor 4; TRPM7, transient receptor potential melastatin 7; MEK, mitogen-Activated protein kinase; ERK, extracellular signal-regulated kinase; Notch3, Notch receptor 3; mTOR, mechanistic target of rapamycin; MCP-1, monocyte chemoattractant protein-1; TNF- α , tumour necrosis factor-alpha; PARP1, poly(ADP-ribose) polymerase-1; ROCK1, Rho-associated coiled-coil-containing protein kinase 1; FBXL2, F-box and leucine-rich repeat protein 2; TCF, T-cell factor; LEF, lymphoid enhancer-binding factor; GPX4, Glutathione Peroxidase 4; SLC7A11, Solute Carrier Family 7 Member 11; PGC-1 α , proliferator-activated receptor gamma coactivator 1- α ; Keap1, Kelch-like ECH-associated protein 1; ALKBH5, alpha-ketoglutarate-dependent dioxygenase alkB homolog 5; TXNIP, thioredoxin-interacting protein; SIRT1, Sirtuin 1; FOXO3a, Forkhead box protein O3 a; STZ, streptozotocin; S1P, sphingosine-1-phosphate; S1P1, Sphingosine 1-phosphate; Drp1, Dynamin-related protein 1; Fis1, fission 1; YTHDF2, YTH N6-methyladenosine RNA binding protein 2; SIRT3, sirtuin 3; GPX1, glutathione peroxidase 1; STAT1, signal transducer and activator of transcription 1; HO-1, heme oxygenase-1; OPN, osteopontin; OCN, osteocalcin; ALP, alkaline phosphatase; AS, atherosclerosis; UDP-GlcNAc, Uridine Diphosphate N-acetylglucosamine; GSDMD, Gasdermin D.

Additional Notes

The plant names used in this article have been verified by Chinese Medicinal Materials Image Database of HONG KONG BAPTIST UNIVERSITY (<https://sys01.lib.hkbu.edu.hk/cmed/mmid/>) and The Plant List (<https://www.theplantlist.org/>). Verification date: 15 January, 2026.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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