

A narrative review of plant and herbal medicines for delaying diabetic atherosclerosis: an update and future perspectives

Zi-Chao Wang^{1,2,†}, Jeremiah Ong'achwa Machuki^{3,†}, Meng-Zhen Li^{1,2}, Ke-Xue Li^{3,*}, Hai-Jian Sun^{1,2,*}

¹Department of Pharmacognosy, State Key Laboratory of Natural Medicines, China Pharmaceutical University, 210009 Nanjing, Jiangsu, China

²Department of Pharmacognosy, School of Traditional Chinese Pharmacy, China Pharmaceutical University, 211198 Nanjing, Jiangsu, China

³Department of Physiology, Xuzhou Medical University, 221004 Xuzhou, Jiangsu, China

*Correspondence: sunhaijian927@163.com (Hai-Jian Sun); kexueli@xzhmu.edu.cn (Ke-Xue Li)

† These authors contributed equally.

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Due to their high prevalence and incidence, diabetes and atherosclerosis are increasingly becoming global public health concerns. Atherosclerosis is one of the leading causes of morbidity and disability in type 1 and/or type 2 diabetes patients. Atherosclerosis risk in diabetic patients is obviously higher than that of non-diabetic individuals. Diabetes-related glycolipid metabolism disorder has been shown to play a central role in atherosclerosis development and progression. Hyperglycemia and dyslipidemia increase the risks for atherosclerosis and plaque necrosis through multiple signaling pathways, such as a prolonged increase in reactive oxygen species (ROS) and inflammatory factors in cardiovascular cells. Notwithstanding the great advances in the understanding of the pathologies of diabetes-accelerated atherosclerosis, the current medical treatments for diabetic atherosclerosis hold undesirable side effects. Therefore, there is an urgent demand to identify novel therapeutic targets or alternative strategies to prevent or treat diabetic atherosclerosis. Burgeoning evidence suggests that plant and herbal medicines are closely linked with healthy benefits for diabetic complications, including diabetic atherosclerosis. In this review, we will overview the utilization of plant and herbal medicines for the treatment of diabetes-accelerated atherosclerosis. Furthermore, the underlying mechanisms of the ethnopharmacological therapeutic potentials against diabetic atherosclerosis are gathered and reviewed. It is foreseeable that the natural constituents from medicinal plants might be a new hope for the treatment of diabetes-accelerated atherosclerosis.

Keywords

Diabetes; Atherosclerosis; Natural medicine; Phytochemicals; Therapeutic target

1. Introduction

Due to metabolic abnormalities, diabetes is a risk factor for cardiovascular diseases, affecting over 350 million people globally [1]. Long-term hyperglycemia is associated with various micro- and macro-vascular complications, including endothelial cell dysfunction, neuropathy, retinopathy, nephropathy, myocardial infarction, heart failure, and atherosclerosis [2]. Atherosclerosis, a chronic inflamma-

tory disease, is characterized by arterial wall thickening and lipid-enriched plaque formation [3, 4]. Diabetes accelerates atherosclerosis progression and worsens the clinical outcomes. Independently, diabetes mellitus increases the risk of atherosclerosis [5] and the risk of atherothrombotic coronary artery disease is higher in diabetic patients [6]. In the presence of diabetes, atherosclerosis progression, inflammatory cell infiltrations into the vascular wall, and plaque necrosis are markedly accelerated [7]. The effects of diabetes on the occurrence and development of atherosclerosis have been shown in murine models with mutations of key molecules involved in the control of lipid metabolism, such as low density lipoprotein receptor (LDLR) and apolipoprotein E (ApoE) [8]. Various molecular mediators and signaling pathways including excessive reactive oxygen species (ROS) production, increased production of oxidized low density lipoprotein (ox-LDL), insulin resistance, mitochondrial dysfunction, inflammatory microenvironment, increased intracellular formation of advanced glycation end-products (AGEs), transcription factors, non-coding transcripts, and gut microbiota dysfunction are necessary for diabetes to aggravate atherosclerosis progression [9]. Recently, accumulative evidence indicates that epigenetic regulation also plays a key role in the onset and development of diabetes and atherosclerosis, such as DNA methylation, histone modification or non-coding RNAs [10–12]. It is being accepted that epigenetic mechanisms might serve as an efficient tool to better understand the pathogenesis of diabetes-accelerated atherosclerosis [13]. Despite advances in elucidation of the mechanisms responsible for diabetes-associated atherosclerosis, the molecular events resulting in accelerated atherosclerosis in diabetes mellitus patients have yet to be fully established. Due to the complicated etiologies and individual heterogeneity in diabetic atherosclerosis, an appropriate strategy for the prevention and treatment of diabetic atherosclerosis is necessary [14–17]. Therefore, it is important to identify novel targets or pharmaceutical agents to inhibit diabetes-accelerated atherosclerotic diseases.

Phytochemicals and traditional Chinese medicine (TCM) have various biologically active substances that can be used for human disease therapy, including diabetes and atherosclerosis [18, 19]. For example, as an antimalarial botanical drug, artemisinin exhibits antidiabetic effects because of its ability to convert pancreatic cells into functional β -like cells by targeting GABAA receptor signaling [20]. Artemisinin has also been shown to exert protective effects against atherosclerosis [21, 22]. Apart from artemisinin, other phytochemicals and herbal products have great potentials as therapeutic options for diabetic atherosclerosis. These molecules are capable of scavenging free radicals, inhibiting cell apoptosis, reducing inflammation, and preventing platelet aggregation [23]. Therefore, these natural constituents are promising candidate drugs for diabetic atherosclerosis prevention and treatment. However, the unfavorable pharmacokinetics and poor bioavailability of these natural drugs may limit their clinical applications [24, 25]. Moreover, multi-target characteristics of herbal medicines can lead to unexpected side effects [26]. Therefore, it is important to develop strategies for overcoming these limitations in order to improve the efficacy of herbal medicines against diabetic atherosclerosis. In this review, we provide an up-to-date overview of the roles and mechanisms of natural constituents in preventing or treating diabetic atherosclerosis, thereby providing a scientific basis for understanding the benefits of herbal medicines on diabetes-associated atherosclerosis. To date, articles regarding the roles of plant and herbal medicines in diabetic atherosclerosis and the relevant mechanisms were strictly screened and retrieved in PubMed database according to the following search terms, including “diabetes”, “diabetic complications”, “atherosclerosis”, “traditional chinese medicine”, “formula”, “curcumin”, “berberine”, “resveratrol”, “salidroside”, “Ginkgo biloba”, “Salvia miltiorrhiza”, “celastrol”, and “TCM formula”.

2. Characteristics of diabetes-associated atherosclerosis

Diabetes, a group of metabolic disorders that are characterized by hyperglycemia, is becoming a serious challenge on global health and economic development [27, 28]. In 2019, globally, a total of 463 million people were diagnosed with diabetes. This number is expected to reach 700.2 million by 2045 [29]. Therefore, diabetes is a global chronic disorder that will impose a huge burden on social, financial, and health systems around the world [30]. Type 1 diabetes is caused by autoimmune destruction of pancreatic beta cells, whereas type 2 diabetes is characterized by β -cell dysfunction and insulin resistance because of inadequate responses to circulatory insulin [31]. Glycotoxicity and lipotoxicity have been observed in both type 1 and type 2 diabetes, contributing to development of various complications, including atherosclerosis [32, 33]. In diabetic individuals, clinical management of impaired glycolipid metabolism should be given a high priority. Regulation of blood glucose and prevention of diabetes-

associated complications are the main goals for diabetes treatment. Diabetes-associated complications, especially cardiovascular complications, are the leading cause of death in diabetic individuals [34]. Microvascular complications associated with diabetes, including retinopathy, nephropathy, and neuropathy, as well as diabetic macrovascular complications, such as premature atherosclerosis ultimately manifest as coronary heart disease, myocardial infarction, cerebral infarction, stroke, and peripheral vascular diseases [35].

Atherosclerosis is one of the most dangerous vascular complications of diabetes. It is characterized by arterial wall thickening, lipid-enriched plaque formation, and weakening elasticity (Fig. 1) [36]. Interactions among various cell types promote fatty streak formation, which progresses to atheromatous plaques, plaque destabilization, and rupture [8]. Since atheroprone endothelial layer is frequently exposed to low shear stress, blood flow frictional forces prime endothelial cells for atherogenesis [37]. Endothelial cell injury is an early event in initiation of vascular homeostasis disturbance, which is reflected by the release of proinflammatory cytokines and adhesion molecules, including tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin [7]. Elevated levels of these molecules synergistically enhance the adhesion of monocytes and T-cells to the vascular endothelium, resulting in infiltrating neointima lesions [38]. The subsequent deposition of foam cells derived from macrophages and vascular smooth muscle cells (VSMCs), activation of matrix metalloproteinases, collagen degradation, VSMCs proliferation and migration, simultaneously promote atherosclerotic plaque formation [39].

There is a direct relationship between diabetes and atherosclerosis [40], that is, atherosclerosis development is accelerated in diabetic patients [41]. A systematic review and meta-regression analysis reported that diabetes is a risk factor for carotid atherosclerosis in Chinese adults [42]. Moreover, a systematic review has reported that diabetes is a risk factor for increased carotid intima-media thickness and carotid plaques [43]. A cross-sectional baseline study was performed to evaluate the prevalence of complications and associated clinical characteristics in 6958 newly diagnosed type 2 diabetic patients. It was found that one-third of type 2 diabetic patients had microvascular and macrovascular complications at the time of diagnosis [44]. Through multidetector computed tomography angiography, the incidence of single and multiple vascular diseases in diabetic patients was found to be higher than in non-diabetic patients [45], suggesting a high burden of atherosclerotic plaque in diabetic patients. Increasing global burden of atherosclerosis necessitates the development of effective preventive health strategies and early-detection of cardiovascular complications, especially in diabetic patients. High-quality epidemiological studies on carotid atherosclerosis should aim at elucidating the prognostic value of differences in plaque characteristics

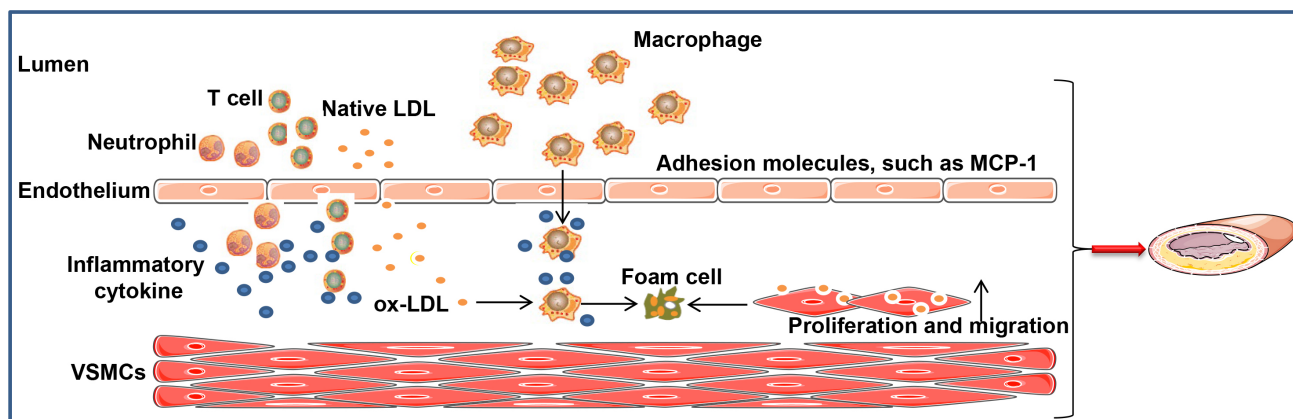


Fig. 1. Formation of atherosclerotic lesions. Vascular endothelial cell injury by pathological wall shear stress, oxidative stress, or other factors induce cholesterol disposition, adhesion molecule expression, and cytokine/chemokine release, resulting in attachment of more monocytes and leukocytes from blood circulation to the endothelium. Immune regulatory factors released by T cells promote atherosclerosis progression. ox-LDL uptake by macrophages is necessary for foam cell generation, facilitating lipid core development. In addition, VSMCs migrate into the intima, where they are proliferative, resulting in overproduction of extracellular matrix. Transformed VSMCs also take up ox-LDL cholesterol, contributing to foam cell formation and atherogenesis. Besides, VSMCs proliferation and migration is an important factor for intimal thickening and sclerosis. ox-LDL, oxidized low density lipoprotein; VSMCs, vascular smooth muscle cells; MCP1, macrophage chemoattractant protein-1.

observed among diabetic patients. Effective strategies for primary prevention and management of carotid atherosclerosis will improve the quality of life for patients with diabetic atherosclerosis.

3. Pathogenesis of diabetes/atherosclerosis coupling

Globally, diabetes and atherosclerosis are highly prevalent, with the number of new morbidities increasing annually. Therefore, studies have aimed at elucidating the molecular mechanisms through which diabetes accelerates atherosclerosis. These studies have used murine models with mutations in key molecules involved in regulation of lipid metabolism, such as ApoE and LDLR under high-fat high-cholesterol diets [46]. Recent studies have documented the molecular mechanisms underlying diabetes-associated atherosclerosis. They include hyperglycemia, glycosylation, AGEs overproduction, insulin dysfunction, endoplasmic reticulum stress, mitochondrial dysfunction, increased production of ox-LDL, decreased adiponectin, decreased nitric oxide (NO) production, gut microbiota, non-coding RNA, vascular calcification, oxidative stress, inflammatory response, and endothelial dysfunction [9, 34, 46–50]. The cross-talk between atherosclerosis and diabetes has been established using novel therapeutics in diabetic atherosclerosis (Fig. 2). High glucose (HG) promotes the expression levels of proinflammatory factors, AGEs formation, ROS generation, fatty acid oxidation, and free fatty acid production in endothelial cells, which are important signs of atherosclerotic endothelial damage [8]. In addition, AGEs interact with their receptors to induce the proliferation and migration of VSMCs, core events in initiation and progression of atheroma [51]. Furthermore, diabetes enhances atherosclerosis

progression by regulating various molecules, such as protein kinase- β (PKC- β) [52], PKC- θ [53], nuclear factor of activated T cells (NFAT) [54], AMP-activated protein kinase (AMPK) [55], Nod-like receptor protein 3 (NLRP3) inflammasome [56], high-mobility group box-1 (HMGB-1) [57], krueppel-like factor 2 (KLF2) [58], peroxisome proliferator activated receptor γ (PPAR- γ) [59], hypoxia-inducible factor [60], and nuclear factor-E2-related factor2 (Nrf2) [61] among others. Recent studies have aimed at evaluating the mechanisms involved in diabetes-associated atheroma formation, plaque instability and thrombus formation (Fig. 3). Despite the fact that both diseases are interconnected and/or independent, the molecular events through which diabetes promotes atherosclerosis progression have not been fully clarified. Therefore, there is a need to elucidate on the pathogenesis of diabetes-associated atherosclerosis to inform the development of novel therapies. Traditional medicinal plants and natural products are considered to be alternative therapeutic strategies for the treatment of diabetic atherosclerosis with lower costs and fewer side effects [62, 63]. Exploiting the active components of TCM formulas and investigating the pharmacological actions of natural plants will enhance disease treatment.

4. Natural compounds with the potential for diabetic atherosclerosis treatment

4.1 Curcumin

Curcumin, a yellow bioactive constituent isolated from Turmeric (*Curcuma longa*), is used as a diet supplement to prevent or treat diabetes-associated complications [64]. Due to its antioxidant and anti-inflammatory properties, curcumin inhibits the development of atherosclerosis and hyperlipidemia [65–67]. Moreover, curcumin reduces diabetes-

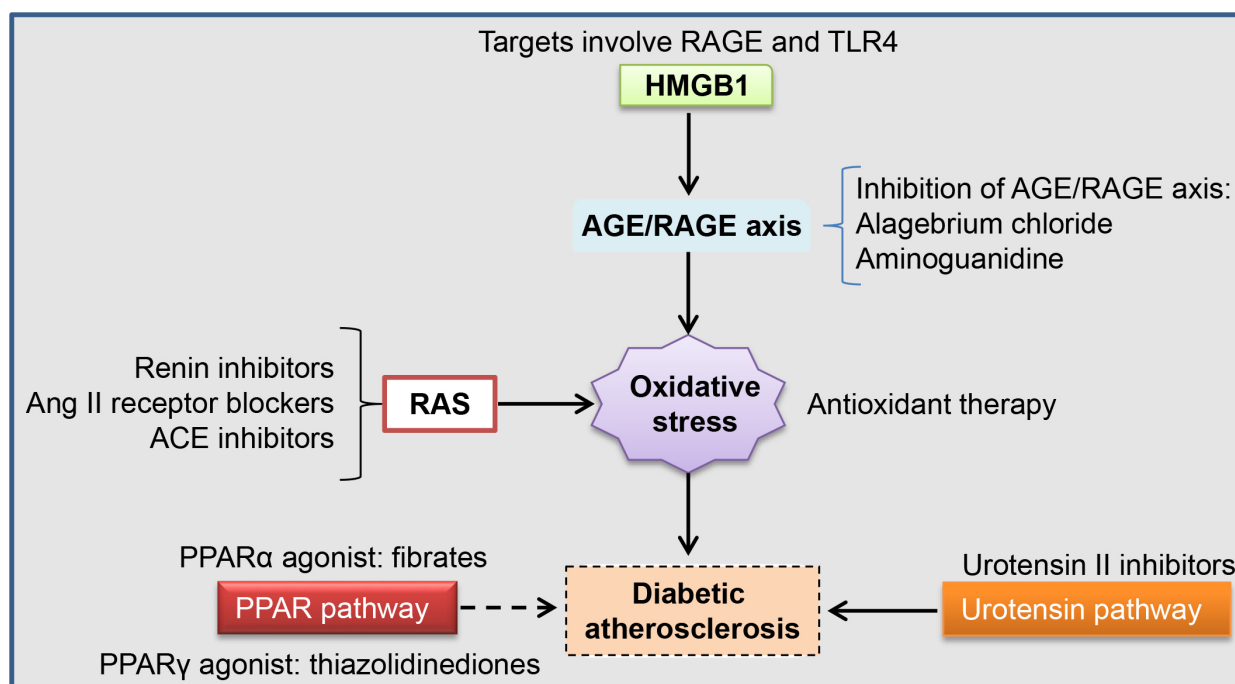


Fig. 2. Current therapeutics in diabetes-associated atherosclerosis. Interplay of several pathways, such as the AGE/RAGE axis, urotensin II, RAS, and PPAR, is involved in diabetes-associated atherosclerosis pathogenesis. The current therapeutic approaches specifically target these pathways, thus, providing promising treatment options for diabetic atherosclerosis. ACE, angiotensin-converting enzyme; AGE/RAGE, advanced glycation end product/receptor for advanced glycation end product; RAS, renin-angiotensin system; TLR4, Toll-like receptor 4.

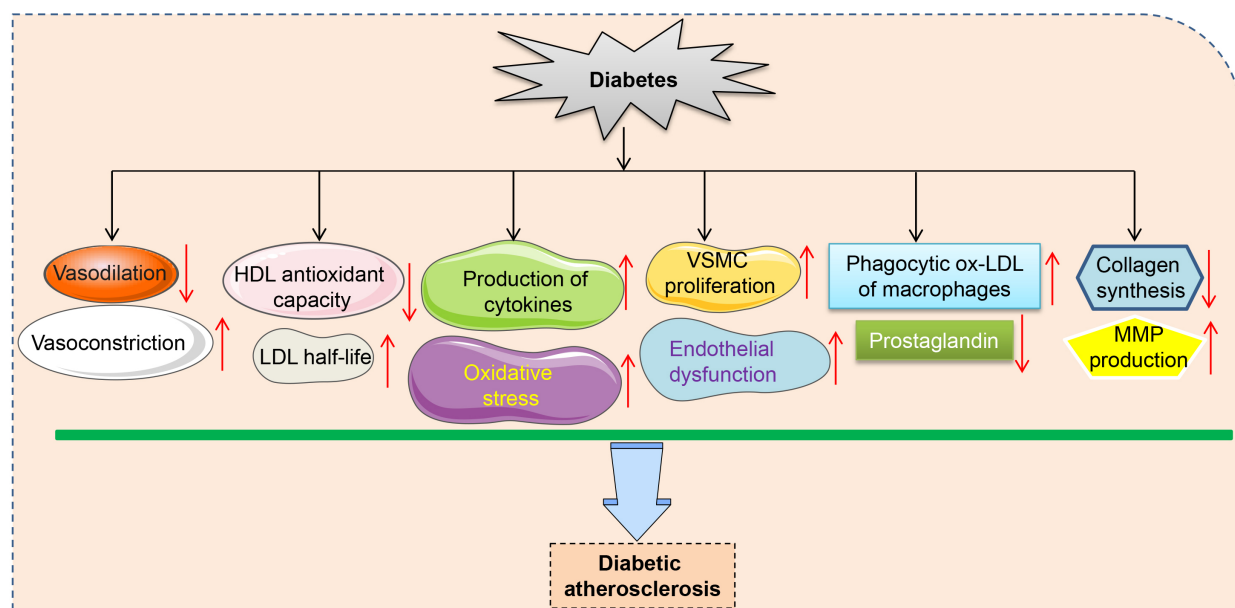


Fig. 3. Schematic presentation of the role of diabetes in atherosclerosis. A chronic hyperglycemia state promotes endothelial-independent vasoconstriction, the half of LDL, cytokine secretion, oxidative stress, VSMC proliferation, endothelial dysfunction, foam cell formation, MMP production, and inhibits endothelial-dependent vasodilation, HDL antioxidant capacity, and collagen synthesis, leading to atherosclerosis development. LDL, low density lipoprotein; VSMCs, vascular smooth muscle cells; MMP, matrix metalloprotein; HDL, high density lipoprotein.

associated cardiovascular risk [67]. A limited number of clinical trials have determined the therapeutic effects of curcumin in diabetes and atherosclerosis patients. A randomized placebo-controlled trial revealed that curcumin treatment for

12 weeks reduces the risk of cardiovascular events in type 2 diabetes and dyslipidemia patients [68]. In healthy people, daily oral administration of curcumin significantly suppressed low-density lipoprotein and apolipoprotein B levels,

but increased high-density lipoprotein and apolipoprotein A levels, indicating its anti-atherosclerosis efficacy [69]. Curcumin treatment for 6 months lowers atherogenic risks in type 2 diabetes patients, as evidenced by reduced pulse wave velocity, leptin levels and increased serum adiponectin levels [70]. Therefore, this extract might be helpful for improving metabolic profiles in diabetes patients with atherosclerosis. Large-scale clinical trials should be performed to characterize the actual potential and molecular mechanisms of curcumin for treating diabetic atherosclerosis.

Although curcumin has various pharmacological effects in cardiovascular and metabolic disorders, its clinical applications are limited by its poor water solubility, rapid metabolism, and low bioavailability [71]. Curcumin derivatives and/or analogs, such as L3 (1, 7-bis (3, 5-di-tert-butyl-4-hydroxyphenyl)-1, 6-heptadiene-3, 5-dione) have been developed to improve the biological activities of curcumin [72]. L3 treatment ameliorated dyslipidemia as well as hyperglycemia and reduced oxidative stress in aortic arch, thereby mitigating atherosclerotic degeneration in diabetic mice [73]. These findings imply that L3 can alleviate diabetic atherosclerosis progression, which provides a scientific basis for clinical applications of L3. Moreover, by suppressing plasma lipopolysaccharide (LPS) levels, improving intestinal barrier functions, and inhibiting macrophage activation, oral curcumin attenuated high fat diet (HFD)-induced glucose intolerance and atherosclerosis in LDL receptor knockout (LDLR^{-/-}) mice [74]. This finding was replicated in a recent study, which showed that curcumin supplementation improved intestinal barrier and attenuated western diet-induced glucose intolerance as well as atherosclerosis in LDLR^{-/-} mice. Therefore, reprogramming intestinal barrier functions by curcumin might be a novel strategy for the management of diabetic atherosclerosis [75]. Curcumin plays a beneficial role in atherosclerotic plaque formation by modulating macrophage polarization, endothelial dysfunction, smooth muscle cell proliferation and migration, as well as foam cell formation (Fig. 4) [67]. Studies should investigate whether the effects of curcumin and its derivatives against diabetic atherosclerosis are at least partially attributed to regulation of the above events involved in the pathologies of diabetes-associated atherosclerosis.

4.2 Berberine

As a protoberberine alkaloid, berberine is abundantly present in several medicinal plants that have a wide spectrum of pharmacological activities, including anti-diabetic and anti-atherosclerotic effects [76, 77]. Glucose- and cholesterol-lowering effects of berberine have been reported. Berberine has been reported to reduce fasting blood glucose levels, glucose intolerance, and hyperlipidemia in type 1 and type 2 diabetes [78, 79]. Berberine enhancement of glucose utilization in adipocytes and myocytes, and suppression of glucose absorption in intestinal cells results in a net hypoglycemic effect [80]. Activation of AMPK is also involved in beneficial metabolic effects of berberine, which reduces lipid

accumulation in the adipocytes and increases glucose uptake in the myotubes [81]. Thus, berberine has antidiabetic properties.

In addition, cholesterol-lowering activities, anti-inflammatory as well as anti-oxidant properties, inhibition of VSMC proliferation, and improvement of endothelial dysfunction by berberine synergistically contribute to its atheroprotective effects [79]. Treatment with berberine for 30 days induced a slightly greater reduction in low-density lipoprotein cholesterol and inflammatory factors in patients with acute coronary syndrome (ACS), following percutaneous coronary intervention when compared to standard therapy alone [82]. In a recent study, berberine treatment reduced aortic ROS production and suppressed serum malondialdehyde (MDA) levels in an ApoE^{-/-} mice model, implying that berberine might prevent atherosclerosis progression by attenuating oxidative stress [83]. Berberine may exert its therapeutic effects against atherosclerosis by regulating multiple signaling pathways, such as MAPK, JNK, nuclear factor kappa-B (NF- κ B), AMPK, ERK, protein kinase B (Akt), PPAR α -NO, AP-1, phosphatidylinositol 3-kinase (PI3K), Trx1/ β -catenin, and PDI/MAPK/ERS [84]. Despite the clinical benefits of berberine, its clinical applications are limited by its poor bioavailability. Therefore, berberine derivatives can enhance its bioavailability. Its derivatives, such as dihydroberberine and 8, 8-dimethyldihydroberberine were superior to berberine in inhibiting inflammation and reducing plaque sizes as well as vulnerability in ApoE^{-/-} mice fed on a Western diet [85]. Therefore, berberine derivatives may exert greater anti-inflammatory and anti-atherosclerotic effects than berberine, which are associated with greater inhibition of p-p38, p-JNK, and nuclear NF κ B p65 translocation in macrophages as a response to dihydroberberine and 8,8-dimethyldihydroberberine [85]. Therefore, berberine derivatives with higher bioavailabilities are likely to translate into higher clinical benefits in the treatment of atherosclerosis. Due to its benefits in diabetes and atherosclerosis, berberine administration might be a potential strategy for the treatment of diabetes-associated atherosclerosis. Berberine preconditioning induced a significant reduction in atherosclerosis plaques in diabetic ApoE^{-/-} mice fed on a HFD for 12 weeks [86]. The anti-diabetic and anti-atherosclerotic effects of BBR are associated with alterations in gut microbiota compositions, implying that berberine treatment may be protective against diabetic atherosclerosis development by modulating gut microbiota [86]. The underlying molecular mechanisms of berberine against diabetes-associated atherosclerosis are shown in Fig. 5. The therapeutic potential of berberine in diabetes-associated atherosclerosis should be further evaluated. Well-designed randomized controlled trials are warranted to test the safety and efficacy of berberine, thereby advancing the clinical transformation of berberine as an adjunct therapy in diabetes and atherosclerosis patients.

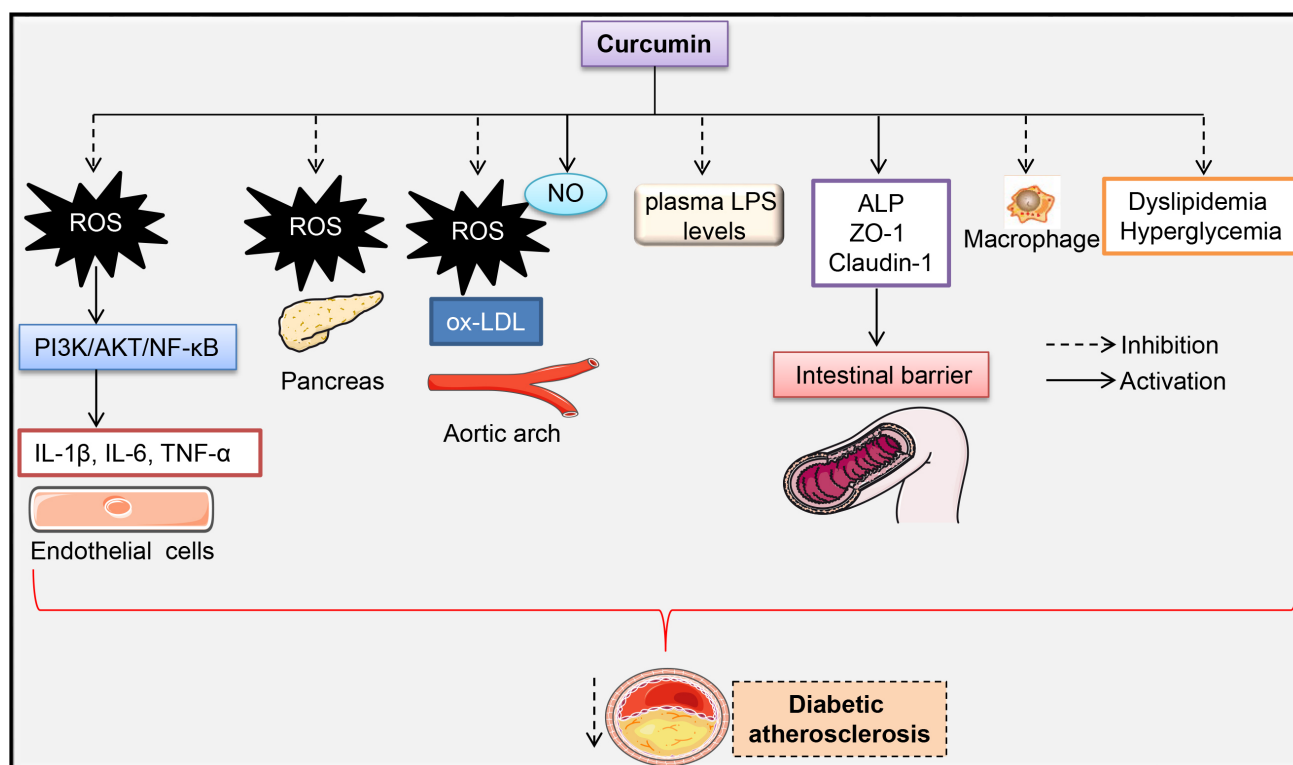


Fig. 4. Signaling pathway by which curcumin alleviates atherosclerosis progression in diabetes. Anti-inflammatory effects of curcumin in rat thoracic aorta endothelial cells were associated with inhibition of the ROS/PI3K/AKT/NF- κ B axis. Curcumin attenuates ROS production in the pancreas and inhibits lectin-like ox-LDL receptor-1 expression in the aortic arch, while increasing NO levels in plasma and aortic arch of diabetic. Curcumin supplementation downregulates plasma LPS levels and improves intestinal barrier functions by upregulating ALP, ZO-1 and claudin-1 levels. Atheroprotective effects of curcumin may be attributed to its inhibitory effects on macrophage activation, dyslipidemia, and hyperglycemia. PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; NF- κ B, nuclear factor κ B; ROS, reactive oxygen species; ox-LDL, oxidized low-density lipoprotein; NO, nitric oxide; LPS, lipopolysaccharide; ALP, alkaline phosphatase; ZO-1, zonula occludens-1.

4.3 Resveratrol

Resveratrol, a natural phytoalexin in enriched plants, foods and beverages, exerts a broad spectrum of biological and pharmacological actions by regulating various targets and signaling pathways [87]. Resveratrol has anti-atherosclerosis, anti-diabetic, anti-aging, anti-obesity, and anti-cancer effects [88]. Cardiovascular protective effects of resveratrol may be attributed to its anti-inflammatory, anti-oxidative, anti-platelet, insulin-sensitizing, and lipid-lowering effects [89]. Moreover, activation of silent information regulator 1 (SIRT1), AMPK, and endogenous anti-oxidant enzymes contributes to its beneficial cardiovascular effects [89].

Resveratrol treatment counteracts pro-atherosclerotic effects of HG on endothelial cells by inhibiting the mRNA expressions of endothelin-1 and E-selectin, and stimulating endothelial nitric oxide synthase (eNOS)/NO signaling. These effects occur in a SIRT1-dependent manner since gene deletion of SIRT1 ameliorates the effects of resveratrol [90]. Endothelial hyperpermeability is the initial step in diabetic atherosclerosis development, therefore, amelioration of endothelial hyperpermeability might exert protective effects against diabetic atherosclerotic complications [18, 91]. In-

creased permeability and caveolin-1 expression in monolayer endothelial cells exposed to HG can be prevented by resveratrol [92]. Blockade of vascular endothelial growth factor (VEGF) and kinase insert domain receptor (KDR) signaling pathway is involved in resveratrol-mediated alleviation of HG-induced hyperpermeability and caveolin-1 overexpression [92]. Resveratrol inhibits the proliferation and migration of VSMCs exposed to HG by inactivating NF- κ B signaling, a function that is analogous to miR-138 inhibitors that induce SIRT1 expression [93]. These findings are corroborated by the reports that Compound C, an AMPK inhibitor, inhibits the beneficial effects of resveratrol on HG-induced oxidative damage in endothelial cells [94]. These results imply a potential protective role of resveratrol against diabetic atherosclerosis. Resveratrol inhibited hyperlipidemia and development of aortic atherosclerosis lesions in type 1 diabetic LDL receptor-deficient mice by activating AMPK signaling [95]. Consistently, resveratrol reduced blood glucose levels, dampened serum triglycerides glyceride and inflammation factors, thereby ameliorating coronary injuries in diabetic rat models with coronary cardiac disease [96]. These beneficial effects of resveratrol are mediated by downregulation of toll-like receptor 4 (TLR4)/myeloid differentia-

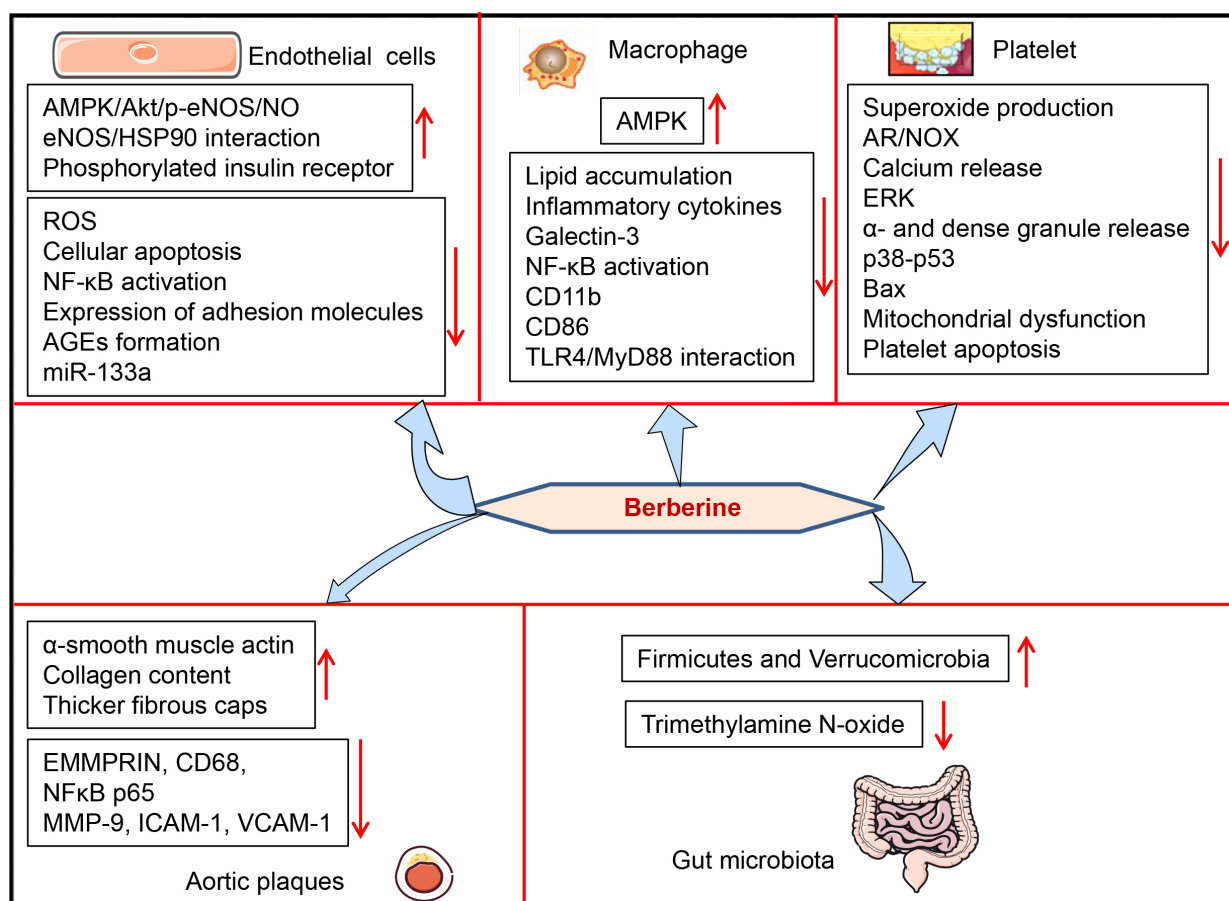


Fig. 5. Atheroprotective effects and mechanisms of berberine in diabetes. Berberine attenuates diabetic atherosclerosis by regulating the functions of vascular endothelial cells, VSMCs, macrophages, platelets, and gut microbiota. Berberine protects against HG-induced apoptosis, ROS production, and inflammation in endothelial cells by upregulating phosphorylation of the insulin receptor and downstream AMPK/Akt/eNOS/NO signaling, promoting the association between eNOS with HSP90, inhibiting AGEs formation, miR-133a and NF- κ B activation. Berberine suppresses ox-LDL-induced inflammatory responses and lipid accumulation by inhibiting galectin-3 upregulation, NF- κ B activation, TLR4/MyD88 interaction, and AMPK inactivation. Moreover, it inhibits high glucose-mediated platelet aggregation and ROS accumulation by diminishing AR, NOX, p38–p53 mediated Bax activation, mitochondrial dysfunction, and platelet apoptosis. Berberine derivatives, dhBBR and Di-MeBBR, mitigate atherosclerotic plaque sizes and improves plaque stability by inhibiting EMMPRIN, CD68, NF- κ B, MMP-9, VCAM-1 and ICAM-1, with concomitant increases in α -smooth muscle actin and collagen levels, as well as formation thicker fibrous caps in aortic plaques. Moreover, antiatherosclerotic effects of BBR are associated with alterations in serum trimethylamine *N*-oxide levels and gut microbiota compositions, such as Firmicutes and Verrucomicrobia. VSMCs, vascular smooth muscle cells; HG, high glucose; ROS, reactive oxygen species; AMPK, adenosine monophosphate-activated protein kinase; AKT, protein kinase B; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; HSP90, heat shock protein 90; AGEs, advanced glycation end product; miR, micro RNA; NF- κ B, nuclear factor κ B; ox-LDL, oxidized low density lipoprotein; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary response 88; ROS, reactive oxygen species; AR, aldose reductase; NOX, NADPH oxidase; Bax, B-cell lymphoma 2 (Bcl-2)-associated X protein; EMMPRIN, extracellular matrix metalloproteinase inducer; MMP-9, matrix metalloproteinase-9; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

tion primary response gene 88 (MyD88)/NF- κ B signaling pathway in cardiovascular tissues [96]. In a double-blind, randomized, placebo-controlled study, resveratrol supplementation improved arterial stiffness and reduced oxidative stress in type 2 diabetes patients, suggesting the potent anti-atherosclerotic effects of resveratrol in clinical trials [97]. However, large-scale cohort studies are required to confirm the beneficial roles of resveratrol in preventing diabetes induced atherosclerosis development. The above findings elucidate on the mechanisms of action of resveratrol, which is a promising therapeutic option for diabetes-

associated atherosclerosis. However, there is a need to elucidate on unfavorable pharmacokinetic and pharmacodynamic profiles of resveratrol [98].

4.4 Salidroside

Salidroside is an important phenylpropane glycoside in medicinal plants of the genus *Rhodiola*. It is associated with remarkable curative effects and few side effects on metabolic, cardiovascular, and neurological diseases [99]. Salidroside has favorable biological as well as pharmacological activities, including amelioration of glucose intolerance, insulin insensitivity, β -cell apoptosis, inflammation, and oxidative stress

[100]. Salidroside is a promising hypoglycemic and lipid-lowering drug that has a good therapeutic potential for diabetes and its complications [101, 102]. Chronic injection of salidroside significantly reduced blood glucose levels and improved insulin resistance in diabetic db/db mice, accompanied by hypolipidemic effects and liver steatosis amelioration [103]. Specifically, antidiabetic effects of salidroside may be associated with activation of mitochondria-related AMPK/PI3K/Akt/glycogen synthase kinase 3 β (GSK3 β) pathway [103]. The AMPK/Akt signaling pathway is a major target of salidroside to stimulate glucose uptake in skeletal muscle cells [104]. Salidroside increased β -cell mass and β -cell replication in both diabetic db/db mice and HFD-induced mice, resulting in beneficial metabolic effects [105]. The efficacy of salidroside in improving β -cell survival is associated with inhibition of ROS production and restoration of mitochondrial membrane potential in Min6 cells, effects that are AMPK activation dependent [105]. Moreover, salidroside improved glucose homeostasis by suppressing inflammation in the epididymal white adipose tissue and activating hypothalamus leptin signaling pathway in obese diabetic mice [106]. Therefore, salidroside may be a potential drug candidate for the treatment of diabetes and its complications, such as atherosclerosis.

Atherosclerosis initiation and pathogenesis are closely associated with ox-LDL-induced endothelial damage. Exposure of human umbilical vein endothelial cells (HUVECs) to ox-LDL dose dependently reduced cell viability and SOD activity, increased lactate dehydrogenase (LDH) release and cellular oxidative stress. These effects were antagonized by pretreatment with salidroside [107]. Under ox-LDL stimulation, salidroside stimulates the SIRT1-FOXO1 pathway to inhibit oxidative stress and to enhance autophagy in HUVECs [107]. Activation of AMPK/SIRT1 signaling by salidroside is also involved in amelioration of ox-LDL-induced oxidative stress and mitochondrial dysfunction in HUVECs [107]. ox-LDL promotes macrophage-derived foam cell formation and apoptosis, while salidroside co-treatment inhibits it, partly by regulating MAPK and Akt signaling pathways [108]. Upregulation of peroxisome proliferator-activated receptor gamma-coactivator-1 α (PGC-1 α) and mitochondrial transcription factor A (TFAM) are important mechanisms through which salidroside promotes mitochondrial biogenesis and mass, thereby protecting against hydrogen peroxide-mediated endothelial dysfunction [109]. Zhang *et al.* [110] reported that salidroside reduced serum lipid levels and plaque areas through the arch to the abdominal aorta in HFD-fed female LDLR^{-/-} mice. These effects were attributed to reductions in MCP-1 and VCAM-1 in the atherosclerotic aorta. Therefore, salidroside is a potential therapeutic option for diabetic atherosclerosis, and its efficacy should be evaluated in diabetic patients.

4.5 *Ginkgo biloba*

Ginkgo biloba is known as the Maidenhair tree, and its leaf extracts are used to treat various pathologies [111]. Ex-

tracts from this plant have various cardiovascular protection functions, which are largely attributed to their free radical scavenging abilities, anti-inflammatory properties, and anti-platelet activation abilities [112]. *Ginkgo biloba* extracts are promising therapeutic agents for cardiovascular and metabolic diseases [113]. *Ginkgo biloba* leaf extracts are mainly composed of terpenoids, flavonoids, alkylphenols, polyphenols and organic acids, which have been shown to have the potential for treatment of metabolic syndromes associated with increased risks of cardiovascular disease events [114]. Terpenoids (bilobalide and ginkgolides A, B, and C) and flavone glycosides (isorhamnetin, quercetin, and kaempferol) are the two major compounds in *Ginkgo biloba* leaves. The special *Ginkgo biloba* leaf extract, EGB761, has been reported to maintain glucose homeostasis by protecting pancreatic β -cells and promoting insulin secretion [115]. Moreover, EGB761 exerted beneficial effects on blood glucose and insulin levels in streptozotocin-induced type 1 diabetes and HFD-induced type 2 diabetes [116]. In addition, *Ginkgo biloba* extracts have been shown to lower blood glucose and improve insulin resistance [117–119]. Therefore, *Ginkgo biloba* extracts might attenuate diabetes-associated atherosclerosis occurrence and progression. Lim *et al.* [120] confirmed that EGB761, a standardized *Ginkgo biloba* extract, reduced neointimal formation and inhibited VSMCs proliferation as well as migration in balloon-injured carotid arteries of obese insulin-resistant rats. Mechanistically, anti-atherosclerosis effects of EGB761 were associated with improved glucose homeostasis, increased circulating adiponectin levels, suppressed endothelial inflammation and monocyte adhesion in type 2 diabetes rat models [120]. Furthermore, *Ginkgo biloba* leaf extracts reduced serum lipid metabolism levels, blood glucose and inflammatory cytokines, with subsequent reductions of plaque area/lumen area and plaque lipid deposition area/intimal area in streptozotocin-induced diabetic ApoE^{-/-} mice [121]. Through network pharmacology analysis, *Ginkgo biloba* leaf extracts were shown to attenuate diabetic atherosclerosis by inhibiting endoplasmic reticulum stress via restoration of autophagy through the mammalian target of rapamycin (mTOR) and NF- κ B signaling pathways [121].

In addition, *Ginkgo biloba* extracts increased resistance of endothelial progenitor cells to oxidative stress in diabetic patients by dose dependently improving SOD activities and reducing the apoptotic rate of endothelial progenitor cells within the peripheral blood of diabetic patients [122]. Zhao *et al.* [123] confirmed that EGB761 pretreatment reduces HG-induced monocyte adhesion and ROS production in human aortic endothelial cells by inducing HO-1 expressions through Akt/eNOS and p38/MAPK pathways. Cui *et al.* [124] showed that pretreatment with Ginkgolide A significantly inhibited the overproduction of IL-4, IL-6, and IL-13 in HG-incubated endothelial cells, this may be attributed to regulation of signal transducer and activator of transcription 3 (STAT3) phosphorylation. *Ginkgo biloba* extract-

derived rutin dose-dependently reduced ROS generation and NLRP3 inflammasome activation in human umbilical vein endothelial cells under HG conditions [125]. Rutin administration restored acetylcholine-induced endothelial diastolic dysfunction in thoracic aortic tissues of high glucose diet-fed rats [125]. Given that hyperglycemia-induced low-grade inflammation and oxidative burst in endothelial cells are key events in the onset and progression of diabetic atherosclerosis, Ginkgo biloba extracts might be promising candidates for attenuating diabetes-associated atherosclerosis by targeting endothelial dysfunction. Despite favorable effects of Ginkgo biloba extracts on diabetic atherosclerosis, studies, especially clinical trials, should aim at evaluating the safety and efficacy of Ginkgo biloba extracts.

5. *Salvia miltiorrhiza* (Danshen) and Salvianolic acid

Salvia miltiorrhiza (Danshen), a traditional Chinese herbal medicine, modulates multiple targets to treat cardiometabolic diseases, including diabetes and atherosclerosis [126]. In the last several decades, studies have aimed at delineating the putative cardiovascular protective effects of this phytochemical through modern scientific research [127]. Salvianolic acid and tanshinones are the predominant bioactive compounds in *Salvia miltiorrhiza*, and both of them were shown to treat atherosclerosis-related cardiovascular and metabolic diseases by targeting multiple signaling pathways [126], such as inhibition of oxidative damage and inflammatory responses, suppression of leukocyte adhesion as well as modulation of endothelial NO production [128, 129].

As the most abundant water-soluble compound in the root of *Salvia miltiorrhiza*, Salvianolic acid B treatment increased NO production, decreased ROS formation, and suppressed endothelial cell apoptosis in isolated mouse aortas, thereby improving endothelial function in diabetic rats with fluctuating blood glucose levels [128, 130]. Salvianolic acid B prevented platelet-derived growth factor (PDGF)-induced proliferation of VSMCs and neointimal hyperplasia in arteries, effects that were Nrf2-dependent [131]. Antiatherogenic effects of Salvianolic acid B are associated with NF- κ B inactivation and enhanced antioxidant capacities in endothelial cells. These effects are ameliorated in the absence of Nrf2, suggesting that Nrf2 plays a crucial role in antioxidant and anti-inflammatory effects of Salvianolic acid B [131]. Salvianolic acid B treatment led to a significant decrease in blood glucose levels and an obvious increase in serum insulin levels in multiple low-dose streptozotocin-induced diabetic rats. Attenuation of systematic oxidative stress and augmentation of pancreatic islets partly mediates the antidiabetic effects of Salvianolic acid B [132]. Overexpressed VEGF is associated with an increased risk of atherosclerosis in diabetic patients, and inhibition of VEGF might potentially benefit clinical outcomes of diabetic populations [133]. Exposure of human microvascular endothelial cells to HG resulted in a significant increase in mRNA expressions of VEGF and mitochondrial

ROS generation, while these changes were antagonized by a hydrophilic extract of *Salvia miltiorrhiza* [134]. These findings imply that Salvianolic acid B is a potential therapeutic option for diabetes-associated chronic vascular complications, such as atherosclerosis. Moreover, tanshinones has potent anti-atherogenic and antidiabetic effects, however, evidence for the direct effects of tanshinones and Salvianolic acid B in the treatment of diabetes-aggravated atherosclerosis is lacking. Studies should confirm the antiatherogenic effects and elucidate on the molecular mechanisms of tanshinones and Salvianolic acid B in diabetic settings, to inform the development of novel therapeutics for diabetes-associated atherosclerosis.

6. Celastrol

Celastrol is a triterpenoid derived from various traditional Chinese medicinal plants, such as *Tripterygium wilfordii* (Thunder God Vine), *Celastrus orbiculatus*, *Celastrus aculeatus*, *Celastrus reglii*, and *Celastrus scandens* [135]. As an active ingredient in plants, celastrol has great potential for treatment of various chronic inflammatory disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and allergies [136]. Studies have reported on the medicinal value of celastrol in diabetes, obesity, and atherosclerosis [137]. By modulating intricate cellular pathways and networks associated with disease pathology, celastrol is effective in treating various metabolic diseases and complications [19].

Celastrol administration for 2 months significantly lowered fasting plasma glucose, glycated haemoglobin (HbA1C) and homeostasis model assessment index (HOMA-IR) levels in type 2 diabetic animal models. Moreover, it improved abnormal lipid metabolism, oxidative stress and proinflammatory cytokine activities in the kidney, liver as well as adipose tissues [138]. In mitochondrial dysfunction and insulin resistance models of human skeletal muscle cells, celastrol augments insulin-stimulated glucose uptake activities by activating the PI3K/Akt pathway and enhancing mitochondrial activities [139]. Chronic low-grade inflammation is involved in the development of insulin resistance in adipose tissues, a noticeable feature in diabetes. Inhibition of proinflammatory cytokines in adipose tissues is an effective strategy for ameliorating insulin resistance in diabetes. In mitochondrial dysfunction-induced insulin resistance in 3T3-L1 adipocytes, celastrol improved metabolic functions with reductions in ROS production and inflammatory factors [140]. These findings imply that by targeting multiple organs or tissues, celastrol may be a therapeutic option for diabetes.

Ji *et al.* [141] reported that celastrol reduced atherosclerotic plaque sizes in ApoE^{-/-} mice by inhibiting the expression levels of lectin-like oxidized low density lipoprotein receptor-1 (LOX-1) and ROS generation in macrophages. Anti-atherosclerotic effects of celastrol were further verified by the fact that it reduced the ratio of the plaque area to arterial wall cross-section area and downregulated serum lev-

els of LDL as well as VEGF in a rabbit experimental carotid atherosclerosis model, suggesting its anti-atherosclerotic potential [142]. These findings imply that celastrol is a potential effective option for atherosclerosis prevention and treatment. Clinical studies should evaluate whether celastrol is a potential adjunct therapy for improving clinical outcomes in atherosclerosis patients under standard treatment. Despite the fact that celastrol confers definite benefits in diabetes and atherosclerosis, studies should evaluate the possible roles of celastrol in the treatment of diabetes associated atherosclerosis.

7. Other herbal medicines

Catalpol, one of the active components in the roots of *Rehmannia glutinosa*, has been found to protect against osteoporosis, neurodegenerative diseases, and diabetic complications [143]. Catalpol decreased plasma glucose levels in streptozocin (STZ)-induced diabetic rats, which was attributed to increased glucose utilization in the liver and skeletal muscles [144]. Inhibitory effects of catalpol on blood glucose levels were reversed by blockade of opioid μ -receptors [144]. Plasma fasting blood glucose and insulin levels, as well as insulin resistance in a homeostasis model were significantly ameliorated in catalpol-treated diabetic rabbits induced by a hyperlipidemic diet plus an intravenous injection of alloxan [145]. Moreover, catalpol treatment ameliorated diabetic atherosclerosis by inhibiting oxidative stress, inflammatory responses, and aggregation of the extracellular matrix [145].

Paeonol is the main active compound isolated from *Cortex Moutan* (*Paeonia suffruticosa* Andrews, Ranunculaceae). It has various beneficial effects, such as anti-atherosclerotic and anti-apoptosis effects [146]. Chen *et al.* [147] evaluated the effects of paeonol on vascular smooth muscle cell (VSMC) proliferation or vascular endothelial cell injury under HG conditions. They found that paeonol inhibited the secretion of VEGF and platelet derivative growth factor B (PDGF-B) from endothelial cells, a critical event for suppression of VSMC proliferation in the co-culture model. Moreover, conditioned medium from paeonol-treated endothelial cells inhibited protein overexpression of Ras, P-Raf, and P-ERK in VSMCs, suggesting that paeonol exerts anti-atherosclerosis activities by regulating the communication between VSMCs and endothelial cells. Paeonol exerted inhibitory effects on apoptosis, oxidative stress, and inflammatory responses in HUVECs exposed to HG and palmitic acid, and these effects were dependent on SIRT1/FOXO3a/NF- κ B pathway regulation [147]. Therefore, paeonol inhibits diabetic atherosclerosis by suppressing VSMC proliferation and vascular endothelial cell injury.

Fisetin (3,3',4',7-tetrahydroxyflavone), a common flavonoid in various fruits and vegetables, has anti-inflammatory, antioxidant, anti-tumorigenic, anti-angiogenic, and anti-diabetic effects [148, 149]. However, its roles in diabetes-associated atherosclerosis have not been

established. Upon exposure to HG, vascular permeability, monocyte adhesion, ROS generation, and NF- κ B activation were shown to be enhanced in HUVECs, while the observed endothelial injury effects were markedly inhibited by fisetin pretreatment [150]. These results indicate that fisetin is a potential therapeutic option for diabetic atherosclerosis. In a recent study, it was found that by downregulating proprotein convertase subtilisin/kexin type 9 (PCSK9), fisetin treatment reduced the area of atherosclerotic plaques and lipid accumulation in the aortic sinus of ApoE^{-/-} mice fed on a HFD [151]. Due to its low toxicity and benefits to health, fisetin is a phytochemical that can be used as a nutritional dietary supplement for cardiovascular protection. However, preclinical studies and clinical trials should be performed to scientifically verify the clinical values of fisetin in treating diabetic atherosclerosis.

8. TCM formulas

Generally, TCM is used as a water decoction with a specific combination of different herbs (also known as formulas), which are prepared in a unique way [152]. Treatment of human diseases requires a comprehensive strategy involving appropriate TCM formulas [23]. Particularly, three classical TCM formulas (Qingfeipaidu Decoction, Huashibaidu Decoction and Xuanfeibaidu Decoction) have been shown to be effective in treatment of coronavirus disease 2019 (COVID-19) [153]. Accordingly, several TCM formulas are associated with remission of cardiovascular disease-related complications [154]. We reviewed various TCM formulas with potential beneficial effects in diabetic atherosclerosis therapy (Fig. 6).

9. Shenqi compound

Shenqi compound is composed of eight Chinese herbs, including yam, salvia, trichosanthin, dogwood, ginseng, astragalus, wine rhubarb, and Raw radix rehmanniae [155, 156]. Shenqi compound ameliorated gluco-lipid metabolism and aortic morphology in diabetic Goto-Kakizaki (GK) rats, which was attributed to increased PTEN mRNA expressions and suppressed PI3Kp85 mRNA expressions in the aorta [157]. Compared to rosiglitazone, shenqi compound was shown to exert better curative effects in the treatment of diabetic vasculopathy [158]. Liu *et al.* [155] reported that Shenqi compound treatment improved polydipsia, polyphagia, weight loss, and vascular injury in a spontaneous diabetic rat model. Gene microarray experiments have shown that the Shenqi compound is an effective therapeutic option for diabetes. It regulates the biological functions involved in sensory perceptions of smell, G-protein coupled receptor signaling pathway, and cytoplasmic translation [155]. A systematic review and meta-analysis reported that Shenqi compound regulates intestinal flora metabolites in type 2 diabetes [159], a critical event involved in diabetic atherosclerosis pathogenesis [160]. A randomized controlled multicenter trial has proven that the Shenqi compound improves lower extremity

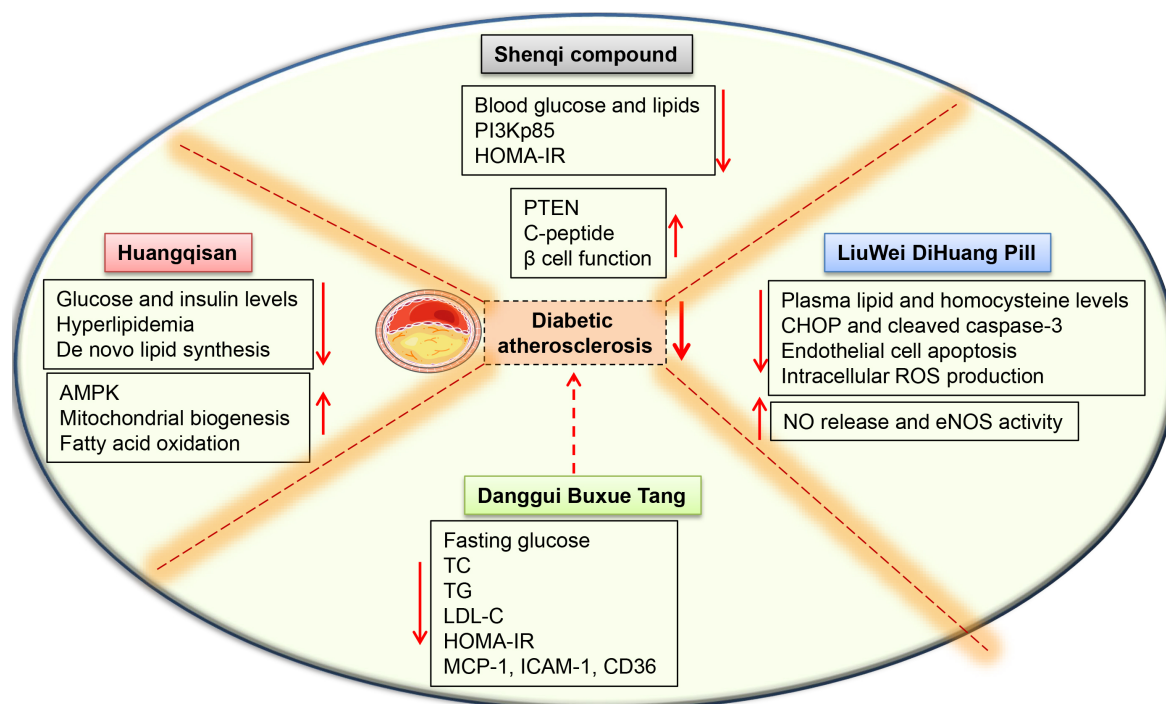


Fig. 6. Schematic presentation of the mechanisms of TCM formulas in diabetes-associated atherosclerosis. LiuWei DiHuang Pill decreased plasma lipid and homocysteine levels in mice models of diabetic atherosclerosis, inhibited homocysteine-induced ROS production, CHOP and cleaved caspase-3 expressions in endothelial cells, and upregulated NO release as well as eNOS activities in HUVECs. Huangqisan normalized glucose and insulin levels, *de novo* lipid synthesis, and improved glucose tolerance in obese rats. Huangqisan is also effective in reversing metabolic disorders by promoting AMPK signaling, mitochondrial biogenesis, and fatty acid oxidation. Danggui Buxue Tang significantly suppressed serum levels of TG, LDL-C and diminished the expressions of lipogenic genes in the aorta of diabetic mice. Shenqi compound ameliorates HOMA-IR, gluco-lipid metabolism, and aortic morphology by elevating PTEN mRNA expressions while suppressing PI3Kp85 mRNA expression in aorta. In addition, Shenqi compound protects islet β cell function by releasing C-peptide. CHOP, C/EBP homologous protein; ROS, reactive oxygen species; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; HUVECs, human umbilical vein endothelial cells; AMPK, adenosine monophosphate-activated protein kinase; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; PTEN, phosphatase and tensin homolog; PI3K, phosphoinositide 3-kinase.

atherosclerosis of type 2 diabetic patients by protecting islet β cell functions, thereby reducing blood glucose level fluctuations [161]. Animal and human studies provide the experimental basis for clinical treatment of diabetic atherosclerosis using the Shenqi compound. However, clinical studies of Shenqi compound in diabetic individuals have been limited by small sample sizes and short follow-up periods. Therefore, large-scale clinical trials should be performed to confirm the actual potential and identify the direct molecular targets of Shenqi compound in treating diabetic atherosclerosis.

10. Danggui Buxue Tang

Among the complex TCM formulations, Danggui Buxue Tang (DBT) is the simplest one, and it has been clinically used in China for over 800 years [162]. The herbal formula contains two herbs: 10 qian Astragali Radix (AR; roots of *Astragalus membranaceus* (Fisch.) Bunge or *Astragalus membranaceus* (Fisch.) Bunge var. *mongholicus* (Bunge) P.K. Hsiao, Huangqi in Chinese) and 2 qian *Angelica Sinensis Radix* (ASR; roots of *Angelica sinensis* (Oliv.) Diels, Danggui in Chinese) (qian is a weight unit in ancient China, where 1 qian is equivalent to ~3 g)

[162]. The TCM Danggui Buxue decoction inhibits inflammatory damage in renal tissues by regulating nuclear factor (NF)- κ B signaling pathway [163]. This decoction is a commonly used prescription for the treatment of migraines, menopausal symptoms, cardiac injury, iron-deficient anemia, and diabetic nephropathy [162, 164–168]. Evidence for the protective effects of Danggui Buxue decoction against diabetic atherosclerosis have been documented by Huang *et al.* [169], who found that administration of the Danggui buxue decoction reduced homeostasis assessment of insulin resistance (HOMA-IR) and serum levels of triglyceride (TG), cholesterol (CHOL), as well as low-density lipoprotein-cholesterol (LDL-C) in Goto-Kakizaki (GK) rats. Danggui buxue decoction-associated lipid metabolism regulation is beneficial for delaying atherosclerosis development in diabetic GK rats, with the mechanism likely to be involving lipid metabolic gene regulation in aorta vessels [169]. Furthermore, oral administration of Danggui buxue decoction decreased blood levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and inhibited mRNA expressions of monocyte chemoattractant protein (MCP)-1, intercellular adhesion molecule (ICAM)-1

and CD36 in aorta tissues from diabetic GK rats, suggesting that the Danggui buxue decoction is a potential therapeutic option for the early stages of diabetes-associated atherosclerosis [170]. Ferulic acid, formononetin, calycosin, astragaloside, caffeic acid, ligustilide, and butyphthalide, which are bioactive metabolites in Danggui buxue decoction, contribute to the protective effects of Danggui buxue decoction against diabetes-associated atherosclerosis [169]. These results show the value of this formula in the treatment of diabetic atherosclerosis. However, clinical trials for Danggui buxue decoction have not been performed. Therefore, well-designed clinical trials, in-depth mechanistic studies, investigations on side effects of Danggui buxue decoction and drug interactions should be the focus of future studies.

11. Huangqisan

Huangqisan is a traditional herbal formula that is derived from Sheng Ji Zong Lu (written in the Song Dynasty of China). This representative formula is composed of Astragali Radix, Pueraria Radix, and Cortex Mori Radicis. These three individual herbs have been traditionally used for the treatment of various diseases for thousands of years [171]. Astragali Radix, Pueraria Radix, and Cortex Mori Radicis have anti-diabetic activities [172–175]. Moreover, Astragali Radix has anti-oxidant, and immunological activities [176]. Astragali Radix was shown to decrease fasting blood glucose levels in diabetic animal models [177]. Puerarin, one of the major constituents of Astragali Radix, may be beneficial in controlling blood glucose levels in type 2 diabetes patients [178]. In addition, other ingredients of Huangqisan, such as Astragaloside IV, Sanggenon D, and 1-de-oxynojirimycin, have glucose-lowering effects [179, 180], indicating that Huangqisan might be a potential formula for treatment of diabetes and its complications.

Huangqisan treatment decreased plasma TC, TG, FFA and FABP4 levels, normalized glucose and insulin levels, and improved glucose tolerance in HFD-fed rats [181]. RNA-Seq analysis combined with qPCR revealed that this formula triggers beneficial effects on glucose-lipid metabolism by regulating mRNA expressions of some important glucose and lipid metabolism-associated genes, such as Acat2, Apoc4, Bhmt, Cyp3a62, Cyp51, Egl3 (Phd3), Fads1, Fads2, Gmmt, Hmgcs1 and Pemt [181]. Huangqisan ameliorates metabolic disorders and maintains glucose homeostasis in hyperlipidemia rats by augmenting mitochondrial biogenesis and fatty acid oxidation to increase thermogenesis and energy expenditure. Therefore, Huangqisan is a stimulator for converting white adipocytes into brown-like adipocytes [182]. Huangqisan administration lowered body weight, fasting blood glucose, and serum lipid levels while improving glucose tolerance and insulin sensitivity in HFD-induced obese mice and db/db mice. Moreover, this prescription blocked the formation of atherosclerotic plaques in LDLR^{-/-} mice [183]. Therapeutic effects of the herbal formula, Huangqisan, on metabolic disorders might be mediated by suppression of de novo lipid

synthesis and activation of adenosine 5'-monophosphate-activated protein kinase (AMPK) signaling [183]. Based on ultra-performance liquid chromatography/quadrupole-time-of-flight mass spectrometry (UPLC/Q-TOF-MS) and multivariate statistical analyses, Xu *et al.* [171] found that Huangqisan regulates metabolic pathways of phospholipid metabolites, thereby improving glucose-lipid metabolism in type 2 diabetic rats. Huangqisan improves glucose and lipid metabolism and exerts protective effects against atherosclerosis in diabetes, and each herb in this formula can be used as a drug and food for ameliorating diabetes-associated metabolic syndromes. However, specific mechanisms through which Huangqisan ameliorates diabetic atherosclerosis have not been established. Particularly, there are no clinical studies on the roles and mechanisms of Huangqisan in diabetic atherosclerosis patients. Therefore, animal and clinical studies should aim at elucidating the effects and underlying mechanisms of Huangqisan on diabetes and atherosclerosis.

12. LiuWei DiHuang pill

LiuWei DiHuang Pill was first mentioned by Qian Yi in the Song Dynasty (AD 1119). It was described as a traditional prescription for the treatment of various diseases, including invigoration of yin, particularly kidney yin [184]. Liuwei Dihuang Pills are comprised of Rehmanniae radix praeparata, Corni fructus, Dioscoreae rhizoma, Alismatis rhizoma, Moutan cortex, and Poria at a ratio of 8:4:4:3:3:3. These herbs play dominant roles in suppression of inflammation and oxidative stress in various cardiovascular disorders [185–188]. Liuwei Dihuang Pills are a safe and effective formula for the prevention and treatment of diabetes and its complications, such as diabetic encephalopathy, diabetic muscle atrophy, and diabetic nephropathy [189–192]. Treatment with Liuwei Dihuang Pills decreased fasting blood glucose levels and attenuated neural apoptosis, overexpression of caspase-3 as well as A β deposition in the hippocampus and cerebral cortex of STZ-induced diabetic encephalopathy rats. These findings suggest that Liuwei Dihuang Pills exert neuroprotective effects in diabetic encephalopathy. Intragastric administration of Liuwei Dihuang Pills significantly decreased serum levels of fasting blood glucose (FBG) as well as fasting insulin, and ameliorated the damaged morphologies of the liver, kidney, pancreatic tissues in male Sprague-Dawley rats subjected to high sugar and HFD combined with a small dose of STZ injection. These effects were mediated by regulation of the canonical PI3K/Akt signaling pathway [189]. In STZ-induced diabetic mice, Liuwei Dihuang Pill water extracts promoted the effects of insulin on gastrocnemius muscle mass and grip strength by reducing oxidative damage and regulating protein synthesis as well as degradation pathways in myotubes [190]. Liuwei Dihuang Pills suppressed renal fibrosis and ameliorated renal functions in STZ-induced diabetic rats by modulating multiple pathways, such as TGF- β /Smad, MAPK, and NF- κ B signaling [191]. Based on a systematic network pharmacology approach, Qin

et al. [193] successfully identified 45 active ingredients in Liuwei Dihuang Pills that were hit by 163 potential targets related to type 2 diabetes. They further revealed that ten of the highly predictive components (quercetin, Kaempferol, Stigmasterol, beta-sitosterol, Kadsurenone, Diosgenin, hancinone C, Hederagenin, Garcinone B, and Isofucosterol) have anti-inflammatory as well as anti-oxidative stress effects and reduce β cell damage [193]. This formula regulates the AGE-RAGE, TNF, and NF- κ B signaling pathways, thereby exerting therapeutic effects against diabetes [193]. In conclusion, Liuwei Dihuang Pills might be beneficial in the treatment of diabetes and its complications [194].

A combination of Ginkgo Leaf Tablets with Liuwei Dihuang Pills downregulated plasma levels of carboxymethyllysine (CML) and 8-isoprostane(8-IsoP) in type 2 diabetes, although macrovascular event occurrence and carotid intima-media thickness were not altered [195]. Zhao *et al.* [194] reported that co-treatment with Ginkgo Leaf Tablets and Liuwei Dihuang Pills remarkably downregulated urinary microalbumin to urinary creatinine ratio (Umalb/cr) levels and diabetic nephropathy prevalence in 140 outpatients with type 2 diabetes. However, the co-treatment had no effect on carotid intima-media thickness levels and incidence of cardiovascular as well as cerebrovascular events, suggesting that these two proprietary herbal medicines are beneficial in diabetic microvascular complications. The efficacy of Liuwei Dihuang Pills as a therapeutic option for diabetic macrovascular complications, such as atherosclerosis, should be evaluated further. Jing *et al.* [196] evaluated the direct effects of Liuwei Dihuang Pills on atherosclerotic lesion development in the aortic root of ovariectomized ApoE-deficient mice. They found that by reducing plasma lipid and homocysteine levels, as well as inhibiting endothelial cell apoptosis and inflammatory responses, Liuwei Dihuang Pills prevented plaque formation in animal models of menopausal atherosclerosis. Therefore, Liuwei Dihuang Pills can potentially be used to halt atherosclerosis-associated vascular diseases in menopausal women. Although Liuwei Dihuang Pills are promising as therapeutic options for diabetes and atherosclerosis, they are associated with several limitations. First, *in vitro* and *in vivo* studies should aim at confirming the preventive and therapeutic values of Liuwei Dihuang Pills in diabetic atherosclerosis. Second, scientific and technologic approaches should be used to elucidate on the efficacy of this formula and its combinations with other prescriptions in treating diabetes. Finally, mechanistic studies and long-term clinical trials, as well as studies evaluating the safety of this selected formula are required to inform its future applications in the treatment of diabetes-associated atherosclerosis.

13. Dietary berries

Nutrition therapy is an important supplementary strategy to treat diabetes and atherosclerosis, and dietary berries have received increasing attention because of its roles in the management of diabetes and its associated complications

[197]. Dietary berries contain plentiful fiber and polyphenols, a small amount of carbohydrates and fats, certain essential micronutrients, including vitamin C, E potassium, manganese, and folic acid, contributing its health benefits in people with diabetes [198]. Several epidemiological studies have revealed that the bioactive compounds from berries could effectively reduce inflammation, oxidative stress, diabetes, and cardiovascular diseases [199–201]. It has been reviewed that supplementation of blueberries, cranberries, strawberries and raspberries might hold beneficial effects in diabetes through augmenting antioxidant abilities, decreasing biomarkers of atherosclerosis, and ameliorating glycemic and lipid profiles [201]. For example, administration of black raspberry extracts for 12 weeks decreased postprandial glucose and surrogate markers of atherosclerosis in adults with pre-diabetes [202]. Strawberries have been reported to improve atherosclerotic risk factors in subjects with metabolic syndrome, such as dyslipidemia and circulating adhesion molecules [203]. A randomized double-blind controlled trial has shown that consumption of freeze-dried strawberry significantly decreases C-reactive protein levels and lipid peroxidation in patients with type 2 diabetes, but does not affect serum glucose concentrations and anthropometric indices [204]. AMPK, a serine/threonine protein kinase, plays a central role in the regulation of cellular metabolism in cells, and this kinase is becoming a potential therapeutic target for the treatment of several chronic diseases, including obesity, diabetes, and cardiovascular diseases [205, 206]. Naturally occurring compounds are beneficial to the human body by acting on the AMPK signaling pathway. Coincidentally, Battino's group has disclosed that a methanolic strawberry extract attenuates lipid accumulation in HepG2 cells by AMPK activation [207]. Later, the same group further found that strawberry supplementation increased antioxidant enzyme activities, mitochondrial biomass, and decreased intracellular oxidative stress in old rats, an effect that is AMPK dependent [208]. These exciting results collectively confirm the involvement of AMPK in the beneficial effects exerted by strawberry against lipid deposition and aging progression. Likewise, it is possible that AMPK activation by strawberry might be used to prevent or delay diabetic atherosclerosis, which needs to be ascertained in the future studies.

As a natural dietary source of (poly)phenols, Red raspberry (*Rubus idaeus*) consumption ameliorates the impaired vasoconstriction and vasorelaxation response in the obese Zucker rat, a model of metabolic syndrome, suggesting that dietary intervention of Red raspberry prevents and/or reverses diabetes-induced vascular complications [209]. In consistence with this, Song *et al.* [210] have found that Red raspberry treatment decreases body weight gain, steatosis grade scores and insulin resistance in HFD-induced obese mice. The protection of Red raspberry against diet-induced obesity and related metabolic disorders may be mediated by a set of genes involved in lipid metabolism and fibroblast growth factor 21 signaling pathway [210]. Physico-

chemical characterization and metabolomic analysis showed that cyanidin 3-O-glucoside and cyanidin 3-O-sambubioside are the main anthocyanins of Andean elderberry, and these bioactive compounds exhibit antioxidant, antihypertensive, antiobesity and antidiabetic properties [211]. Consumption of a tropical highland blackberry beverage is found to mitigate plasma levels of triglycerides, total cholesterol, and glucose levels in healthy individuals on a high-fat, high-carbohydrate diet challenge, indicating that drinking this beverage from a blackberry micro-filtered juice is beneficial for lipid and glucose metabolism in people [212]. Overall, scientific evidence has highlighted the beneficial effects of berries as a dietary supplement in the treatment of human diseases, including diabetes and atherosclerosis [213]. More *in vitro*, *in vivo* and clinical studies are necessary to reaffirm the preventive and therapeutic activities of dietary berries in human disorders. Dietary berries could be highly developed in the nutraceutical and functional food industries. Although the favorable effects of dietary berries on the prevention and management of human illness, they should be recommended as part of a healthy diet.

14. Plant polyphenols and flavonoids

The daily diet contains a wide range of secondary metabolites, with polyphenols and flavonoids being highest in abundance, which may prevent the onset of various chronic diseases, including diabetes and atherosclerosis [214, 215]. As the highest components of plant secondary metabolites, polyphenols contain a benzene ring with hydroxyl (OH) moieties, ranging from simple flavonoids and phenolic acids to complex procyanidins [214, 215]. A number of scientists tested the therapeutic potential of polyphenols and flavonoids, and found that both phytochemicals possess anti-diabetic, anti-oxidative, cardioprotective, neuroprotective, anticarcinogenic, anti-inflammatory effects, to name a few [216–219]. Actually, polyphenols and flavonoids in colorful fruits and vegetables confer anti-diabetic actions in experimental animal models and human studies [220]. Molecular studies have shown that polyphenols and flavonoids contribute to human health by regulating metabolic and signaling pathways at various levels [214]. The potential effects of polyphenolic compounds on glucose and lipid homeostasis have been studied from *in vitro*, *in vivo*, and clinical studies. A systemic review and meta-analysis has demonstrated that intake of polyphenols is capable of preventing or treating diabetic complications [221]. A clinical study has revealed that supplementation of polyphenols, flavonoids, and stilbenes could reduce the risk of diabetic patients at high risk of cardiovascular disorders [222]. Consistent with clinical studies, cellular and animal studies support the benefits of various individual polyphenols in diabetes and its complications, including flavan-3-ols (EGCG), flavonols (quercetin), isoflavones (genistein), flavanones (naringenin), anthocyanidins, phenolic acids (caffeic acid and gallic acid), stilbenes (resveratrol) and curcumin [214]. For instance, polyphenols,

including resveratrol (a major polyphenol in red wine), apigenin, and S17834 (a synthetic polyphenol), are documented to inhibit the acceleration of aortic lesion development in diabetic LDL receptor-deficient mice [223]. Further studies have shown that the beneficial abilities of such polyphenols are abrogated by overexpression of dominant-negative AMPK mutants, suggesting the involvement of AMPK signaling in polyphenols effects [223]. Numerous studies have indicated that flavonoids might be beneficial for diabetes and its complications through reducing insulin resistance, inflammation, and oxidative stress in skeletal muscle and fat, reducing apoptosis and promoting proliferation of pancreatic β -cells, and improving glucose and lipid metabolism disorder in hepatocytes [214, 215]. Based on the observational results on the association of plant polyphenols and flavonoids with human health, there is an urgent need to determine the exact roles and underlying mechanisms of polyphenols and flavonoids in diabetes, obesity, and metabolic dysfunction, as well as their related cardiovascular disorders. In addition, the variability of polyphenols and flavonoids in different plants and their processed forms should be considered in clinical research, especially in terms of explaining their impacts on clinical results.

15. Conclusions

Natural constituents from medicinal plants have the potential for the prevention and treatment of diabetic atherosclerosis. We reviewed the current therapeutic potential and mechanisms of plant and herbal medicines in diabetic atherosclerosis. However, the clinical evidence associating various herbs and their benefits in diabetes-associated atherosclerosis is not extensive. First, most of the clinical trials on herbal medicines used small sample sizes, presented incomplete data, and did not use random designs. Moreover, exclusion and inclusion criteria are unspecific in several clinical studies, thereby limiting clinical applications of herbal medicines in patients with diabetic atherosclerosis. In this regard, rigorous clinical trials with large sample sizes and randomized, controlled designs are warranted to confirm the therapeutic efficacies of these medicines in diabetic atherosclerosis. Second, unlike patent drugs, most of the formulas prescribed by doctors might contain different amounts of ingredients and treatment cycles may vary from patient to patient. Therefore, there is a need to systematically and accurately evaluate the efficacy of TCM formulas in the management of diabetic atherosclerosis. Third, it is more likely that Chinese herbal medicines are used to treat human diseases together with other drugs in modern medical practice. Therefore, interactions between herbs and other drugs should be carefully assessed. Fourth, some herbs have toxic side effects. However, Chinese herbal medicine combinations have reduced toxicities and improved efficacies. Unfortunately, adverse effects of Chinese herbal medicines have seldom been mentioned in published *in vivo* studies. Organ-specific toxic effects and pharmacological doses of most herbal medicines

should be probed in both animal studies and clinical studies. Fifth, diabetic atherosclerosis is a multi-stage disease caused by multiple factors. However, most of the published documents evaluated the effects of Chinese herbs by assessing one or several aspects of diabetic atherosclerosis. The underlying mechanisms of Chinese medicines in diabetic atherosclerosis should be systematically evaluated. Last, active components in distinct compounds have not been defined, and their molecular targets are inconclusive. Therefore, emergence of systems biology and network pharmacology provides great possibilities for comprehensively analyzing and predicting large-scale drug target interactions. Despite these challenges, well-designed clinical trials and experimental studies should be performed to establish the mechanisms of Chinese medicines in order to promote their modernization for the prevention and treatment of diabetes-associated atherosclerosis. In addition, identification of novel molecules and signaling cascades in diabetes and atherosclerosis will enhance our understanding of multifaceted characteristics of diabetes-associated atherosclerosis. Systems biology, such as proteomics, genomics, transcriptomics, and metabolomics, single cell transcriptomics, and spatial transcriptomics may serve as tools for exploring interventions of herbal medicine in diabetes-associated atherosclerosis. Evaluation of multi-target mechanisms of herbal medicine will inform the development of drugs for treatment of diabetic atherosclerosis.

Although studies have shown that herb medicines, dietary berries, plant polyphenols and flavonoids can potentially be used in diabetic atherosclerosis, clinical translation of these findings should be done carefully. Additionally, unfavorable pharmacokinetics, pharmacodynamics, poor water solubility, rapid metabolism, and low bioavailability might limit extensive clinical applications of some herbs. Therefore, a number of their derivatives and analogs or novel delivery methods have been developed. Comprehensive investigations of herbal medicines in diabetic and atherosclerosis will improve our understanding of their pharmacological actions and inform on novel therapeutic targets for human diseases. Overall, plant and herbal medicines present a promising direction for the treatment of diabetes-associated atherosclerotic disease. In future, the combination of herbal and western medicines might facilitate the treatment of diabetic atherosclerosis. Therefore, exploration of drug interactions and adverse effects are mandatory.

Author contributions

All authors contributed significantly to this review. ZCW and HJS proposed the concept and wrote the manuscript. MZL helped to draw schematic diagrams. JOM, KXL, and HJS were responsible for reviewing and editing the original draft.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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