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Review

Pharmacological management of vascular endothelial dysfunction in diabetes: TCM and western medicine compared based on biomarkers and biochemical parameters

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ABSTRACT

Diabetes, a worldwide health concern while burdening significant populace of countries with time due to a hefty increase in both incidence and prevalence rates. Hyperglycemia has been buttressed both in clinical and experimental studies to modulate widespread molecular actions that effect macro and microvascular dysfunctions. Endothelial dysfunction, activation, inflammation, and endothelial barrier leakage are key factors contributing to vascular complications in diabetes, plus the development of diabetes-induced cardiovascular diseases. The recent increase in molecular, transcriptional, and clinical studies has brought a new scope to the understanding of molecular mechanisms and the therapeutic targets for endothelial dysfunction in diabetes. In this review, an attempt made to discuss up to date critical and emerging molecular signaling pathways involved in the pathophysiology of endothelial dysfunction and viable pharmacological management targets. Importantly, we exploit some Traditional Chinese Medicines (TCM)/TCM isolated bioactive compounds modulating effects on endothelial dysfunction in diabetes. Finally, clinical studies data on biomarkers and biochemical parameters involved in the assessment of the efficacy of treatment in vascular endothelial dysfunction in diabetes was compared between clinically used western hypoglycemic drugs and TCM formulas.

1. Introduction

The International Diabetes Federation estimates about 463 million adults, representing 9.3 % of the world population, have diabetes mellitus. Projected to rise to 10.2 % and 10.9 % by 2030 and 2045, respectively [1]. The rise in the number of diabetics is a severe concern in developing countries, especially in India and China. The epidemic of diabetes continues to expand, and it is witnessing a shift in diabetes prevalence from the affluent to the less privileged, urban to rural areas and all and sundry. Most diabetic patients suffer from microvascular and macrovascular complications [2]. Multi clinical trials have clarified that cardiovascular disease risks are three-to-four-fold higher in diabetic patients with vascular complications [3]. Moreover, the impact of vascular disease on diabetic patients is a significant reason for precipitating death.

In the early stages of type I diabetes mellitus (T1DM) and type II diabetes mellitus (T2DM), vascular endothelial cells (ECs) function are abnormal with the impairment of vasodilation and reduced nitric oxide (NO) bioavailability. This phenomenon is termed endothelial dysfunction [4]. European Diabetes Prospective Complications Study exhibited that endothelial dysfunction, assay by von Willebrand factor (vWF), is significantly associated with the accretive cases of diabetic neuropathy in T1DM patients [5]. In addition, endothelium-dependent vasodilation assay and flow-mediated brachial artery reactivity test have a strong correlation between the risk for vascular diseases occurring in a diabetic patient and the number of endothelial progenitor cells [4,6] A pathological study recommended that macrovascular endothelial dysfunction is a progressive step of atherosclerosis and erectile dysfunction [7]. Besides, microvascular anomalies in diabetes are consociated with elevated vascular permeability and impairment of autoregulation of vascular tone. Thus, a study on the molecular mechanism responsible for endothelial dysfunction underlies the pathogenesis of diabetes

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complication and which may provide new therapeutic targets for diabetes-induced cardiovascular diseases.

The homeostatic stability of the endothelium is characterized by NO production via endothelial nitric oxide synthase (eNOS) with its co-factors and physiologic release of prostacyclin (PGI_2) and low levels of reactive oxygen species (ROS). On the other hand, the distortion of the balance by AMP-activated protein kinase (AMPK) dephosphorylation, inflammasome inactivation, endoplasmic reticulum (ER) stress, autophagy deficiency, and mitochondrial dysfunction, are critical cellular events mediated by diabetes [8,9]. In response, endothelial cells increase expression levels of biochemical markers and cell adhesion molecules such as intracellular adhesion molecule 1 (sICAM-1), endothelin-1 (ET-1), C-reactive protein (CRP), etc. that alters vascular endothelium-dependent relaxation and function [10–12]. However, hypoglycemic drugs show beneficial effects in regulating the levels of the endothelial dysfunction biochemical markers [13–15]. Therefore, clinically, endothelial dysfunction biomarkers are often used in assessing the efficacy of treatment among different classes of drugs or therapeutic approaches in clinical trials involving subjects with diabetes and vascular endothelial disorder [16,17].

Traditional Chinese Medicines (TCMs) have been in existence for several decades and customarily as a primary health system in China and other parts of the world [18]. In line with fact that recent studies on herbs or bioactive ingredients have increased dramatically, researchers are advancing in high throughput and cutting edge research approaches to add up to the advances in knowledge. It is, therefore, not out of line for research to show that TCM or bioactive ingredients modulate molecular cascades events to ameliorate diseases, including diabetes-induced endothelial dysfunction [19,20].

Therefore, this review highlighted the cellular and molecular mechanisms of diabetes endothelial dysfunction, pharmacological management spots, and molecular actions of some TCM and bioactive ingredients' effect on diabetes vascular endothelial dysfunction. Also, clinical trial studies data on biomarkers and biochemical parameters were compared between clinically used western antidiabetic drugs and TCMs formula for basal comparative assessment of efficacy and safety of treatment in vascular endothelial dysfunction in diabetes.

2. Diabetes mellitus

2.1. Type I and type II diabetes mellitus: pathology, diagnosis, and complications

Diabetes mellitus (DM) is a metabolic disease defined by continual high blood glucose levels with irregularities in carbohydrate, fat, and protein metabolism. Microvascular, macrovascular, and infectious complications of diabetes are associated with social network characteristics [21]. Casual plasma glucose concentration ≥ 200 mg/dL, fasting plasma glucose ≥ 126 mg/dL, or an oral glucose tolerance test (OGTT) ≥ 200 mg/dL and HbA1c ≥ 6.5 % is diagnostic of DM. American Diabetes Association (ADA) divide DM into four major categories: T1DM, T2DM, secondary diabetes, and gestational diabetes mellitus (Table 1) [22]

Beta-cell destruction by pathogenic viruses or other environmental factors triggers islet autoimmunity, resulting in absolute insulin deficiency, which is the primary reason for type 1 diabetes mellitus (T1DM). Absent circulating insulin fails to regulate blood glucose uptake in the liver, muscles, and adipocytes, resulting in hyperglycemia and occasional bouts of ketoacidosis. Diabetic ketoacidosis, accumulation of ketone bodies, caused by compensatory fatty acid metabolism due to inadequate or absence of circulating insulin triggers a shortage of body water and electrolyte. However, progressive diabetes complication, such as cardiovascular diseases (CVD), microvascular diseases, and diabetes-related infection, causes organ failure and mortality in the late stage of T1DM patients [23].

Insulin resistance and relative insulin deficiency define type 2

Table 1
Types of diabetes, risk group, etiology and incidence rate.

Type	Other names	Age/Risk group	Etiology	Incidence rate
Type 1 diabetes	Insulin-dependent diabetes	Adolescents	Autoimmune-driven destruction of beta-cell, absolute insulin deficiency	5–10 %
Type 2 diabetes	Non-insulin-dependent diabetes	> 40years	Advancing insulin secretory defect on the backdrop of insulin resistance	90 %
Gestational diabetes	Pregnancy-induced diabetes	Pregnant women	Possibly, placenta hormones suppressing insulin actions on the backdrop of insulin resistance	2.5 %
Specific types of diabetes due to other etiologies	Secondary diabetes		Monogenic diabetes syndrome, exocrine pancreatic diseases pharmacological drug/ or chemical-induced diabetes	

diabetes mellitus (T2DM). Obesity, increasing age, sedentary lifestyles, and stress trigger insulin resistance in skeletal muscle, adipose tissue, and liver, leading to relative insulin insufficiency of peripheral demands. As the disease progresses, pancreatic islet function falters, and insulin secretion insufficiency induces hyperglycemia [22], which alters physiological processes and destabilizes internal homeostasis.

2.2. Diabetes mellitus and cardiovascular disease

Diabetes mellitus is a well-substantiated and independent risk factor for CVDs. The overall crude mortality rate is higher among diabetic obese than non-diabetic obese patients (29 per 1000 person-years versus 7 per 1000 person-years among women, respectively). Although death due to cancer, infectious diseases are relatively higher, an adjustment in baseline age, sex, smoking status, and body mass index (BMI) shows that death from CVDs is more elevated than cancer and other diseases [24,25]. VADT (Veterans Affairs Diabetes Trial) clinical trial examined the association between the incidences of CVDs risk in T2DM. The result indicated that the variability of fasting glucose among T2DM patients is involved in the development of CVD complications. In addition, CVD risks were highest in patients receiving intensive glucose management [26]. Moreover, ACCELERATE trial concluded that baseline fasting plasma insulin levels prognosticate a risk for cardiovascular outcomes and atherosclerotic vascular disease in T2DM [27]. In T1DM, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study exhibited that intensive diabetes therapy (mean HbA1c 7.3 %) decreases CVDs (nonfatal myocardial infarction, stroke, death from CVDs, confirmed angina, or the need for coronary-artery revascularization) and progression of intima-media thickness compared with conventional therapy (mean HbA1c 9.1 %) [28–30].

3. Endothelial dysfunction in diabetes

3.1. Localization and function of endothelium in the blood vessel

Endothelium, a thin layer of ECs located in the remote surface of blood vessels, controls the passage of macromolecules and fluid between the blood and interstitial space. The vascular endothelium participates in various physiological processes that contribute to vascular homeostasis. An essential function of the endothelium is the production of short-lived vasodilators, including NO, bradykinin, prostacyclin, and endothelial-dependent hyperpolarizing factor (EDHF) in response to physiologic stimuli [31]. NO plays a pleiotropic reaction to prevent vascular disease. The pivotal role of NO is regulation relaxation of vascular tone. Besides, NO prevents monocyte adhesion and platelet aggregation to the endothelium. NO also inhibits the over-proliferation of vascular smooth muscle cells (VSMCs) [32]. Moreover, endothelial ectoenzymes play a required step in the production of vasoactive hormones, such as angiotensin II. Endothelial dysfunction described as a disequilibrium in the synthesis and/or the discharge of various endothelial signaling molecules may account for the inception of cardiovascular disorders, their development, and complications [33].

3.2. Pathophysiological features of endothelial dysfunction in diabetes

ECs secrete relaxation factors by multi pharmacological activators and shear stress. Furchgott and Zawadzki first described endothelium-derived relaxing factor (EDRF) A-induced relaxation using isolated stripes of the aorta in the presence of acetylcholine (Ach). Ach released during parasympathetic activation, induce artery relaxation [34]. Ach binds with muscarinic receptors to activate the IP3 pathway. Thus, high intracellular calcium ion (Ca^{2+}) promotes the conversion of L-arginine to NO via calmodulin/tetrahydrobiopterin dependent pathway. Ach is the most routinely used agonist for the detection of endothelial function. In both macro vessels and microvessels of diabetic mice model, Ach-stimulated endothelial-dependent vasorelaxation was impaired while the vascular relaxation response to NO donor was preserved. Moreover, eNOS cofactors deficiency and oxidative stress might also contribute to the deterioration of endothelial function [35].

3.3. Clinic diagnostic of endothelial dysfunction

In human subjects, endothelial dysfunction correlated with high-risk factors for CVDs and events [36]. As a result, a clinical assay of *in-vivo* endothelial function is necessary to evaluate the pathogenesis of CVD. Several methodologies are established, e.g., Brachial Artery Flow-mediated Dilation (FMD), Venous Occlusion Plethysmography, and Iontophoresis in combination with Laser Doppler Imaging, Pulse-wave Analysis, and Retinal Arterial Abnormalities. Among these methods, Brachial FMD by ultrasound imaging is the most widely used clinically because of its non-invasiveness and feasibility. Shear stress by reactive hyperemia in brachial artery induced endothelium to release NO. FMD calculates the percentage of increase in diameter from baseline to the maximum value from ultrasound B-mode images or ultrasound RF-data after shear stress or pharmaceutical administration [37].

Multiple population-based studies have examined the association between FMD and adjudicated incidence of CVD events in human subjects. Results suggest that brachial FMD is a prognosticator of CVDs in adults [37–39]. FMD-J Study demonstrated that cardiovascular events (glucose, systolic and diastolic blood pressure, age, high–density lipoprotein cholesterol (HDL-C), BMI, and triglycerides) correlate with an increase in FMD and baseline brachial artery (BBA) diameter. However, BBA diameter is insensitive to FMD for evaluation of cardiovascular risk in male subjects used for the study [39]. Moreover, a study proposed cutoff-values of normal endothelial function and VSMCs function evaluated by nitroglycerin-induced vasodilation (NID) and FMD of the brachial artery as 15.6 % and 7.1 % respectively for Japanese subjects with or without cardiovascular risk factors [37]. However, genetic variance, ethnicity, age, gender, and among others are some limitations to endothelial dysfunction assessed by FMD of the brachial artery in clinical studies. Hence, it is imperative to develop new methods and broaden the scope of clinical studies that evaluate microvessel endothelial dysfunction.

3.4. Endothelial dysfunction in macrovascular endothelial complications of diabetes

Hyperglycemia impacts negatively on large vessels, leading to macrovascular complications, which are the primary cause of high mortality rates recorded in diabetes patients. Coronary artery disease, peripheral artery diseases, shock, and heart failure are some of the macrovascular complications associated with diabetes. High levels of oxidized-low density lipoprotein (ox-LDL) via HG-induced ROS production mediate atherosclerosis pathogenesis. Also, endothelial activation, a factor in the progression of atherosclerosis, promotes formation of foamy macrophages, release of adhesive molecules, and cytokines that promote thickening of the intima and support endothelial dysfunction.

However, animal studies confirm accelerated endothelial dysfunction in streptozotocin (STZ)-induced ApoE knockout ($ApoE^{-/-}$) and LDL receptor knockout ($LDLr^{-/-}$) mice [40,41]. Also, many endothelial dysfunction mice model, such as $eNOS^{-/-}$, Ang II treatment, could accelerate atherosclerosis development in diabetes [42,43]. In addition, both glucosamine administration (5 % w/v in drink water) and hyperglycemia accelerates endothelial dysfunction and atherosclerosis in $ApoE^{-/-}$ mice fed with chow diet [44]. AMPKα2 deficiency triggered endothelial dysfunction in cells via activation of NAD(P)H oxidases. Interestingly, in a high-fat diet (HFD)-fed AMPKα2/ApoE double knockout mice, the aortic lesions developed dramatically than $ApoE^{-/-}$ mice [45].

In hyperglycemic conditions, FoxO1 translocates into nucleus [46],

following binding with inducible nitric oxide synthase (iNOS) promoters. This subsequently generates excess ROS production, which contributes to eNOS uncoupling and LDL oxidation by reaction with superoxide anion ($O_{2^{\cdot}}^{-}$) to peroxynitrite ($ONOO^{-}$). Accili's lab generates vascular ECs-specific FoxO1 knockout mice (Tie2-cre/FoxO1-flox/flox) and silences all FoxO isoforms in LDL receptor knockout mice. The effect of endothelial dysfunction and atherosclerosis lesion attenuated after an HFD feed. In addition, iNOS, adhesion molecules, and lipid peroxides were significantly lower in STZ-injected Tie2-cre/FoxO1flox/flox mice than WT mice [47,48].

3.5. Endothelial dysfunction in microvascular endothelial complications of diabetes

Endothelium-dependent vasodilation to physical and/or pharmacological stimulants (e.g., Ach) is impaired in the vasculature of diabetic patients, leading to microvascular endothelial complications [49]. Consistent with endothelial dysfunction features such as increased endothelial permeability and leakage, inflammation, and endothelial barrier breakdown is observed in diabetic patients and animal models of diabetes microvascular complications-neuropathy, nephropathy, and retinopathy [50]. eNOS KO mice, as endothelial dysfunction animal models, are injected with STZ to establish a diabetic microvascular complication model. Diabetic eNOS KO mice (STZ-$eNOS^{-/-}$) demonstrated alterations in genes regulation of oxidative stress, apoptosis, and glomerular endothelial cell (GEC) proliferation compared to control. However, STZ-$eNOS^{-/-}$ GEC gene modifications were higher than STZ-WT. Moreover, diabetes-driven angiogenesis genes, Lrg1, and Gpr56 were altered in STZ-$eNOS^{-/-}$ GEC [51]. Also, changes in blood urea nitrogen, creatinine, albuminuria, oxidative state, eNOS expression, and glomerular basement membrane thickness are observed in STZ-induced diabetic nephropathy [52].

Moreover, in lipopolysaccharide (LPS) treated retinal microvascular ECs, MCP1, endoplasmic reticulum (ER) stress, and activating transcription factor 4 (ATF4) expression were highly increased. The study also demonstrated that overexpression of ATF4 correlates with an increase MCP1 secretion. More so, the effect of LPS-induced MCP1 production was blunt in retinas of $ATF4^{-/-}$ mice and deficient ECs [53]. Consistently, suppressing vascular endothelial growth factor (VEGF) and TPL2/ATF4/SDF1α axis proves to alleviate diabetes retinal microvascular abnormality [50]. TNFα-induced endothelial activation further worsens by HG activates ER stress and persistent inflammation in diabetic tie2-TNF mice, which resultantly cause changes in endothelial junction proteins hence visual deficit [54].

4. Molecular mechanisms of endothelial dysfunction in diabetes

4.1. eNOS-NO axis

4.1.1. Nitric oxide production and bioavailability

NO bioavailability relies on the equilibrium between its synthesis and consumption. The primary source of vascular NO is from eNOS in ECs. Many endogenous bioactive stimulants, e.g., Ach, serotonin, bradykinin, thrombin, and high intracellular Ca^{2+} ($[Ca^{2+}]_i$) level, activate calmodulin-dependent eNOS activation. eNOS activation with heat shock protein 90 (Hsp90) converts L-arginine to L-citrulline and NO in the existence of the redox-sensitive cofactor tetrahydrobiopterin (BH_4) (Fig. 1). In diabetes, the reduction of NO production and high NO consumption by ROS decrease NO bioavailability. Also, the transformation of L-arginine to NO by eNOS is lower than healthy persons [55]. Although eNOS expression has a compensatory increase in diabetic rats [56], eNOS is functionally inactive without binding with Hsp90. In addition, the reduction of eNOS phosphorylation (phos-eNOS) and BH_4 decreases NO production, resulting in endothelial dysfunction. Two independent pathways are involved in eNOS inactivation, I-kappa-B kinase beta (IKKbeta), and protein kinase A (PKA). Hyperglycemia increases IKKbeta mRNA, protein expression, and activity in bovine aortic ECs (BAECs). The competitive binding of IKKbeta to eNOS disrupts the eNOS-Hsp90 complex, resulting in eNOS inactivation. On the other arm, PKA-dependently induces phosphorylation of Hsp90 at Thr89 and translocation from cytoplasm to the membrane, leading to disruption of Hsp90-eNOS complex [57].

Insulin induces NO production and vessel relaxation by activation of the IRS-1/PI3K/Akt/eNOS pathway [58]. Modification of the insulin receptor by tyrosine nitration, the principal reason for insulin resistance, blocks the insulin/IRS-1/PI3K/Akt/eNOS pathway and causes endothelial dysfunction. Catalytic inactivation of one SHIP2 allele selectively in ECs of ($ECSHIP2^{\Delta/+}$) mice impaired insulin and Ach-driven vasodilation as well as aortic NO bioavailability, although basal elevation of expression and activation of Phosphoinositide 3-kinases (P13K), Protein kinase B (Akt) and eNOS were observed. Inhibitors of P13K and NAD(P)H oxidase 2 attenuates $O_{2^{\cdot}}^{-}$ levels in $ECSHIP2^{\Delta/+}$ ECs [59]. Insulin-induced Akt and eNOS-phos. were blocked by Protein kinase C beta (PKCbeta) activation in obese mice as well. Cyclic guanosine monophosphate (cGMP) as a measure of NO bioavailability decreases [60].

Consumption of NO is another principal reason for endothelial dysfunction in hyperglycemia. In physiological condition, NO has a slow degradation via auto-oxidation (Kinetics is $1 \times 10^7\ M^{-1}s^{-1}$). However, hyperglycemia-increased excess O_2-, which rapidly reacts with NO to form peroxynitrite (ONOO-)(kinetics is $7 \times 10^9\ M^{-1}s^{-1}$), resulting in the consumption of NO and hence low NO bioavailability. Superoxide dismutase (SOD) transforms O_2- with a rate constant of $2 \times 10^9\ M^{-1}s^{-1}$ to form H_2O_2. The reaction between NO and O_2- is faster than both NO auto-oxidation and O_2- self-consumption [61].

4.1.2. eNOS uncoupling

eNOS is constitutively expressed as a significant origin of NO in ECs. eNOS, a catalytically active enzyme, is a dimeric structure comprised of two identical subunits. Carboxy-terminal reductase domain of eNOS contains binding sites for NAD(P)H, flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), and calmodulin. N-terminal oxygenase domain of eNOS provides multiple binding sites: heme, L-arginine, and BH_4 [62]. The dimeric form of eNOS transfers electrons from NAD(P)H binding on C-terminal with FAD and FMN to L-arginine on N-terminal; subsequently, terminal guanidine-nitrogen of L-arginine and oxygen react to generate NO. In the endothelium of diabetic mice, eNOS undergoes uncoupling, and reduction of activity [63]. eNOS uncoupling disrupts the flow of electrons and generates O_2^{-} but not NO, leading to endothelial dysfunction.

Raman exhibited that zinc thiolate cluster conserved cysteine residues at the dimerization interface of eNOS by x-ray crystallography. Zinc thiolate cluster is composed of a tetracoordinate zinc ion held by four thiols from two monomers eNOS [64]. Zou et al. clarified that $ONOO^{-}$ treatment-induced eNOS uncoupling via division of zinc thiolate cluster. Oxidation of the zinc-thiolate bond by O_2^{-} contributes to $ONOO^{-}$-dependent eNOS uncoupling [65]. The $ONOO^{-}$ triggered eNOS uncoupling might contribute to hyperglycemia-induced endothelial dysfunction. In addition, HOCl, the primary oxidant of leukocyte-derived myeloperoxidase, dissociates the eNOS dimers into monomers via $ONOO^{-}$ pathway and directly induce eNOS uncoupling as well [62]. S-glutathionylation, a redox-sensitive post-translational modification of protein cysteine residues through the conjoining of tripeptide glutathione, also induce eNOS uncoupling. The thiyl radical formation leads to S-glutathionylation of Cys689 and Cys908 of eNOS, and this subsequently disrupts eNOS dimer.

Glutathione disulfide and exogenous superoxide both induce S-glutathionylation and uncoupling of eNOS, leading to decreased activity and NO production [66]. However, it is not clear whether S-glutathionylation of eNOS contributes to eNOS uncoupling under hyperglycemic conditions.

Interestingly, increase $[Ca^{2+}]_i$ load required for the inception

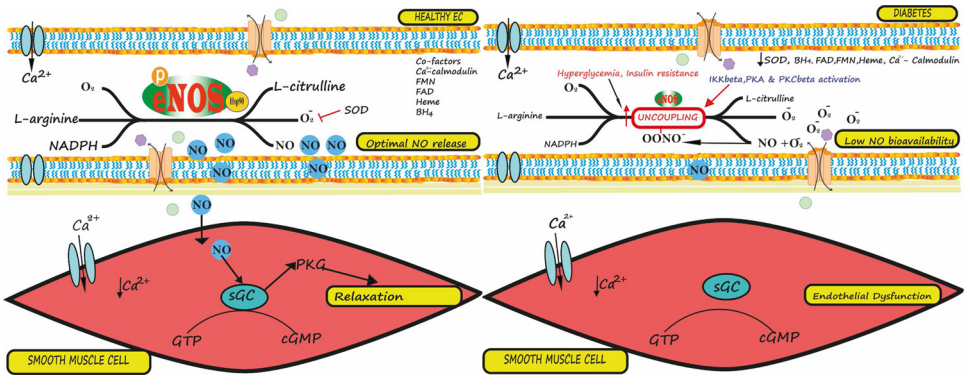

Fig. 1. Mechanism of nitric oxide generation and eNOS uncoupling.
(Left shear) Biologic factors such as acetylcholine, shear stress increase intracellular calcium ion level and mediate Ca2+/calmodulin–dependent activation of eNOS. eNOS association with Hsp90 sustains eNOS activating conformation and release of eNOS from caveolin-1. Molecular oxygen, L-arginine, and NADPH initiate the activation of eNOS with co-factors to produce NO, L-citrulline, and superoxide ion. SOD neutralized superoxide ions generated. NO leaks across the endothelium to activate soluble guanylyl cyclase induce cGMP-dependent activation pathways of PKG in VSMCs. Following a reduction in intracellular Ca2+ concentration steers the relaxation of the vessel.
(Right shear) Hyperglycemia and insulin resistance increases eNOS uncoupling by impairment of eNOS activation and association with Hsp 90 and decreased levels of co-factors such as BH4, FMN. IKKbeta and PKA activation in hyperglycemia increase IKKbeta protein expression and phosphorylation of Hsp90-alpha, respectively. IKKbeta protein competitively binds with eNOS, disrupts the eNOS-Hsp90 complex. Phosphorylation of Hsp90-alpha at Thr89 by PKA leads to translocation of Hsp90 from cytoplasm to plasma membrane. Activation of PKCbeta blocks the induction of eNOS. Decreased in the catalytic activity of antioxidant enzymes, e.g., SOD increases the generation of peroxynitrite ion, which promotes eNOS uncoupling via oxidation of zinc-thiolate. eNOS uncoupling leads to endothelial dysfunction and low bioavailability of NO; hence cyclic GMP-dependent activation impaired. Subsequent VSMCs relaxation inhibited.

activation of eNOS cycle equally triggers eNOS uncoupling through the activation of calpain (a protease responsible for the proteolytic degradation of eNOS) via its translocation to the membranes. However, eNOS-Hsp90 complex protects against calpain-mediated degradation [67], but hyperglycemia and oxidized and glycated-LDL (HOG-LDL) promote Hsp90 dissociation, increase $[Ca^{2+}]_i$ and calpain activity and eNOS translocation to cytosol, thence inducing eNOS uncoupling and heighten degradation [68,69].

4.1.3. Caveolin and eNOS

Caveolae, flask-shaped invagination structure with diameters in the range of 50–100 nm, occupying about 30 % of cell surfaces of capillaries. The vast myriad of caveolae in ECs includes multi receptors, e.g., Ach receptor and insulin receptor, to regulate signaling transduction. eNOS is co-localized with caveolin-1(cav-1), a caveolae structural protein, in the caveolae of the plasma membrane and Golgi apparatus, where it is topically inhibited by binding to cav-1 [70]. Disruption of caveolae structure by filipin or methyl-β-cyclodextrin impairs endothelial-dependent relaxation via reduction of NO production [71]. In STZ-injected rat and non-obese diabetic mice, cav-1 expression is significantly enhanced in aorta and corpus cavernosum tissue, which was associated with endothelial dysfunction. Results from *in vitro* studies confirm that both HG and free cholesterol treatment increase Cav-1 expression and enhance Cav-1-eNOS binding affinity [72,73], hence suppressing eNOS activity. Moreover, insulin and ACE inhibitors prevent the upregulation of Cav-1, contributing to eNOS activation. Likewise, in Cav-1 KO mice, high response to Ach promotes NO, cGMP, and enhancement of endothelial relaxation [74,75]. However, caloric restriction in Cav-1 KO mice showed an elevation in CVD risk factors compared with WT mice, which was associated with inappropriate adaptive responses in the renin-angiotensin-aldosterone system (RAAS) [76].

4.1.4. GTPCH1 and its metabolism BH_4

BH_4 (6R-L-erythro-5,6,7,8-tetrahydrobiopterin) is synthesized from guanosine triphosphate (GTP) in an Mg^{2+}-, Zn^{2+}- and NADPH-dependent reaction mediated by three enzymes, GTP cyclohydrolase I (GTPCH I), 6-pyruvoyltetrahydropterin synthase and sepiapterin reductase (SR). BH_4 functions as a necessary cofactor for eNOS generation of NO [77]. Takeda found that high risk of endothelial dysfunction is associated with low plasma BH_4 levels and a reduction in BH_4/BH_2 ratio in disordered cardiovascular patients [78]. Meanwhile, in both T1DM and T2DM mice, the total biopterins and BH_4 level decrease in correlation with the downregulation of phos-eNOS [79,80]. Inhibition of BH_4 biosynthesis deepens eNOS uncoupling [81]. Thus, a lower concentration of BH_4 may act as a predictor of endothelial dysfunction and a risk factor for CVD in diabetics [82].

Therapeutic modalities that target BH_4 serve as a preventive measure to restore endothelial dysfunction. BH_4 administration increases mRNA and protein expression levels of cGMP, Protein kinase G (PKG), eNOS dimer, as well as NO production [83]. Oral intake of sepiapterin, a stable precursor of BH_4, also prevents endothelial dysfunction in sedentary rats by improving insulin tolerance, Ach-induced vasodilation, and mitochondrial activity [84]. GTPCH I, a rate-limiting enzyme for the *de novo* BH_4 synthesis. GTPCH I expression is lower than normoglycemia mice, contributing to the reduction of BH_4 level and endothelial dysfunction. Mesenteric arteries from endothelial cell-specific KO of Gch1 (encoding GTPCH I) - $Gch1^{fl/fl}$ Tie2cre mice demonstrated a decrease in GTPCH protein and BH_4 levels together with loss of Ach endothelium-driven vasodilation [85]. Overexpression of GTPCH I by adenovirus-mediated transfection attenuates endothelial dysfunction via an increase in NO and BH_4 production and upregulation on eNOS dimer: monomer ratio in type I and type II diabetic aorta [86,87].

The mechanism involved in the reduction of GTPCH I expression is via enhancement of proteasomes activity in hyperglycemic conditions. Hyperglycemia decreases GTPCH I protein expression associated with the ubiquity of GTPCH I but not alter mRNA levels. Meanwhile, 26S proteasomes activity also increases. [88]. The result possibly suggests that accelerated degradation of GTPCH I might cause GTPCH I expression reduction after high glucose (HG) treatment.

4.2. Oxidative stress

4.2.1. ROS and RNS production

Oxidative stress, excess ROS and RNS, causes endothelial dysfunction and atherosclerosis in diabetes. In a diabetes model, hyperglycemia induces ROS production, eventually leading to oxidative stress in ECs. Superoxide radical is the first oxygen-free radicals formed by the mitochondria, NAD(P)H oxidases, and from eNOS uncoupling [59]. The reaction rate between $O_2^{\cdot -}$ with NO is faster than scavenge of $O_2^{\cdot -}$ by SOD and autoxidation of NO. Therefore, excess ROS production contributes to a reduction of NO bioavailability and the increase generation of $ONOO^-$. Moreover, nitrated tyrosine, as $ONOO^-$ footprint, is found in the endothelium of blood vessels, kidney, retina, heart, and peripheral nerves of diabetics [89].

A typical reaction of $ONOO^-$ is the nitration of protein-bound

tyrosine residues. $ONOO^-$ mediates tyrosine nitration of PA700/S10B, a major catalytic protease of 26S proteasome. PA700 nitration increases 26S proteasomes activities to accelerate the degradation of GTPCH I [90]. Less GTPCH I synthesizes insufficient BH_4 for eNOS activation. Meanwhile, an increase in 26S proteasomes activity induces NFκB activation via enhancement of IκBα degeneration. NFκB activation induces expression of NAD(P)H oxidases [91].

$ONOO^-$ also causes eNOS dimer destabilization via oxidation of the eNOS zinc-thiolate cluster and irreversible destruction of heme. Peroxynitrite treatment induces Zn^{2+} release from eNOS and decreases eNOS dimer/monomer ratio in EC culture. Moreover, $ONOO^-$ oxidizes both free and eNOS-bound BH_4 to dihydrobiopterin, which competes with BH_4 for binding to eNOS, resulting in eNOS uncoupling [92]. Besides NO production, other endothelial-dependent vasodilators are irreversibly blocked by $ONOO^-$ [93]. Prostaglandin synthase (PGIS) catalyzes the conversion of prostaglandin H_2 (PGH_2) into prostacyclin (PGI_2), an effective vasodilator.

In diabetic mice, 3-nitrotyrosine due to eNOS uncoupling induces tyrosine nitration of PGIS to decrease PGI_2 production, as evidenced by high expression of 6-Keto-PGF1α. Meanwhile, the inactivation of PGIS leads to the accumulation of PGH_2. PGH_2 is a substrate for the thromboxane-prostanoid receptor, which causes the tetanic contraction of the aorta. Thus, hyperglycemia blunts PGI_2-dependent relaxation and induces PGH_2-mediated vasospasm via RNS production [94]. Also, thromboxane A2 (TxA2) mimetic increases O_2^- and peroxynitrite via PKCbeta-NAD(P)H oxidases pathway. Moreover, TxA2 mimetics increase PGIS nitration and reduce the formation of PGI_2, resulting in endothelial dysfunction [95]. Overall, oxidative stress induces endothelial dysfunction via regulation of endothelium-dependent vasodilator substances secretion.

4.2.2. Down-regulation of anti-oxidative enzymes

The oxidant and antioxidant systems control intracellular reduction-oxidation (redox) balance. Enhancement of the oxidant system and reduction of the antioxidant system causes an imbalance between redox and oxidative stress. SOD is a crucial defense antioxidant enzyme against $O_2{\cdot}^-$ in cells. SOD includes three isoforms, mitochondrial manganese-containing SOD (MnSOD), cytosolic copper/zinc-containing SOD (CuZnSOD), and extracellular SOD (SOD3). Hyperglycemia promotes the expression of CuZnSOD, MnSOD, and SOD3 in ECs [96,97]. In db/db mice, MnSOD expression also increases compared with db/m mice. However, the activity of MnSOD decreases by nitrotyrosination [98]. Moreover, SOD3 deficiency decreases Ach-induced vasodilation, adiponectin expression, as well as Akt-eNOS pathway [99]. Also, studies have reported that activity for CAT was down-regulated in hyperglycemia-induced endothelial cells, suggesting decreased clearance of reactive species in ECs [100].

Furthermore, animal studies have shown that the deficiency of GPx-1 accelerates diabetes-associated atherosclerosis in $ApoE^{-/-}$ mice via the upregulation of the proinflammatory and fibrotic pathway [101]. Thioredoxin reductase (TrxR) is an antioxidant enzyme that aids in thiol-dependent cellular reductive processes. HG disrupts the thiol-reducing system by decreasing TrxR activity. Reduced thioredoxin and glutathione, as reducing equivalents for lipid hydroperoxides, decrease as well. However, thioredoxin mimetic peptide (TMP) supplementation aborted HG and methylglyoxal driven ROS production and enhanced survival of HUVECs [102]. Thioredoxin Interacting Protein (Txnip), an endogenous inhibitor of TrxR, interacts with the catalytic center of reduced Trx. HG also increases Txnip mRNA and protein expression via p38 and FoxO1 in HAEC and downregulation of miR-17 expression [103].

Consistently, Txnip deficiency by siRNA inhibits HG-induced ROS production [104]. Heme oxygenase-1 (HO-1) degrades heme from destabilized heme protein and converts biliverdin to bilirubin, leading to an antioxidant effect. HO-1 also produces carbon monoxide that has regulatory actions of vasodilation [105]. In STZ injected Sprague-Dawley rats, the expression and activity of HO-1 decreased. Apolipoprotein A1 mimetic peptide treatment increases HO-1 expression, leading to the prevention of ROS production and reduces vascular and white matter damage in db/db T2DM stroke mice [106]. Moreover, HG and H_2O_2 upregulated the expression of nuclear factor erythroid 2-related factor-2 (Nrf2), a transcriptional factor that coordinates the expression of numerous ROS detoxifying and antioxidant genes, in ECs. Resveratrol prevents endothelial dysfunction by an HFD via activation of Nrf2 [107], indicating that an adaptive activation of Nrf2 provides endothelial protection under diabetic conditions [108]. In all, endothelial oxidative enzymes maintain endothelial function by suppressing oxidative stress at the protein and genes levels.

4.3. AMPK inactivation

AMPK, a serine/threonine kinase, activated by increasing AMP: ATP ratio and two upstreams, LKB1 and calmodulin-dependent protein kinase (CaMKK). AMPK's principal function is maintaining intracellular energy homeostasis in multi organs, e.g., liver and muscle. Many literatures suggested the protective outcome of AMPK on endothelial function through eNOS activation and oxidative stress inhibition. Phos-AMPK induces association of hsp90 with its downstream target-eNOS to form hsp90-AMPK-eNOS complex, eventually increasing phos-eNOS at Ser1177 [52]. Nevertheless, AMPKalpha1 inhibitory phos-eNOS on Thr495 attenuate endothelial NO relaxing effect; however, AMP-Kalpha1 deletion reduces phos-Thr495, but not Ser1177 [109]. Exhaustive treadmill exercise on mice activates phos-AMPK-172 and its downstream eNOS-S1177 in the endothelium of aorta. Also, other phosphorylation sites: Ser617, Ser635, and Thr649, regulated by Akt and PKA, remain unchanged after acute exercise [110].

Moreover, AMPK activation attenuates endothelial dysfunction via regulation of redox balance. Firstly, AMPK activation attenuates both NAD(P)H oxidases-and mitochondria-derived O_2^- production [111]. In AMPKalpha2 KO mice, high 26S proteasome activity and NFκB-dependently increases expression of NAD(P)H oxidases subunits, including gp91phox, p47phox, p67phox, NOX2, and NOX4, were observed, which contribute to both increase in oxidative stress and low BH_4 levels thence promoting endothelial dysfunction in AMPKalpha2 KO mice [88,112]. Furthermore, the upregulation of NOX2 expression and NAD(P)H oxidases activation enhances O_2^- and $ONOO^-$ formation in AMPKalpha1 KO aorta [113]. AMPK activation upregulates UCP2-increases mitochondria generation and expression of MnSOD, peroxisome proliferator-activated response-gamma coactivator-1α (PGC-1α), nuclear respiratory factor-1 (Nrf1), and mitochondrial DNA transcription factor A, of which all exert some beneficial effects on maintaining redox balance ECs [114].

Secondly, AMPK activation increases the expression of antioxidant enzymes. AICAR upregulates the expression of thioredoxin, an antioxidant enzyme responsible for cysteine thiol-disulfide exchange with oxidative protein, via FoxO3 [115]. Besides, AMPKalpha1 siRNA decreases the appearance of antioxidative enzymes, including MnSOD, catalase, and thioredoxin, and increases mitoROS in ECs [116]. Finally, AMPK activation relaxes aorta via the reduction of HG-derived endothelium-derived contracting factors (EDCF), including TxB2, PGE2, and cyclooxygenase [117].

In diabetes, HG treatment induces inactivation of AMPK by dephosphorylating AMPK and reducing its activity in ECs. Three possible pathways are exhibited: polyphosphate multikinase (IPMK), protein phosphatase 2A (PP2A), and high ATP. HG increases phos-IPMK at tyrosine 174, a member of the IP6 kinase family enzymes, which facilitates binding of phos-IPMK with AMPK, leading to the blockage of phos-AMPK [118]. Besides, HG increases the expression of PP2A to dephosphorylate AMPK at Thr172 [119]. Lastly, hyperglycemia mediates changes in AMP/ATP ratio. HG increases cellular ATP levels in ECs, which compete with AMP for the AMP binding site on subunits of AMPK, resulting in inhibition of AMPK activity [120] (Fig. 2).

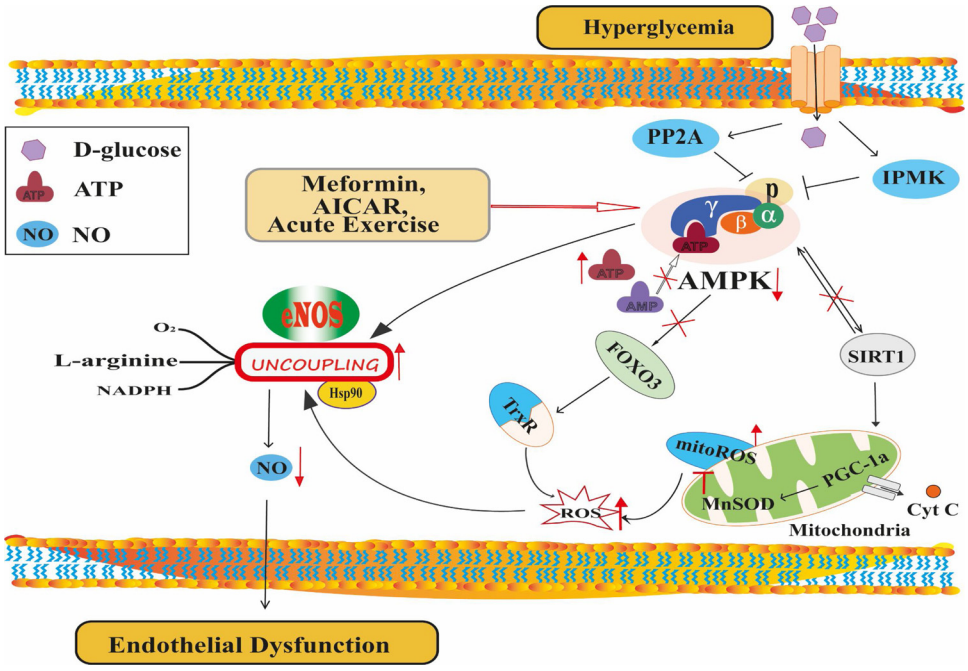

Fig. 2. Mechanism of inactivation of AMPK in diabetes-induced endothelial dysfunction.
Hyperglycemia induces phosphorylation of IPMK at tyrosine 174, increases the expression of PP2A, and intracellular ATP levels. Phosphorylated-IPMK blocks AMPK phosphorylation. Increased expression of PP2A dephosphorylate AMPK at Thr172. Increased intracellular levels of ATP competes with AMP for the AMP binding site on γ-subunit of AMPK, resulting in inhibition of AMPK activity. Decreased AMPK phosphorylation inhibits Hsp90-AMPK-eNOS complex interaction, which decreases eNOS phosphorylation at Ser-1177, resultantly a decrease in eNOS activity. Also, the inactivation of AMPK downregulates the expression of FOXO3 and phosphorylation of SIRT1. FOXO3 promotes the activity of TrxR, which is involved in the clearance of ROS. SIRT1 deacetylates PGC-1α to promote MnSOD expression and activity. Downregulation of MnSOD and TrxR increases MitoROS and ROS (oxidative stress), which eventually increases eNOS uncoupling. Increased eNOS uncoupling decrease NO bioavailability, with subsequent progression of endothelial dysfunction. Metformin, AICAR, and acute exercise promote AMPK phosphorylation.

Lastly, treatment with AMPK activators such as AICAR, metformin, etc. ameliorates impaired endothelial function. For example, metformin induces phos-eNOS with increase cGMP and NO levels from STZ-injected mice [121]. Also, an herb derived compound, berberine, AMPK-dependent activation increases phos-eNOS and NO production in ECs. Moreover, berberine relaxes aorta in an endothelial-dependent manner and prevents HG-impaired endothelial function [122]. Fenofibrate and resveratrol, isolated from red wine, both increase AMPK activation with restoring endothelial dysfunction in diabetic mice [123–125]. Moreover, endothelium-selective activation of AMPK aborts DM-triggered vascular reactivity and stimulate reendothelization and EPC activity via increase expression of HO-1 and release of stromal cell-derived factor (SDF-1α) [126]. Collectively, hyperglycemia mitigates AMPK beneficial effects on endothelial function.

4.4. Mitochondrial dynamics

Mitochondria, a highly dynamic double-membrane organelle, generates ATP and $O_2^{\cdot -}$. The structural dynamics of mitochondrial are regulated by the fusion or fission process [127]. Mitochondria fusion includes outer membrane connection by mitofusin (MFN) 1 and 2 and inner membrane fusion by optic atrophy 1 (Opa1). Mitochondria fission is majorly regulated by dynamin-related protein 1 (Drp1) and fission 1 (Fis1). Drp1, a cytoplasmic protein, is modified by both phosphorylation and SUMOlation, subsequently, anchor on Fis1. Multi accumulated Drp1 in mitochondria produces contractile force to divide tubular mitochondria into fragments. Mitochondrial fragmentation facilitates mitochondrial ROS (MitoROS) production, cytochrome C (Cyt C) release, and mitochondria movement along with cell skeleton. Mitochondria undergo augmented fragmentation in hyperglycemic ECs [128,129]. In hyperglycemic states, oxidative stress regulates mitochondrial fragment through five (5) pathways; 1. The upregulation of p53 transcription activates the expression of Drp1 [130]. 2. Co-localization of Protein kinase C delta (PKCδ) with Drp1 induces phos-Drp1 at Ser579 (mice) and Ser616 (humans) and translocation to mitochondria [131]. 3. An increase in binding activity of Rho-associated coiled coil-containing protein kinase 1 (ROCK1) with Drp1 mediates phos-Drp1 at Ser600 and Ser637, in mice and humans, respectively, and translocation to mitochondria [132]. 4. The blockage of autophagy-dependent Drp1 degradation [133]. 5. Depleted levels of Protein disulfide-isomerase 1(PDIA1) mediates sulfenylation of Drp at site C644 to activate Drp1 [134].

Furthermore, Fis1 protein expression levels are increased in hyperglycemia state [135], and MFN1 siRNA decreases the phos-eNOS and cGMP production [136]. Consistently, silencing Fis1 or Drp1 expression with siRNA prevented hyperglycemia-induced mitochondrial fragmentation and restored the reduction of phos-eNOS and cGMP production [135]. Also, mutants of Drp1 reduce mitochondrial $O_2^{\cdot -}$, mitochondrial permeability transition, and apoptosis in BAECs. More so, impairment in mitochondrial fusion by HG is mediated by translocase of mitochondrial outer membrane (TOM) 22. Report indicated that TOM 22 regulates mitochondrial biogenesis and oxidative phosphorylation (OXPHOS) via interacting with MFN1 in ECs [137] (Fig. 3). Altogether, HG mediates changes in mitochondrial fission and fusion-related proteins, which contribute to oxidative stress in ECs.

4.5. ER stress

ER is a vital cell organelle whose function is mainly protein translation and folding. Incorrect protein coupling or $[Ca^{2+}]_i$ accumulation trigger ER stress. ER stress induces unfolded protein response (UPR) and finally causes cell death. In ECs, hyperglycemia, hexosamine, homocysteine, and oxidized phospholipids all induce ER stress, evidenced by three ER-resident proteins activation, namely, activating transcription factor-6 (ATF6), inositol requiring protein-1 (IRE1), and protein kinase RNA-like ER kinase (PERK) [138–140].

Prolonged ER stress and compensatory UPR trigger endothelial dysfunction and atherosclerosis. ER stress in ECs decreases phos-eNOS and NO production via minimizing neutral sphingomyelinase 2 activity [141]. Also, another reason for endothelial dysfunction is due to oxidative stress during ER stress. Tunicamycin, an inhibitor of N-glycosylation, induces ER stress via UPR, which was mediated by the accumulation of p62 proteins. The association of UPR and p62 promotes ROS mediated mitochondrial apoptosis [142].

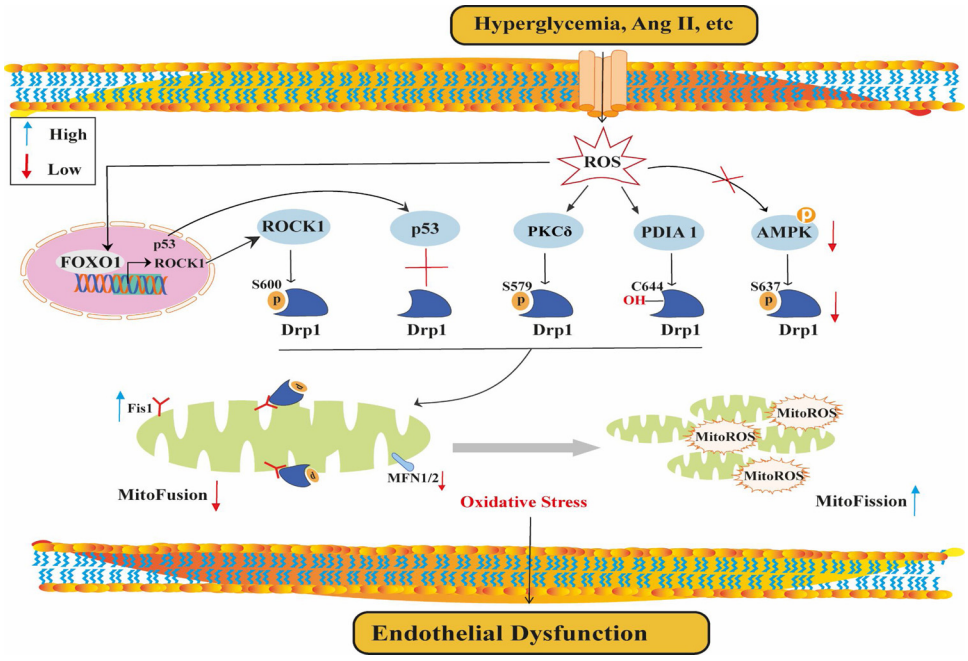

Fig. 3. Cellular mechanism of mitochondrial dynamics in diabetes-induced endothelial dysfunction. Hyperglycemia-induced increased in ROS upregulates FOXO1 increased transcription of ROCK1. ROCK1 phosphorylate Drp1 at sites S600 (mice) and S637 (human). ROS-upregulated expressed p53 binds with Drp1 to activate Drp1 and mitochondria translocation. Also, increased ROS enhances the colocalization of PKCδ with Drp1, which facilitates the phosphorylation of Drp1 at sites S579 and S616 in mice and humans, respectively. Likewise, depleted levels of PDIA1 mediates sulfenylation of Drp1 at the C644 site to activate Drp1. However, hyperglycemia deactivates AMPK and its phosphorylation of Drp1 at S637. Activation and translocation of Drp1 to mitochondria by these proteins except AMPK enhances activated Drp1 association with Fis1. Decreased MFN1/2 and increased Fis1-Drp1 levels in the mitochondria induces decreased mitochondria fusion and increased mitochondrial fission, respectively. Mitochondrial fission potentiates with increased levels of mitochondrial fragments, which subsequently facilitates the production of MitoROS and EC senescence. High levels of ROS and MitoROS induces oxidative stress in the endothelium, which exacerbates eNOS uncoupling with decreased NO bioavailability, leading to endothelial dysfunction.

Moreover, ER stress promotes apoptosis, endothelial permeability, and inflammation, which contribute to impairment in endothelial function. In ApoE$^{-/-}$ mice, Spliced X-box binding protein 1 (sXBP1) is significantly expressed, which correlated with the development of atherosclerotic lesion and ECs apoptosis via downregulation of vascular endothelial cadherin (VE-Cadherin) [143]. Also, ER stress-induced translocation of Glucose regulated protein 78 (GRP78) to plasma membrane foster O-GlcNAcylation of endothelial barrier proteins, mainly VE-Cadherin leading to destruction of the barrier integrity and increased endothelial permeability to migration of monocytes [144]. More so, P38MAPK and NFκB-dependent downregulation of claudin-5 in ER stress triggers human retinal microvascular ECs permeability [145]. Similarly, 58-kilodalton inhibitor of protein kinase (P58IPK), targeting ER-stress proteins: PERK and eukaryotic translation initiation factor 2 alpha (eIF2α), modulates effect on vascular permeability in the retina of diabetic rats [146].

Increased levels of glycated low-density lipoproteins (glyLDL) and ox-LDL are observed in diabetic patients. Its possible implications have been associated with the induction of ER stress-mediated inflammation [147]. For example, ox-LDL triggers the expression of inflammatory genes such as TNFα, IL-6, 8, MCP1, and CXCL3 via ATF4 and sXBP1 in ECs [148]. However, preconditioning with ER stress activation of XBP1 in diabetes suppresses ICAM1 and VCAM1 expression and TNFα-driven activation of NFκB. XBP1 negatively regulates phos-IRE1α. Therefore, XBP1 activation may be a possible target to improve ER stress-protective pathway to attenuate endothelial inflammation in diabetes [149].

Furthermore, contemporary studies demonstrate some novel ways to ameliorate HG-induced ER stress; therefore, below, we highlight these novel strategies. Changes in tissue and circulatory levels of microRNAs (miR) have been observed in T2DM patients, and their expression levels have been implicated as predictive markers for endothelial dysfunction. Notably, among them are miR-126, miR-149-5p, miR-146a, and miR-21. Restoration of miR-149-5p levels demonstrated protective action against increase expression levels of ER markers such as PERK, GRP78, and CHOP in HG-HUVECs [150]. Also, Protein tyrosine phosphatase 1B (PTP1B) inhibition and PTP1B$^{-/-}$ mice ameliorate ER stress and endothelial function via promoting PERK protective pathway and increased NO production [151].

However, thapsigargin treatment, a Sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) inhibitor, and HOG-LDL reduce SERCA via oxidation to increase $[Ca^{2+}]_i$ to trigger ER stress and activate calcium/calmodulin-dependent protein kinase IIγ (CaMKIIγ) [152]. CaMKIIγ induces Cyt. C release and Fas receptor expression, promoting apoptosis of ECs [153]. Likewise, increase $[Ca^{2+}]_i$ in ER stress mediates 12/15-lipoxygenase (12/15-LO) and its metabolite,15-HETE(15-hydroeicosatetraenoic acid) activation of NAD(P)H oxidases, which increases ROS production. Suppressing 12/15-LO in human retinal ECs decreases HG-mediated leukostasis and ICAM1 expression [9].

Also, Gipie, a girdin family protein, stabilizes the interaction of GRP78 with IRE-1 by binding with GRP78, resulting in blockage activation of IRE-1 during UPR. Gipie expression prevented the IRE1-JNK pathway and inhibited ECs apoptosis during UPR [154]. Conversely, miR-204, and glycated paraoxonase (PON) 1 promotes ER stress via suppressing endothelial SIRT1 and PON1glycation by HG, respectively [155,156]. In addition, 4-hydroxy-*trans*-2-nonenal (HNE) treatment in HUVECs leads to alterations of ER-resident proteins and endothelial activation mediated partly by UPR to ER stress [157].

In contrast, HO-1 induction prevented HG-induced increase of mRNA and protein expression of crucial ER stress-resident proteins. HO-1 promoted NO release and angiogenic capacity of HUVECs [8]. MGO-induced aortic endothelial dysfunction was diminished in CHOP deficiency mice and CHOP siRNA KO, indicating CHOP as a potential target for MGO-mediated endothelial dysfunction [158]. AMPKα2$^{-/-}$ mice and reduced AMPKα2 expression remarkably increase expression of ER stress-resident protein markers, $[Ca^{2+}]_i$, and elevate oxidized SERCA levels with repressed SERCA activity. The use of adenoviral overexpression constitutively active AMPK mutants abrogate ER stress, restore SERCA activity, and control $[Ca^{2+}]_i$ homeostasis [159]. Metformin also inhibits modified LDL-induced endothelial dysfunction via blockage of ER stress [152]. Metformin activation of AMPK-mediated PPARδ activation suppresses tunicamycin-induced ER stress and impairment of endothelium-dependent vasorelaxation in mouse aorta and aortic ECs. Cotreatment with PPARδ antagonist blunted metformin action, whereas PPARδ agonist effect was unaffected by AMPK inhibitor [160] (Fig. 4).

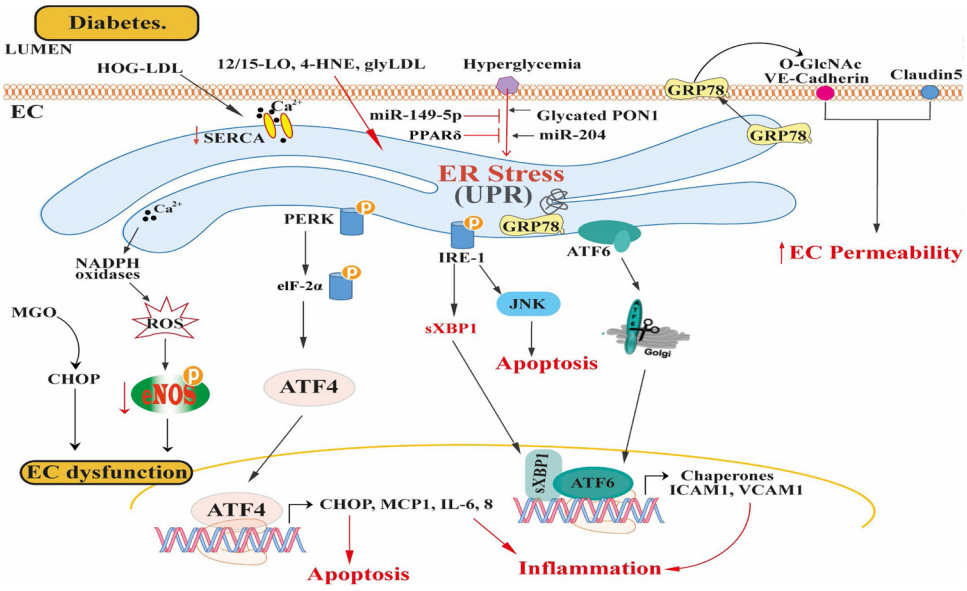

Fig. 4. Molecular mechanism of ER stress as a legate of endothelial dysfunction in diabetes.

HG-induced ER stress increases the induction of UPR. UPR signals through PERK, IRE1, and ATF6. PERK activation phosphorylates eIF2α, initiating a selective translation of ATF4, which induces the production of CHOP, IL-6, and IL-8. Also, activated IRE1 association with GRP78 phosphorylate JNK to induce apoptosis. Likewise, IRE1 dimerization catalyzes splicing XBP1 to mediate increase expression of chaperones. Moreover, ATF6 translocation to Golgi results in its cleavage of the luminal domain by protease and further transported into the nucleus to induce expression of adhesive molecules such as ICAM1, VCAM1, etc. Also, GRP78 translocation to the plasma membrane mediates O-GlcNAcylation of VE-Cadherin. Downregulation of Claudin-5 and O-GlcNAcylation of VE-Cadherin increase EC barrier leakage and permeability. HOG-LDL oxidation of SERCA increases the release of Ca2+ from ER, possibly involved in elevating the activity of NAD(P)H oxidases, result in an increased ROS production and downregulation of eNOS hence EC dysfunction. MGO-mediates EC dysfunction via CHOP. PPARδ activation and miR-149-5p increased expression levels attenuates HG-induced ER stress, whereas glycated PON1 and miR-204 enhance HG-induced ER stress. Also, 12/15-LO, 4-HNE, and glyLDL induce ER stress. Collectively, increased apoptosis, inflammatory mediators, EC permeability, and decreased eNOS phosphorylation via ER stress promote endothelial dysfunction.

4.6. Inflammasome

Inflammasome is a cytosolic multiprotein oligomer consisting of ASC, NLRP3, and caspase1. Inflammasome contributes to the progression of insulin resistance by mediating processes leading to the release of IL-1β and IL-18 in macrophage and adipocyte. Hyperglycemia and hyperlipidemia induce inflammasome formation to active caspase1; resultantly, increasing IL-1β production in macrophage. HG triggered IL-1β production, upregulates Txnip, and caspase1 activity in adipocyte [161]. Moreover, AMPK inactivation triggers inflammasome formation via ROS production by autophagy deficiency [162]. Likewise, ER stress triggers the activation of NLRP3 inflammasome [163].

In diabetes, especially in T1DM, IL-1β induces beta-cell destruction and impairs glucose-stimulated release of insulin in the presence of TNF-α/IFNγ [164]. Free fatty acid (FFA) activated NLRP3 inflammasomes and IL-1β release both *in vivo/vitro*, with subsequent impairment in Akt-ser473, eNOS-ser1177, IRS-1(tyr) phosphorylation and Ach-driven endothelium-dependent vasodilation. However, Lentivirus, siRNA, and AICAR inhibited FFA-induced IL-1β release and restored endothelial function [165]. IL-1β breaks endothelium junction through ROS/Src/EGFR-p38MAPK/PTEN pathway and PKC-θ activation in human microvascular endothelium [166,167]. Moreover, IL-1β from LPS–treated THP-1 monocytic cells increases the expression of adhesion molecules (ICAM-1, VCAM-1, and E-selectin) via phos-ERK and NFκB activation in ECs [168].

IL-18 is another cytokine-mediated by inflammasome. IL-18 and its receptor are highly expressed in human atheroma-associated EC, SMC, and macrophage. Mechanistic study showed that IL-18 signaling evoked effectors of atherogenesis, e.g., IL-6, IL-8, ICAM-1, and matrix metalloproteinase-1/-9/-13 (MMP-1/-9/-13) [169]. IL-18 also induces EPC dysfunction by blockage differentiation from EPC and circulating angiogenic cells into mature ECs [170]. Endothelial NLRP3 inflammasomes trigger HMGB1 production, which enhances endothelial hyperpermeability by the destruction of inter-endothelial tight junction [171]. Also, FFA induces NLRP3 inflammasome protein complex (ASC, p20, HMGB-1, NLRP3) expression, which exacerbate endothelial dysfunction [172].

4.7. Autophagy

Autophagy, lysosomal catalytic biological process, including the formation of membranous intracellular vesicles and ensuing engulfment and release of diverse cellular components such as damaged organelles, unfolded proteins, etc. to lysosomes for break down and recycling. Most cells experience basal levels of autophagy consistently to maintain the internal metabolic homeostasis of the cell environment and adaptation to stress. Nutrient deprivation, hypoxia, ROS, DNA damage, misfolded proteins, ox-LDL, and some naturally occurring compounds trigger the inception of autophagy in cells [173–175]. Deficiency of mitophagy receptor FUNDC1 enervates mitochondrial biogenesis and worsen dietary-induced obesity and metabolic syndrome [176]. AMPK induction of autophagy enhances cell survival rates under stressors [177].

HG treatment inhibits activation of autophagy via AMPK-dependent pathway in ECs. Interestingly, reactivation of AMPK with AICAR inhibited phos-ULK1 and autophagy, possibly AMPK uncouples from autophagy under hyperglycemic condition [178]. Also, hyperglycemia upregulates Txnip and controls dysregulation of tubular autophagy and mitophagy via BNIP3 transcription [179]. BNIP3 phosphorylate LC3 at ser-17 and ser-24 and cross-link with the PINK1-Parkin pathway to promote mitophagy under oxidative stress in ECs [180–182]. In addition, the deacetylation of FoxOs by SIRT1 inhibits the Akt negative modulation effect, leading to FoxO activation. FoxOs induce autophagy via increasing the transcription of autophagy-related genes [183–185]. Downregulation of SIRT1 in endothelial cells by HG inhibits the process.

Increased cell viability against oxidative insults, upregulation of eNOS expression, increased NO bioavailability, reduced inflammatory mediators, and oxidative stress shows the beneficial effect of autophagy [186–188]. Likewise, autophagy deficiency in HG and HFD beta cells had shown to cause excessive cell death, insulin resistance, UPR, and obesity progression in mice [189]. eNOS dysfunction in hyperglycemic condition has been related to reducing autophagic flux and not autophagy induction, suggesting that maintaining an intact autophagic flux but not autophagy induction, is likely to restore hyperglycemia-induced eNOS dysfunction [190]. Inhibition of autophagy with 3-methyladenine accentuated AGEs-induced cell death, buttressing the cytoprotective role of autophagy [191].

4.8. Some risk factors of diabetes and Endothelial Dysfunction

Obesity is a critical risk factor in the establishment of insulin resistance and an independent risk factor for CVD [192]. In metabolic syndrome mice model, mesenteric resistance arteries exhibit impairment of endothelium-dependent relaxation. ROS production, eNOS uncoupling, and nitrotyrosine expression levels increased in the endothelium of the aorta [193]. Moreover, perivascular adipose tissue significantly exacerbates endothelial dysfunction in arteries [194]. In fa/fa rat aorta and HFD-feed mouse aorta, PGIS and eNOS activity decreases. Agents with Antilipolytic actions, which reduce fatty acid release from adipose cells, and inhibit the rate-limiting enzyme for long-chain fatty acid oxidation, restore PGIS, and eNOS activity [195]. Leptin, an adipose-derived hormone that regulates energy intake and expenditure. In metabolic syndrome swine, perivascular adipose tissue releases leptin to activate PKCbeta in coronary arteries. Both leptin antagonists and PKCbeta inhibitor could block endothelial dysfunction in arteries with perivascular adipose tissue [196]. Jarrod also observed high leptin levels within the plasma of obese rats and dogs. Leptin (0.1–3.0 ug/min ic) concentration significantly attenuates dilation to graded intracoronary doses of Ach [197].

Cytokines contribute to endothelial dysfunction in diabetes. Excess adipose triggers macrophage recruitment to release TNF-α, IL-1β, and MCP1 [198]. After intra-arterial TNF-α infusion in T2DM, endothelial-dependent relaxation monitored by forearm plethysmography is significantly impaired, but not nitroprusside-induced vasodilation [199]. TNF-α and IL-1β plus HG treatment significantly aggravate glucose utilization, mitochondrial O_2^- generation, ERK, and JNK phosphorylation, NFκB activation, and caspase 1 activation than hyperglycemia-induced ECs [200].

However, adiponectin level was low in obesity-prone Osborne-Mendel (OM) rats with an increased risk of CVD and endothelial dysfunction biomarkers [201]. In db/db mice, anti-TNFα peptide restores endothelium-dependent vasodilation to Ach in coronary arterioles and aortas. Moreover, anti-TNFα treatment upregulates the expression of adiponectin that induces AMPK-dependent promotion of endothelial function [202]. However, a study showed the adverse results that chronic TNF-α neutralization did not improve endothelial function in metabolic syndrome men [203].

Besides TNF-α and IL-1β, MCP1 is involved in endothelial dysfunction in diabetic mice. Anti-MCP1 antibody restores vasodilation to endothelium-derived vasodilator in coronary arteriole in db/db mice. Moreover, an antibody against MCP1 attenuates O_2^- production, and expression of nitrotyrosine [204]. MCP1 also increases brain endothelial permeability via induction reorganization of the actin cytoskeleton and redistribution of tight junction proteins, including ZO-1, 2, occludin, and claudin5 [205].

5. Therapeutic targets of vascular endothelial dysfunction in Diabetes

Hyperglycemia modulates diverse molecular mechanisms to induce vascular dysfunction. In this section, we focus on discussing highlights from clinical and animal studies' primary therapeutic targets that have been projected to alleviate the detrimental effect of diabetes on endothelial function. We hope this will add up to available knowledge and streamline future research intervention on endothelial dysfunction that might prevent and remedy diabetes complications as well.

5.1. AMPK

As discussed earlier above, AMPK plays a significant activity in regulating NO bioavailability via eNOS activation and anti-oxidant effect. Therefore, AMPK is an attractive therapeutic target for endothelial dysfunction in diabetes. Up to date, multi-type oral anti-diabetic drugs induce AMPK activation with restored endothelial function in diabetics. Metformin stimulates AMPK in diabetic patients and animal models [206,207]. Insulin-sensitizing agents, such as thiazolidinediones (TZDs), directly induce AMPK activation and adiponectin production [17]. Other therapies for diabetes, e.g., acute exercise and low-calorie diet, also restore AMPK activity. Importantly, AMPK activators prevent endothelial dysfunction in diabetic animal models. AICAR protects against endothelial dysfunction induced by hyperglycemia, hypercholesterolemia, aged, or 20-Hydroxyeicosatetraenoic acid [208,209]. AICAR directly relaxes muscle resistance arteries via AMPK activation and phos-eNOS. AICAR also increases muscle microvascular blood volume and recruitment of microvascular perfusion [210]. AICAR inhibits EDCF-mediated contraction via down-regulation of COXII [211]. A study on the mechanism of endothelial protective effects suggested that AICAR prevents oxidative stress together with impairment of the eNOS-Hsp90 association. Metformin ameliorates endothelial functions via suppressing vasoconstrictor prostanoids and reducing oxidative stress in mesenteric arteries from aged Otsuka Long-Evans Tokushima fatty rats [117].

FIELD study concluded that fenofibrate reduced the development and advancement of diabetic retinopathy. The activation of AMPK by fenofibrate might be involved. AICAR or constitutively active AMPK prevents palmitate-induced NFκB activation in retinal pericytes and ECs [212,213]. Meanwhile, metformin and AICAR inhibit TNF-α-induced proinflammatory cytokines and cell adhesion molecules, e.g., VCAM1, E-selectin, ICAM-1, and MCP1 by a rapid NO-dependent mechanism in ECs [214–216]. AICAR and A769662 increase HO-1, which mediates the anti-apoptotic effect of AMPK in ECs [217]. Moreover, AMPK activation has recorded success in alleviating ER stress in HG-treated ECs and STZ-induced diabetes animal models. Activation of AMPK suppressed SERCA oxidation in HOG-LDL-induced BAECs and promoted endothelium-dependent vasorelaxation in isolated mouse aortae [152]. Treadmill exercise activates AMPK to increase NO bioavailability, endothelium-dependent vasorelaxation, and activation of PPARδ-mediated suppression of ER stress in db/db mice [218]. Similarly, omentin-1 induced phos-AMPK and PPARδ expression to protect against HG-induce ER stress, oxidative stress and reduced NO bioavailability in isolated mouse aortas and mouse aortic ECs (MAECs) [49]. In the future, we speculate that AMPK activator may contribute to the beneficial impact on reducing endothelial dysfunction in diabetic patients since AMPK exclusively affects almost every signal pathway impaired by HG in ECs.

5.2. Adiponectin

Adiponectin is an ample adipocyte-derived plasma protein. Adiponectin safe-guides the vascular system partly through activation of endothelial NO production and endothelium-dependent vasodilation. Moreover, low adiponectin expression accounts for endothelial dysfunction in diabetes. In T2DM and metabolic syndrome patients, the plasma adiponectin is lower than in a healthy person [219,220]. In ob/ob mice, the serum adiponectin is decreased [221]. Moreover, adiponectin KO mice disclose impairment on endothelial-dependent relaxation in response to Ach. Adiponectin deficiency decreases phos-eNOS and NO production and increases ROS and RNS in vessels [222,223]. TZDs upregulates the expression of adiponectin. Besides TZDs, adiponectin administration improves endothelial dysfunction in diabetic mice. Adiponectin and its paralog, CTRP9, directly induce endothelium-dependent vasorelaxation. CTRP9 also promotes endothelial function in aortic rings from HFD-fed mice via AMPK-eNOS activation [224].

Adiponectin restores endothelium-dependent vasodilation to Ach in both coronary arterioles and aortas in T2DM mice [202]. Adiponectin binds with its receptor AdipoR1 and AdipoR2 with interaction with APPL1 to activate AMPK. Adiponectin increases the formation of eNOS-Hsp90 complex and phos-eNOS, resulting in NO production via AMPK activation [225]. Adiponectin also decreases C-reactive protein (CRP) via regulation of NFκB inactivation in HG-induced HAECs [226].

Moreover, adiponectin prevents hyperglycemia-induced oxidative stress and cell death via the AMPK pathway [227,228]. HG and high lipids affect AdipoR1/Cav-1 interaction, with subsequent reduction of Cav-1 expression, which potentiates adiponectin resistance contributing to diabetic endothelial dysfunction [229].

Adiponectin suppresses activation of IKKβ and degradation of IκBα in HG-treated HUVECs. Both cAMP/PKA and AMPK pathways are implicated in the inhibition effect of adiponectin [230]. In addition, adiponectin submerges leukocyte-endothelium interactions, preceding to an increase in NO bioavailability [231].

5.3. SIRT1

Sirtuin 1, well known as NAD-dependent deacetylase sirtuin-1 (SIRT1), is a member of sirtuins, the group of mammalian class III histone deacetylases. SIRT1 mainly located in the nucleus of most cells; however, its mitochondrial and cytoplasmic appearance result in distinct functional and physiological processes. SIRT1 and its downstream target, PGC-1α both deacetylase, within the mitochondria to promote mitochondrial biogenesis, limiting mitochondrial DNA damage and prevention of the activation of mitochondrial damaging MMP-9. SIRT1 also regulates transcription factors such as FoxOs, PPARγ, p53, p65 subunit of NFκB, etc. Moreover, its genetic knockout and inhibition have been linked to endothelial dysfunction [232].

SIRT1 also regulates endothelial NO and endothelium-dependent vasodilation by deacetylating eNOS. SIRT1 binds to eNOS and regulates its post-transcriptional activation [233,234]. Hyperglycemia downregulated SIRT1 by upregulating miR-195. Qin et al. exhibited that the activation of SIRT1 with SRT1720 inhibited endothelial cell apoptosis and endothelial dysfunction in diabetes via inhibiting the mitochondrial-dependent apoptotic pathway primarily by limiting Cyt. C leakage. In addition, SIRT1 vitiates mitochondrial fission via the JNK pathway by regulating mitochondrial fission factor (Mff) in hyperglycemia-induced endothelial dysfunction. Likewise, the absence of SIRT1 contributed to the upregulation of Drp1. Plethoric mitochondrial fission increased mitochondrial cellular energy disorder and mitochondrial permeability transition pore (mPTP) opening and Cyt. C leakage, hence activation of the mitochondria-dependent apoptotic pathway [235]. Increase cellular NAD^+ enhances SIRT1 activity via AMPK. Ang II-induced endothelium ROS production and heighten telomerase activity were blunted by the apelin/APJ axis via AMPK/SIRT pathway [236]. Collectively, SIRT1 plays an important role in the deacetylation of targets that exert favorable effects against endothelial dysfunction; therefore, target compounds may contribute to overall improvement.

5.4. Aldose reductase

Aldose reductase (AR), also termed as an Aldo-keto reductase, catalyzes the reduced NADPH-dependent decrease of carbonyl compounds, including glucose. Reducing glucose to sorbitol, the latter oxidized to fructose. AR, involved in the initiation steps of the polyol cycle. Its modulatory activity in hyperglycemic-induced endothelial dysfunction has been established, and its activation promotes peroxynitrite and tyrosine nitration formation and eNOS uncoupling [237]. Inhibition of AR averts hyperglycemia-induced increase in inflammatory mediators in macrophages, VSMCs, and ECs in diabetic mice by inactivation of NFκB, AP1-induced proinflammatory signals [238,239]. In addition, preincubation with AR inhibitor prevents hyperglycemia and cytokine-induced multiplication of vascular cells and apoptosis of macrophages [239–241]. AR inhibitor, fidarestat, prevents hyperglycemia-induced Thp1 cell death by induction of Nrf2 expression, DNA binding activity, and expression of HO-1, NQO1, SOD, and CAT via activation of AMPK-α1, accounting for the anti-inflammatory effects [237].

In addition, human AR amplifies impaired atherosclerosis regression in diabetic mice, likely altering with plaque macrophage inflammation [242]. Vedantham et al. proved that human AR expression in $apoE^{-/-}$ mice and ECs accelerates diabetic atherosclerosis, with AR inhibitor terminating the effect.

It propounded that overage flux of glucose via AR impaired nicotinamide phosphoribosyltransferase (NAMPT)-mediated NAD^+ synthesis. Reduced NAD^+ levels inactivate SIRT1, which triggers acetylation and prolonged-expression of early growth response protein 1(EGR1), leading to elevation of VCAM-1, ICAM-1, and tissue factors (TF). Zopolrestat, AR inhibitor, negated these actions [243], and also vitiated the impaired Ach-stimulated NO production and repressed endothelial pyknosis, nitrotyrosine formation, and ROS generation [244].

Sorbinil and Alagebrium, both AR inhibitors, equally reversed impaired Ach-mediated vasodilation, with Sorbinil improving NO bioavailability via increasing eNOS cofactor-NADPH and reducing peroxynitrite formation as well as restoring of C-fiber functions and glutathione levels, whiles Alagebrium act mainly as AGEs breaker and AGEs formation suppressor to meliorate diabetic neuropathy and vascular dysfunction [245,246]. However, a study reported that Sorbinil deteriorates diabetes-induced modifications in aortic function and contractile responses, and its actions might be independent of AR inhibition [247]. Contemporary, AR inhibition or KO decreased ROS generation and expression of BCL-2, BAX, and inactivated Caspase-3, prevented the adhesion of Thp1 monocytes, ICAM1, VCAM1, and expression of iNOS in HG-induced HUVECs. Besides, the lab demonstrated that AR inhibition restores SIRT1 activity and phos-AMPKα1 together with inhibition of mTOR [248]. Also, AR inhibition downregulated the expression of NLRP3 inflammasome factors in STZ-induced diabetic mice aorta and heart [249].

Moreover, Aminoguanidine treatment mitigated diabetes-induced endothelial dysfunction via AR inhibitory activity, repressing AGEs formation, profound secretion of vasodilatory mediators, increase the elasticity of vessels, and antioxidant activity. Furthermore, Aminoguanidine improves vascular reactivity, and Epalrestat ameliorates erectile dysfunction via increased SMCs and endothelial content-upregulation of never growth factor and the restoration of nNOS expression in dorsal nerve [250,251]. In contrast, Ponalrestat did not improve vascular reactivity to noradrenaline or defective dilation to Ach in isolated perfused mesentery from STZ-induced diabetic rats [252].

6. Diabetes mellitus treatment rescues endothelial dysfunction

6.1. Insulin therapy

Insulin synthesized in β cells of the pancreatic islet in response to changes in blood glucose concentration. The function of insulin is facilitating blood glucose uptake, regulating carbohydrate and fat metabolism. Insulin therapy for compensating insulin insufficient remains the predominant method for effectively treating T1DM and end-stage T2DM. Besides hyperglycemia, the effect of insulin insufficiency/resistance on endothelial dysfunction has been studied with insulin receptor (Insr)/insulin receptor substrate-1 (Irs1) double heterozygous ApoE KO mice ($Insr^{+/-}Irs1^{+/-}ApoE^{-/-}$) which mated to mimic insulin resistance. Insulin-induced phos-eNOS and endothelial-dependent relaxation were impaired in $Insr^{+/-}Irs1^{+/-}ApoE^{-/-}$ mice. In this model, western diet increases atherosclerotic lesions associated with high fasting insulin than in $ApoE^{-/-}$ mice [253]. Rask-Madsen et al. also generated endothelial cell-specific $Insr^{-/-}$ mice in the $ApoE^{-/-}$ background. HFD induces endothelial dysfunction than $ApoE^{-/-}$ mice without affecting insulin levels.

Insulin receptor deficiency attenuates eNOS expression and insulin-driven phos-eNOS in ECs, leading to impair endothelial function and enhance leukocyte adhesion [254]. Therefore, insulin therapy may be one of the surest ways of alleviating endothelial dysfunction in diabetes-induced endothelial dysfunction. Insulin directly stimulates NO production via the activation PI3K-Akt-eNOS pathway after binding with the insulin receptor [46]. In T1DM, the insulin receptor works

well, and insulin-PI3K-eNOS pathway not impaired. Also, the relaxation effect of insulin is higher in endothelium-intact aorta than denude aorta, suggesting that the primary target of insulin are ECs. [255].

In addition, insulin blocks malondialdehyde (MDA) and TNF-α increase and restores GSH deficiency in diabetes aorta [256]. Galactosamine plus D-chiro-inositol (DCI) or Myo-inositol (Myo-INS) treatment has insulin-like activity. In diabetic rats, both DCI and myo-INS prevent hyperglycemia-induced endothelial dysfunction as well as ROS production in aortic rings and arteriolar mesenteric bed [257]. A study exhibits that insulin has multiple opposing effects on vessel relaxation. Insulin induces activation of Ras-Raf1 to phosphorylate MAPK, resulting in endothelin-1(ET-1) production, as a vessel contractor [258]. In insulin resistance mice model, selective impairment of PI3K/Akt pathway-dependent eNOS activation and the augmented ERK1/2 signaling in vascular endothelium led to decreased eNOS level and increased ET-1 production, tilting the equilibrium between the vasodilator and vasoconstrictor effects of insulin. Instead, insulin continues to induce endothelial dysfunction. Thus, the relaxation effect of insulin is impaired in T2DM [11,259].

6.2. Pharmacological management of vascular endothelial dysfunction in diabetes

Aside from low-calorie diet, exercise, and insulin therapy, pharmacological agents are invariably needed to control blood glucose levels and reduce the incidence of diabetic short or long-term vascular complications. Over the years, various clinical trials and animal studies have shown that western hypoglycemic drugs, such as metformin, TZDs, sulfonylureas prove to be effective in improving diabetes-induced vascular endothelial dysfunction; however, issues on side effects and poor medication adherence have contributed to their limited use in patients [260]. TZDs, known as glitazones, are insulin sensitizers. Pioglitazone and rosiglitazone, the two most popular TZDs. Multiple clinical trials have associated TZDs to increase risk of heart failure, fractures, edema, etc.; hence their clinical use is withdrawn [261]. Although TZDs show some promising protective effects against HG-induced endothelial dysfunction. Moreover, current western hypoglycemic drugs are far from satisfactory in the modulation of their activity [262–264] and have been recommended for combinational therapy for better improvement in biochemical parameters for diabetes complications and glycemic control [265,266].

Nevertheless, TCM is becoming more appealing to western healthcare systems and other countries due to the holistic and comprehensive approaches used in the management of diseases [267]. TCMs have demonstrated promising results in clinical, *in vivo, and in vitro* studies on protecting endothelial dysfunction in diabetes animal models and patients with minimal-to-no side/adverse effects associated with western hypoglycemic drugs [18]. Besides, TCM therapies are welcoming, and culture friendly to patients as well as the economic burden is low [268].

TCMs and their bioactive ingredients modulate favorably and ultimately ameliorate molecular cascade of events that contribute to disease treatment and management and, thus, have multi-modal cellular mechanisms of action. In addition, studies have established that TCMs/bioactive ingredients prevent endothelial dysfunction, dysfunctional vascular alterations, platelet activation, lipid peroxidation, ROS production, and macrophage atherogenicity [77,269]. The western antidiabetic drug, metformin, widely used in clinics, was isolated and developed from *Galega officinalis* [270]. Given all these therapeutic abilities, it is not surprising that TCM is being absorbed into evidence-based therapies for the elimination and treatment of disease. Therefore, in this section, we focus on TCM herbs with in *vivo and in vitro* activities, and compare the efficacy of TCMs formula to western hypoglycemic drugs on improving vascular endothelial dysfunction in diabetes. Table 2 shows the molecular actions of some TCMs and their isolated compounds on diabetes vascular dysfunction.

6.2.1. Danshen

Danshen, *salviae miltiorrhizae Bge,* a popular TCM used widely in China due to its multiple cardiovascular protective functions. It is used in the management of cardiac, diabetes, and cerebrovascular diseases. In addition, Danshen, one of the critical ingredients of Xiao-Ke-An TCM formula, which has been identified to exert endothelial protective function due to its phenolic acid components [271]. Meanwhile, Danshen injection is widely used in clinics to treat T2DM [272].

Moreover, in an ovariectomized (OVX) hyperlipidemic (HFD) rat model, the aqueous root extract of Danshen improved serum lipids and reduced body weight and prevented fatty liver. Also, increased in endothelial-dependent vasorelaxation, primarily by stimulating NO production, downregulating the mRNA expression levels of TNFα,ICAM-1, VCAM-1, and upregulating the mRNA expression of eNOS in aortic cells, supported its clinical use in diabetes and dyslipidemia in postmenopausal women [273].

Danshen contains two major groups of bioactive ingredients, lipid-soluble tanshinones, and water-soluble phenolic acids. Salvianolic acid A decreased the level of serum vWF and ameliorated Ach-induced relaxation and KCl-triggered contraction in aortic rings of HFD-fed and STZ-induced diabetic rats. Reduced serum MDA and nitric oxide synthase (NOS) activity plus a decreased expression of eNOS protein were reported as well, which indicates that salvianolic acid A protects against endothelial dysfunction by the repressive effect on oxidative stress and AGEs-induced endothelial dysfunction in diabetes [274]. Salvianolic acid B relax aorta via activation of AMPK and eNOS [275] and inhibited ox-LDL/HG-induced endothelial dysfunction via mediating reductions in apoptosis-related proteins, phos-Drp1, and Fis1 proteins through the downregulation of ROCK1-triggered apoptosis/mitophagy pathway [276].

Tanshinone IIA (TANS IIA) relaxes aorta via activation of AMPK-eNOS axis [275]. TANS IIA improved cell viability and ameliorated cellular oxidative stress induced by MGO in bovine retinal ECs. Exposure of MGO gave rise to mitochondrial fission and decrease expression of OPA1 and MFN1. Nevertheless, TANS IIA reduced mitochondrial fragmentation and promoted the mRNA levels of MFN1 and OPA1. Also, glyoxalase 1 (GLO1), an enzyme that participates in festering MGO was overexpressed. Knocking out GLO1 by siRNA abolished the effect, suggesting that TANS IIA ameliorated mitochondrial abnormalities and apoptosis triggered by AGEs through enhancing the levels of GLO1 [277]. Also, TANS IIA and Astragaloside IV combined treatment suppressed IL-6, MMP-9, TNF-α, and CRP expression and upregulates eNOS expression in ApoE$^{-/-}$ mice and ox-LDL-driven RAW 264.7 macrophages [281].

Collectively, Danshen and its bioactive compounds show potential activity to attenuate oxidative stress, and inflammation and also to promote the restoration of mitochondrial biogenesis and activation of AMPK/eNOS in diabetes-induced endothelial dysfunction, hence a possible therapeutic drug for alleviating ECs abnormalities and micro/macrovascular complications of diabetes.

6.2.2. Ginseng

Ginseng, an ancient cultivated plant with history dated over 2000 years ago. It is a common and popular TCM plant in China as well as some Asian countries including, Korea, Japan, and Vietnam. In addition, North American countries widely use the plant. The most commonly used ginsengs across the globe including, *Panax ginseng, Panax notoginseng, Panax quinquefolium* L., and *Panax japonicas.* Various experimental studies have demonstrated that ginseng extracts have antihyperglycemic, anti-microbial, anti-fatigue, improving body adaptability, anti-hypertensive, insulin sensitization, anti-atherosclerosis, and anti-hyperlipidemic effects [278–281].

Ginsenosides, bioactive constituents isolated from ginseng, have shown protective effects in diabetes-triggered endothelial dysfunction [282]. Similarly, Panax notoginseng saponins also improved endothelial function in diabetic rats via regulation of eNOS/NO/cGMP

Table 2
Molecular actions of TCM extract and isolated compounds from TCM on diabetes-induced endothelial dysfunction.

Source	Compound	Experimental Model	Molecular Actions	Ref.
Astragalus membranaceus, Astragalus mongholicus (Bge.)	Astragaloside IV	STZ-induced diabetic rats/mice, db/db mice, HG-induced HUVECs, rat aortic ECs-incubated with L-NAME, and HG-incubated podocytes	Inhibits acetylation of eNOS, increases NO production and phos-eNOS-1177, and decreases cell permeability and apoptosis. Suppresses inflammatory responses and apoptosis by inhibiting JNK signaling. Decreases Drp-1, MFF, and Fis1 expression and deregulates PINK1/Parkin-mediated mitophagy. Promotes eNOS/NO/cGMP pathway inhibits TLR4/NFkB pathway and regulates PI3K/Akt/eNOS. Increases the expression of SERCA2b and phos-AMPKα. Regulates AMPKα activation-dependent autophagy induction.	[292,293,294,295,296,297,298]
Angelica sinensis, Pheretima, Hirudo, Atractylodes macrocephala Koidz., Salvia miltiorrhiza bge., Ligusticum chuanxiong Hort, Borneol, Ilexpubescens, Peach kernel, and Cynanchum otophyllum	Huayu Tongmai Granules	STZ-induced diabetic Rats, HG-induced HUVECs	Decreases serum ROS and increases serum NO levels. Suppresses endothelial cell death via adjusting miR-185/RAGE axis.	[299]
Scutellaria baicalensis	Baicalin	STZ –induced diabetic mice, HG-induced –HUVECs, and HAOECs.	Suppresses ROS generation and inflammation via Akt/GSK3B/Fyn-mediated Nrf2 activation.	[300]
Olive oil	Hydroxytyrosol -NO	STZ –induced diabetic mice, HG-induced HUVECs	Increases NO level and upregulates SIRT1 expression and phos-eNOS. Inhibits ROS production and increase SOD levels.	[301]
Oranges, lemons, mandarin, and bergamot	Didymin	STZ-induced Mice, HG-induced HUVECs	Prevents loss of cell viability and ROS production. Prevents lipid peroxidation, activation of caspase-3, ERK1/2, Bcl2 family proteins, and inflammatory markers. Inhibits monocyte adhesion and NFκB activation. Suppresses elevation of iNOS and increases eNOS expression.	[302]
Laminaria japonica Areschoug	Low molecular weight fucoidan	STZ-induced diabetic rats	Decreases serum levels of TC, TG, LDL-C, and $O_2^{-\cdot}$. Increases glutathione content, SOD activity, and suppresses ROS production. Averts COX-2 stimulation and restores the deregulation of thromboxane synthase and 6-keto-PGF1α.	[303]
Angelica sinensis and Astragali radix	Ferulic acid and astragaloside IV (combination)	STZ-induced diabetic rats	Improves endothelial wall structure, suppressing the increase of HbAlc, TG, TC, LDL-C, and Ox-LDL. Promotes the release of NO, phos-eNOS, and protect against activation of MCP-1, TNF-α, and NFκBp65.	[304]
Eucommia ulmoides Oliv.	Water – extract	STZ-HFD-induced diabetic rats	Increases NO, cGMP levels, serum SOD, GSH-Px, and decreases MDA levels. Activates the Akt-eNOS pathway to recover endothelial function.	[305]
Ruellia tuberosa L.	Hydroethanolic extract	HFD/STZ-induced diabetic rats	Reduces the serum level of TNF-α and IL-6 and decreases endothelin-1 and endothelial NO contents. Reduces monocyte chemoattractant protein-1, VCAM-1and vWF. Enhances SOD and CAT activity and also improves lipid profile	[306]
Garlic	S-Allylcysteine	STZ-nicotinamide -induced diabetic rats	Decreases insulin resistance and oxidative stress. Promotes insulin sensitivity, and elevates antioxidant enzymes. Promotes mRNA levels of NOS, argininosuccinate synthase, and argininosuccinate lyase.	[307]
Ligusticum chuanxiong Hort.	Tetramethylpyrazine	STZ-induced diabetic rats	Increases body weight, reduces blood glucose levels and improves urinary protein excretion and creatinine clearance. It suppresses the transcription of VEGF and its expression.	[308]
Boswellia dalzielii, Hibiscus sabdariffa, Euterpe oleracea, and Allium cepa	Protocatechuic acid	STZ-induced diabetic rats	Increases NO production and decreases $O_2^{\cdot -}$. Normalizes activities of gluconeogenesis and G6Pase, F-1, 6-bisPase, and glucokinase. Decreases MDA and increases SOD and CAT.	[309]

(*continued on next page*)

Table 2 (*continued*)

Source	Compound	Experimental Model	Molecular Actions	Ref.
Andrographis paniculata	Andrographolide	STZ-induced diabetic retinopathy mice	Decreases increased VEGF and vitreous cavity. Reduces retinal mRNA expression of VEGF and its receptors. Abrogates NFκBp65 and EGR-1, and reduces phos-NFκBp65. Decreases mRNA expression of TNF-α, IL-6, IL-1β, serpine1, and TF in serum/retina.	[310]
Carthamus tinctorius L.	Hydroxysafflor yellow A	HG-induced HUVECs	Reduces oxidative stress, and apoptosis via the NOX4 pathway. Decreases the expression of VCAM-1, ICAM-1, E-Selectin, VEGF and bFGF	[311]
Epimedium plant species	Icariin	HG-induced HUVECs	Reduces ROS production via suppression of NAD(P)H oxidase-mediated pathway and increases protein levels of SOD. Decreases phos-NFκBp65 and IL-6 levels but increases IkB protein levels. Inhibits nucleus translocation of NFkBp65, and attenuates IL-6 release. Reduces mRNA and serum levels of ICAM-1, VCAM-1, and E-selectin. Inhibits phos-ERK1/2.	[312]
Panax notoginseng	Ginsenoside Rg1	HG-induced HUVECs	Impedes endothelial glycocalyx loss and heparanase mRNA expression. Elevates transendothelial electrical resistance and reduces endothelium permeability. Maintains endothelial barrier activity and reduces transendothelial albumin passage.	[313]
Red sandalwood	Pterostilbene	HG-induced hRECs	Suppresses hRECs over proliferation, decreases TNF-α and IL-1β, inhibits NFκB protein expression, reduces ROS, and increases SOD.	[314]
Glycyrrhiza uralensis	Glycyrrhizic acid	AGEs-induced HUVECs	Increases SOD activity and decreases MDA. Inhibits AGEs-induced ROS. Decreases expression of proinflammatory cytokine TGF-β1 and downregulates AGEs-induced RAGE and NFκB protein expressions.	[315]
Glycyrrhiza glabra	Liquiritin	AGEs-induced HUVECs	Reduces apoptosis, ROS production, and MDA. Increases AGEs-reduced SOD activity. Downregulates TGF-β1, RAGE expression, and ameliorates endothelial dysfunction via RAGE/NFκB axis.	[316]
Morus alba L.	4,4'-diphenylmethane-bis (methyl) carbamate	AGEs-induced HUVECs	Decreases AGE-induced ROS generation and HMGB-1-induced apoptosis and ROS generation.	[317]
Smilax glabra Roxb	Hydroethanolic extract	AGEs-induced HUVECs	Attenuates endothelium apoptosis and downregulates TGF-β1 expression, ROS overproduction, MDA content, phos-ERK1/2, and NFκB activation. Increases SOD activity.	[318]
Rhodiola rosea	Salidroside	AGEs-induced HUVECs	Reduces levels of TNF-α, IL-1β, and IL-6, and suppresses VCAM1 and ICAM1 expression. Elevates SOD activity, increases CAT and GSH-Px levels, and prevents the generation of ROS and MDA. Promotes phos-AMPK and inhibition of NFκBp65 and NLRP3 inflammasome activation.	[319]
Astragali radix	Calycosin	AGEs-induced macrophages infiltration HUVECs.	Reduces macrophage migration and attachment to ECs. Downregulates TGF-β1, ICAM-1, and RAGE expressions. Elevates estrogen receptor expression and reverses ERK1/2 activation and phos-NFκB and nucleus translocation.	[320]
Plantago asiatica	Plantamajoside	Glyceraldehyde-AGEs-induced HUVECs	Suppresses mRNA levels of MCP-1, TNF-α, IL-6, VCAM-1, ICAM1 expression. Inhibits ROS production and phos-JNK and p38 activity. Modulates effects via MAPK/NFκB pathways.	[321]
Longya Aralia chinensis L.	Total saponins of Aralia elata (Miq.) Seem	TNFα-induced HUVECs	Inhibits TNFα-induced HUVEC apoptosis, mitochondrial membrane potential depolarization, and downregulates levels of (IL-6, MCP-1, and VCAM-1). Suppresses NFκB transcription and mediates effects via PI3K/Akt signaling pathway.	[322]

signaling pathway [283]. Among the ingredients, Ginsenoside Re and Rb1 could vasodilate aorta via eNOS and COX pathway [284]. Meanwhile, ginsenoside Rb1 prevented homocysteine-induced endothelial dysfunction via VEGF/p38MAPK and SDF-1/CXCR4 activation [285] and PI3K/Akt activation and PKC inhibition [286]. Interestingly, blood glucose fluctuation potentially exacerbates the advancement of vascular endothelial dysfunction in diabetes. Panax Quinquefolius saponin ameliorates HG fluctuation by reducing vessel stress, inhibiting vasoconstrictor, ET-1, generation, preventing decrease NO levels, and inflammatory responses [287].

Yang et al. showed that ginsenoside Rg1 improves angiogenesis of diabetic ischemic hindlimb, and the potential mechanism may be related to an increase in eNOS activation and upregulation of VEGF expression [288]. Ginsenoside Rb1 partially prevented the increase in MDA content and GSH levels in rat retina. The upregulation of the levels of Nrf2, glutathione cysteine ligase catalytic subunit (GCLC), and glutathione cysteine ligase modulatory subunit (GCLM) expression was observed with ginsenoside Rb1 treatment, thus attenuates diabetic retinal endothelial dysfunction secondary to diabetic nephropathy in STZ-induced diabetic rats via regulating oxidative stress [289].

Panax ginseng extract ameliorated HG-impaired vasodilation and downregulated endothelial dysfunction-related gene expression levels of adhesion molecules, inflammatory cytokines, and chemokines to exert protective effects on endothelial function. Meanwhile, its endothelial protective effects were associated with the upregulation of expression of lipid metabolism-related genes, mainly PPARγ, a target of TZDs drugs [269]. VEGF-triggered intracellular ROS generation, stress fiber formation, and VE-Cadherin disruption amount to an increase in oxidative stress and endothelial permeability in retina cells. Dammarenediol-II, a triterpenoid saponin of Panax ginseng, treatment massively suppressed the above detrimental effects of VEGF in HUVECs. Also, intravitreal injection of dammarenediol-II inhibited microvascular leakage in the retina of diabetic mice [290]. A double-blind, placebo-controlled, parallel study concluded that 3 g of Panax-quinquefolius L. extract improves arterial stiffness to enhance endothelial function in T2DM and concomitant hypertensive patients [291]. In summary, Ginseng is a potential therapeutic drug that can help alleviate diabetes endothelial dysfunction and microvascular complications of diabetes, notably diabetic retinopathy.

7. Efficacy and safety of TCM against western medicine on vascular endothelial dysfunction in diabetes

TCM has gained a unanimous role in the primary healthcare management of China and other countries, and TCM formula effects in the management or use as an adjuvant to western antidiabetics have been reported in several clinical trials [323,324]. To show its efficacy and tolerable adverse effects, meta-analysis study reported that the use of TCMs in the clinical management of T2DM shows massively favorable hypoglycemic effects, improved altered biochemical markers, reduction in body weight, and fewer tolerable side/adverse effects with additional beneficial effects compared to oral western antidiabetic drugs use only [325].

Besides the hypoglycemic effects, TCM formula and its ingredients have been investigated in clinical studies for their endothelial function enhancement and anti-atherosclerotic properties.

In a single-blind randomized controlled trial of 168 patients with T2DM and vascular dementia, post-treatment of Sancaijiangtang powders plus pioglitazone hydrochloride improved HbA1c, HOMA-IR and decreased plasma ET-1 and increased NO bioavailability better than pioglitazone hydrochloride control group. The increase in NO levels and vasoconstrictor, ET-1 decreased levels enhanced endothelial function, whereas improved HbA1c and HOM-IR values showed an improvement in insulin sensitivity in the patients. Also, regarding safety data, Sancaijiangtang powders plus pioglitazone hydrochloride group had few side effects that are nausea and vomiting compared to nausea, vomiting, moderate diarrhea, and abdominal distention reported for pioglitazone hydrochloride control group [267].

In addition, a comparative clinical study demonstrated with metformin, berberine (an alkaloid isolated from a lot of Chinese herbs) exhibited a similar effect on diabetic biomarkers involved in the regulation of glucose metabolisms, such as HbA1c, FBG, postprandial blood glucose (PBG), fasting insulin and postprandial insulin. Berberine also improves FMD and decreases serum levels of MDA and circulating endothelial microparticles (CD31 + /CD42-) to partly reduce oxidative stress of vascular endothelium in humans. On safety, no serious adverse events occurred, but mild to moderate constipation occurred in some participants receiving berberine [326].

Also, a clinical study of N = 21 T2DM patients with microalbuminuria was given the decoction of Astragali Radix and Rhizoma Ligustici Chuanxiong per os 150 ml q.d. for 6 months. Patients were examined using high-resolution ultrasonography to determine changes of the brachial artery in response to reactive hyperemia (endothelium-dependent relaxation) and glyceryl trinitrate (endothelium-independent relaxation). At the end of treatment, endothelium-dependent vasorelaxation improved (7.49 ± 2.98 % − 12.73 ± 5.36 %, $P < 0.001$). Similarly, PAI-1 activity and the levels of MDA and CRP were significantly decreased. However, no significant change was reported for intima-media thickness of common carotid arteries (CCIMT) and endothelial independent vasorelaxation. The results indicate that Astragali Radix and Rhizoma Ligustici Chuanxiong have the potential to positively promote endothelial function similar to western medicines [327]. Meanwhile, Perilla oil, extracted from the seeds of Perilla, has been demonstrated to downregulate the levels of CRP, PAI-1, and TNF-α in serum to improve endothelial function in patients [328]. Perilla oil supplementation is associated with nausea and vomiting as clinical side effects without any adverse effects on the kidney and liver [329].

Conclusively, these clinical trials and other *in vivo* studies involving the use of TCMs have demonstrated beyond thought about their beneficial effects in diabetes and vascular endothelial dysfunction. Likewise, TCM formula and its ingredients positively impact on altered biochemical markers observed in diabetes endothelial dysfunction levels in these patients, if not better at least comparable to similar effects observed for western medicines. Also, Table 3 further shows some comparative effects between TCM formula and western medicine on diabetes endothelial dysfunction biochemical markers in clinical studies.

Moreover, most of these clinical studies were conducted with TCM formula medicine as add-ons to western medicine in these patients for an improved comparative effect analysis, safety, and better efficacy profile, which is necessary since integrative medicine has recently become the hope and hallmark for future medical practice. Likewise, co-administration of Astragali radix and pioglitazone does not affect pharmacokinetics parameters of pioglitazone, western antidiabetic drug [330].

However, limited clinical trial data is available on the assessment of TCMs on biomarkers of diabetes-induced vascular dysfunction compared to western antidiabetic drugs [12,331]. Therefore, we recommend more clinical trials with a large population on the combination of western medicines and TCMs formula as well as TCMs formula only in diabetic vascular endothelial dysfunction.

8. Conclusion and perspective

The action of endothelial cells is vital to the biology of vascular wall, kidney, retina, and nerves. Understanding diabetes mediated changes in endothelial cellular processes and its association with the development of CVDs will aid in developing a unified therapeutic approach to improve the physiology of the afflicted organs. The discussed molecular signaling pathways and pharmacological targets present the recent findings, advances, and current knowledge in the area of endothelial dysfunction induced by diabetes. Although these studies have demonstrated possible therapeutic targets and approaches that support

Table 3
Comparative effects between TCM and western medicine on diabetes endothelial dysfunction biochemical markers in clinical studies.

TCM Formula	TCM Formula ingredients	Placebo/Control	Patient Population	Treatment duration	Biochemical markers outcomes	Ref.
Shengmai injection (生脉注射液)	Red ginseng, Ophiopogon japonicas, Schisandra chinensis	conventional hypoglycemic drugs (western medicine)	N = 120 established complicated T2DM patients, hypertension grade II, and coronary heart disease.	3 weeks	**Shengmai injection:** Increases NO (69.8-120.1 μmol/l. $p < 0.01$); reduced ET-1 (70.1- 46.2 ng/l, $p < 0.01$) & Ang-II (81.3- 50.2 ng/l, $p < 0.01$). Structurally, increases brachial arterial post-congestion rate (389.4-459.3 %), $p < 0.01$. **Control:** NO (70.1-73.2 μmol/l); ET-1 (70.7- 77.6 ng/l) & Ang-II (81.4- 80.6 ng/l)	[332]
Astragalus injection	Astragali radix	Metformin hydrochloride	N = 124 established T2DM patients.	1 month	**Astragalus injection:** increases VEGF (90.45-124.68); GSH-px (236.28 μg/ml); SOD (19.37 μg/ml) and Ang I (89.53-97.64) ($p < 0.05$). Decreases TGF-β1 (39.78-23.77), MDA (16.35 μ/l) & advanced oxidation protein Products (AOPP) (42.32 μmol/l), $p < 0.05$. **Control**: VEGF (87.15-114.3); GSH-px (179.89 μg/ml); SOD (12.24 μg/ml); Ang I (87.46-89.48); TGF-β1 (38.89-35.65), MDA (24.16 μ/l) and AOPP (74.32 μmol/l).	[333]
Pushen capsule (蒲参胶囊)	Polygonum multiflorum, pollen typhae augustifolia, salvia miltiorrhiza, Rhizoma Chuanxiong, Radix Paeoniae Rubra, Hawthorn, Rhizoma Alisma, Codonopsis pilosula	Metformin + Atorvastatin	N = 120 established T2DM patients with hyperlipidemia	12 weeks	**Pushen capsule:** Increases serum NO (7.52-12.96 μmol/l, $p < 0.05$) and decreases ET-1 (79.43-53.56 ng/l, $p < 0.05$), $P < 0.05$. **Control:** NO (7.48-10.48 μmol/l) and decreases ET-1 (78.39-62.27 ng/l)	[334]
Curcuminoids capsule (姜黄素胶囊)	Curcumin	250 mg of starch	N = 240 established T2DM patients	6 months	**Curcuminoids capsule**: increases adiponectin levels (9.24-23.91 ng/ml) and reduces leptin levels (17.38-5.8 ng/ml); triglycerides (158.24-82.98 mg/dl). Structurally, decreases pulse-wave velocity significantly, $p < 0.001$. **Placebo**: adiponectin (9.91-9.28 ng/ml), leptin (16.92-17.19 ng/ml) and triglycerides (166.94-166.87 mg/dl)	[335]
Salvia miltiorrhiza hydrophilic extract	Salvia miltiorrhiza	Placebo + conventional drugs (Glybenzoylamide, glipizide and acarbose)	N = 62 established diabetic patients with coronary heart disease	60 days	**Salvia miltiorrhiza hydrophilic extract**: Reduces sVCAM-1, $p < 0.05$; vWF, $p < 0.05$; oxLDL, $p < 0.01$. **Control:** No observed effects on sVCAM-1, vWF, and ox-LDL.	[336]
Modified Shenqi compound (参芪复方加味)	Ginseng, Astragali radix, Rhizoma dioscoreae, Cornus officinalis, Radix rehmanniae, trichosanthes root, salvia miltiorrhiza, prepared rhubarb, dried tangerine peel, Poria cocos, Pinellia ternata, Angelica sinensis, Rhizoma chuanxiong.	Metformin	N = 46 established T2DM patients with microvascular complication	12 weeks	**Modified Shenqi compound:** increases NO (4.46-5.64, $p < 0.05$) & SOD (63.06-79.91, $p < 0.05$), $p < 0.05$. **Control**: increases NO (4.53-5.81) and SOD (62.24-73.15) **Effective rate:** modified Shenqi compound was 95 % effective in treatment compared to Metformin (65 %)	[337]
Shenqi fu zheng injection (参芪扶正注射液)	Codonopsis pilosula, Astragali radix	Routine, conventional hypoglycemic drugs (western medicine)	N = 51 established T2DM patients with early nephropathy complication	4 weeks	**Shenqi fu zheng:** Decreases ET-1 (111.7-79.4 ng/l,$p < 0.01$) and TXB_2 (88.1-77.0 ng/l, $p < 0.01$) significantly. Increases 6-keto-PGF1α (12.7-16.6 ng/l, $p < 0.05$). **Control:** ET-1 (109.4-90.1 ng/l); TXB_2 (87.4-82.6 ng/l) and 6-keto-PGF1α (11.9-12.4 ng/l).	[338]
Yiqi Yangyin Formula (益气养阴胶囊)	Radix heterophylla, Angelica sinensis, Radix rehmanniae, Prepared rehmannia glutinosa, Cornus officinalis, Astragali radix, Rhizoma dioscoreae, Ophiopogon japonicas, Rhizoma alisma	Irbesartan + TCM placebo	N = 60 established early diabetic nephropathy	6 month	**TCM Formula**: decreases ET-1 (167.45-74.46 ng/L); IL-6 (21.96-14.33 ng/L); CRP (8.8-4.42 ng/L) and TNFα (67.15-44.74 ng/L) ($p < 0.05$). Increases NO (45.86-76.83 μmol/L), $p < 0.05$. **Control**: ET-1 (170.16-145.25 ng/L); IL-6 (22.12-17.16 ng/L); CRP (9.16-6.13 ng/L); TNFα (66.96-58.08 ng/L) and NO (43.72-50.16 μmol/L)	[339]
Dahuangtangsheng capsule (大黄糖肾胶囊)	Rheum officinale, Astragali radix, Hirudo, Herba leonuri, Rhizoma polygonatum, Semen Cuscutae, Rosa laevigata michx fruit, Schisandra chinensis, radix scrophulariae, Radix rehmanniae	Conventional hypoglycemic drugs (western medicine)	N = 105 established early diabetic nephropathy	12 weeks	**Dahuangtangsheng capsule**: Decreases serum and urine ET-1, (91.20-58.73 ng/l, $p < 0.01$) and (51.43-27.96 ng/l, $p < 0.01$), respectively. **Control**: observed changes in serum and plasm ET-1, (88.31-85.79 ng/l) and (49.72-47.83 ng/l), respectively.	[340]

(*continued on next page*)

Table 3 (*continued*)

TCM Formula	TCM Formula ingredients	Placebo/Control	Patient Population	Treatment duration	Biochemical markers outcomes	Ref.
Shenkang injection (肾康注射液)	Rheum Officinale, salvia miltiorrhiza, safflower, Astragali radix	Enalapril	N = 90 established diabetic patients with nephropathy complication	4 weeks	**Shenkang injection**: decreases MCP-1(327.29-231.72 pg/ml) and ICAM-1 (453.82-271.19 ng/ml) ($p < 0.05$). **Control**: MCP-1(330.24-287.66 pg/ml) and ICAM-1 (460.04-330.81 ng/ml). **Effective rate**: Shenkang injection was 91.11 % effective in treatment compared to control (77.78 %) ($p < 0.05$)	[341]

$p < 0.05$, $p < 0.01$ significant compared to control.

the restoration of NO bioavailability and maintenance of endothelial cell activity, different and distinct target pathways were reported. This was likely, seeing the multiple pathways and interconnected events mediated by hyperglycemia such as AMPK inactivation, mitochondrial fission, ER stress, inflammasomes activation, etc., in endothelial dysfunction. Moreover, we speculate that future investigation may include, but not limited to, the following directions: non-coding RNA, exosome, and gut microbiota.

However, on the targeting of the above molecular signals, several antidiabetic medicines, including metformin, TZDs, show positive effects, but these modulatory effects are exclusive of some endothelial dysfunction biomarkers altered in the pathophysiology of diabetes-induced vascular diseases. Accordingly, recent development for eminent therapeutic strategies has demonstrated in clinical trials that a combination of TCM formula and western antidiabetic drugs exhibit beneficial effects on the endothelial dysfunction biomarkers and better safety profile. Moreover, TCM or its bioactive ingredients have shown a positive impact in achieving an improved endothelial function *in vivo* and *in vitro* studies. Haven said these, more retrospective and comparative clinical trial studies are needed to assist in elucidating risks, safety, drugs-herb interaction, and pharmacodynamics assessments on the broader population. Also, deciphering into the cons and pros of these multiple molecular pathways will aid in embarking on further studies on this subject matter, thence facilitate the pharmacological knowledge, clinical management of the disorder, and drug development.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any financial or commercial or financial relationships that could be construed as a potential conflict of interest.

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