Review

Roles of Reactive Oxygen Species in Vascular Complications of Diabetes: Therapeutic Properties of Medicinal Plants and Food

Yi Tan †, Meng Sam Cheong †[ID] and Wai San Cheang *[ID]

State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Avenida da Universidade, Taipa, Macau 999078, China; mc05845@um.edu.mo (Y.T.); mc05846@um.edu.mo (M.S.C.)
* Correspondence: annacheang@um.edu.mo; Tel.: +853-8822-4914
† These authors contributed equally to this work.

Abstract: The rising prevalence of chronic metabolic disorders, such as obesity and type 2 diabetes, most notably associated with cardiovascular diseases, has emerged as a major global health concern. Reactive oxygen species (ROS) play physiological functions by maintaining normal cellular redox signaling. By contrast, a disturbed balance occurring between ROS production and detoxification of reactive intermediates results in excessive oxidative stress. Oxidative stress is a critical mediator of endothelial dysfunction in obesity and diabetes. Under a hyperglycemic condition, the antioxidant enzymes are downregulated, resulting in an increased generation of ROS. Increases in ROS lead to impairment of endothelium-dependent vasodilatations by reducing NO bioavailability. Chronic treatments with antioxidants were reported to prevent the development of endothelial dysfunction in diabetic patients and animals; however, the beneficial effects of antioxidant treatment in combating vascular complications in diabetes remain controversial as antioxidants do not always reverse endothelial dysfunction in clinical settings. In this review, we summarize the latest progress in research focused on the role of ROS in vascular complications of diabetes and the antioxidant properties of bioactive compounds from medicinal plants and food in animal experiments and clinical studies to provide insights for the development of therapeutic strategies.

Keywords: reactive oxygen species; diabetes; vascular disease; antioxidants; medicinal plants; food

1. Introduction

Diabetes is a chronic metabolic disease with high prevalence all over the world. According to statistics from the International Diabetes Federation (IDF), an estimated 10.5% of people around the world were suffering from diabetes in 2021. It is predicted that by 2024, the number of diabetic patients will rise to 783 million. Type 1 diabetes is an autoimmune condition in which the pancreas is attacked to lose the ability to produce insulin in the body. More than 90% of diabetes cases are type 2 diabetes which is closely linked to unhealthy living styles such as physical inactivity as well as a high-fat and high-carbohydrate diet. Hyperglycemia and hyperlipidemia are widely considered to contribute to vascular dysfunction, leading to the occurrence of cardiovascular disease. Cardiovascular disease is one of the most severe complications of diabetes and the major cause of death in diabetic patients. People with diabetes have twice the risk of cardiovascular disease than people without diabetes. According to the statistics from 2007 to 2017, cardiovascular disease accounted for half of all deaths from type 2 diabetes [1]. Cardiovascular disease includes macrovascular and microvascular complications such as coronary heart disease, peripheral artery disease, stroke, nephropathy, diabetic retinopathy, and cardiac autonomic neuropathy [2]. In diabetes, excess reactive oxygen species (ROS) play a critical role in the occurrence and development of cardiovascular disease [3]. Elevated glucose and free fatty acids (FFAs) contribute to the release of ROS from mitochondrial electron chain, NADPH oxidases, xanthine oxidase, arachidonic acid, and uncoupling of NOS, and so on [4,5]. The

accumulation of ROS reduces NO bioavailability and induces intracellular inflammation and apoptosis, which mediate the occurrence of cardiovascular disease [6]. Numerous studies have shown that suppressing oxidative stress helps improve diabetes-associated cardiovascular disease [4,7,8]. Therefore, antioxidant therapy is the hot spot of medical research in this area.

Many different antioxidants such as vitamin C and E, α-lipoic acid, glutathione, vitamin A and the carotenoids, vitamin B and folic acid, coenzyme Q10 (CoQ10), estrogen, probucol, chelation of iron and minerals were demonstrated to have a positive effect in diabetic animal models and in vitro experiments [8–11]. Although previous studies reported that some antioxidants play a positive role in the cardiovascular events of diabetic patients, most studies have shown that antioxidants have limitations or no effect in the clinical trials of diabetic cardiovascular disease [12–15]. In addition, the minimum effective dose of antioxidants is ambiguous in the human body; and importantly, a high-dose, redundant or continuous supplement of antioxidants may increase health risks in some cases [10,16,17]. For example, vitamin E may have a potential harm to hemorrhagic stroke as suggested in a long-term trial of male physicians; and β-carotene was associated with lung cancer incidence in smokers [17,18]. Antioxidants are also prone to be oxidized during preservation, which can have adverse effects on treatment [19,20]. Antioxidants generally have no significant therapeutic effect on advanced cardiovascular disease [8,21]. To date, there are no clinically approved antioxidants that can effectively treat diabetic cardiovascular disease [10].

Medicinal plants and food are commonly recommended as sources of natural antioxidants to reduce the risk of cardiovascular diseases, and their efficacy has been proven in clinical trials [22–26]. According to NIH, compared with artificial antioxidants, the antioxidant ingredients in natural plants and food are not a single compound but might work together to achieve antioxidant activity. The overall cost of cardiovascular disease therapy is increasing, which puts pressure on society and medical resources. Nowadays, people have paid more attention to natural products. This review aims to provide insights into the development of diabetes-related vascular therapeutic strategies based on the antioxidant properties of bioactive compounds from medicinal plants and food.

2. Involvement of Oxidative Stress in the Pathogenesis of Diabetes-Associated Vascular Dysfunction

ROS play a critical role in the development, growth, differentiation, and proliferation of multicellular organisms; and as crucial transduction molecules to regulate critical metabolic and regulatory pathways in cells [27,28]. In cellular metabolism, ROS are co-products that are mainly produced by mitochondria [29]. The overproduction or lesser elimination of ROS attributed to an imbalance between oxidants and antioxidants can cause oxidative stress, potentially leading to cell damage [30,31].

Endothelial cells (ECs) and smooth muscle cells (VSMCs) are two primary cell types in the blood vessel playing essential roles in maintaining vascular homeostasis. The endothelium is not only acting as a selectively permeable barrier, but also regulates the vascular tone and structural basis. The vascular endothelium is constructed by a monolayer of ECs that lines the entire inner surface of the blood vessel [32]. The endothelium plays crucial physiological functions, including sustaining vascular tone, repairing vessel inflammation, modulating the growth of blood vessels, and regulating aggregation and coagulation of platelet [33]. The ECs sense and respond to the stimuli from blood flow to induce contraction or relaxation from VSMCs by producing vasoactive substances, such as NO (vasodilator) or angiotensin II (Ang II, vasoconstrictor) [34]. Furthermore, physiological levels of ROS are essential for signal delivery that maintains vascular homeostasis. Almost every cell type in the blood vessel wall can produce ROS and is regulated by ROS [35,36]. A low concentration of H_2O_2 plays a significant role in the normal function of ECs as an endothelium-derived hyperpolarizing factor to induce vasodilatation [37]. The balance between ROS production and elimination is also necessary for activating the signaling

pathways that participate in the normal function of the endothelium [38]; however, under the condition of diabetes mellitus, redox homeostasis is altered, contributing to the pathogenesis of endothelial dysfunction [39]. ECs can reduce the production of ROS in VSMCs by thioredoxin upregulation, which is functionally associated with growth inhibition, indicating that ECs protect VSMCs from oxidative stress and thus maintain vascular integrity [40].

3. ROS Production in Diabetes

ROS generation can either form exogenous or intracellular through many different sources. Usually, the generation and elimination of ROS are dependent on enzymatic and non-enzymatic pathways. The formation of superoxide anion ($O_2^{\bullet-}$), which is the precursor of most other ROS, is produced by the univalent reduction of oxygen [41]. The production of $O_2^{\bullet-}$ is mediated by enzymes, including NADPH oxidases and xanthine oxidase or the redox-reactive compounds such as the semi-ubiquinone compound of the mitochondrial electron transport chain [42,43]. As the $O_2^{\bullet-}$ itself can affect vascular function, the generation of other types of ROS is also associated with it. Hydrogen peroxide (H_2O_2) is the production of $O_2^{\bullet-}$ dismutation mediated by superoxide dismutase (SOD) [41]. Partially reducing H_2O_2 can form hydroxide ions and hydroxyl radicals ($OH^{\bullet}$) by reducing transition metals, or entirely reducing to H_2O by catalase and glutathione peroxidase (GPx). When H_2O_2 is metabolized by myeloperoxidase (MPO), it generates hypochlorous acid. Almost all vascular cells can produce $O_2^{\bullet-}$ and H_2O_2 [44].

Diabetes is a high-risk factor of vascular dysfunction, and chronic diabetes complications include microvascular and macrovascular diseases [45]. In addition, cardiovascular disease is the primary cause of mortality in diabetes [46]. ROS contribute to the developing processes of diabetes-related cardiovascular disease. Hyperglycemia is the characteristics of diabetes, increasing generation of ROS and oxidative stress involved in vascular dysfunction [47]. Different models that induced hyperglycemia for studying diabetes complications result in oxidative stress [48–51]. There are many possible mechanisms by which hyperglycemia increases ROS production. A widely accepted pathway is diacylglycerol (DAG)-protein kinase C (PKC)-and NADPH oxidase pathway activated by hyperglycemia and eventually result in the acumination of ROS [52–54]. Multiple pathways can induce increased levels of DAG under hyperglycemia conditions. For example, by activating phospholipase C (PLC) and phospholipase D (PLD), both can act on phosphatidylcholine (PC) and phosphatidylinositol bisphosphate (PIP2) to trigger the generation of DAG [55,56]. PKC isoforms can be divided into different families, some of which can be activated by DAG (α, βI, βII, γ, δ, ε, η, and θ) [52,57]. PKC then activates NADPH-oxidase to stimulate ROS production. NAPDH is the cofactor of glutathione (GSH) reductase (GR). High glucose can enhance the activity of NADPH oxidase which increases expend of NADPH and decreases the generation of GSH, resulting in damage of ECs [58,59]. Under hyperglycemia, glucose generates pyruvate through the glycolysis pathway, and provides an increased amount of hydrogen donors (NADH and $FADH_2$) through the tricarboxylic acid cycle to the mitochondrial respiratory chain, promoting the production of ROS, especially $O_2^{\bullet-}$ [60]. The enzymatic antioxidative system of mitochondria includes SOD and GPx. SOD catalyzes dismutation of $O_2^{\bullet-}$ to H_2O_2 and O_2, while GPx reduces H_2O_2 to H_2O under the synergism of glutathione-S-transferase (GST) to block the cell damage from $O_2^{\bullet-}$; however, excessive blood glucose can bind to the lysine, which is the active center of SOD, and lower the activity of SOD by glycation [61]. The reaction reducing monosaccharides under the catalysis of transition metal ions, such as Fe^{3+} and Cu^{2+}, is known as glucose autoxidation and results in the increased production of ROS [62]. The active polyol pathway in diabetes promotes ROS generation by depleting NADPH and GSH during the conversion of sorbitol to fructose; and increased accumulation of fructose also augments oxidative stress via nonenzymatic glycation forming advanced glycation end-products (AGEs) [63].

Hyperlipidemia is highly associated with the risk of vascular dysfunction in diabetes, where the increase in circulating low-density lipoproteins (LDLs) is one of the major

vascular risk factors [64]. $O_2^{\bullet-}$ can induce the oxidation of LDLs and promote vascular inflammation through increasing monocyte/macrophage infiltration into the vessel wall, subsequently leading to foam cell formation [65,66]. In ECs, eNOS can produce a large amount of ROS through uncoupling L-arginine from NO. In addition, adding LDLs or oxidated LDLs (oxLDLs) leads to the decrease of the eNOS cofactor tetrahydrobiopterin (BH4) by BH4 oxidation to form 7,8-dihydrobiopterin (BH2) and results in increased ROS production [67]. NADPH oxidase is one of the most important regulators in ROS production in ECs. The activation of NADPH oxidase requires the assembly of different subunits into lipid rafts, which need a specific content of lipid components [68]. The pathological changes in raft composition and structure affect the production of ROS. For example, the reduction of free cholesterol decreases ROS production [69,70].

Nitric oxide (NO) is an endothelium-derived relaxing factor biosynthesized from L-arginine, oxygen, and NADPH [71]. NO produced in ECs prevents ECs apoptosis and neutrophil and platelet adhesion to the vessel wall, which can also penetrate VSMCs to regulate vascular tone and proliferation, mediate flow-induced adaptive vascular modeling, and regulate platelet-derived growth factors [72]. The eNOS is expressed in blood vessels and is an essential enzyme in the cardiovascular system catalyzing the formation of NO [73]. The activity of eNOS is regulated by multiple sites, where the most studied site is the activation site Ser1177 [74]. Activating eNOS by phosphorylating Ser1177 can increase NO production in response to vascular stimuli. NO bioavailability is reduced by oxidative stress. Vessel under prolonged exposure to hyperglycemia generates $O_2^{\bullet-}$, which can act on NO to form peroxynitrite ($ONOO^-$); and such reactive nitrogen species (RNS) with reduced NO availability contribute to vascular dysfunction in diabetes [75]. In addition, hyperglycemia blunts phosphorylation of eNOS at Ser1177 to diminish the activity of eNOS and enhances eNOS uncoupling, leading to further accumulation of ROS [76,77]. The mechanisms of ROS generation in diabetes-related to vascular dysfunction were summarized in Figure 1. Besides, a decrease of antioxidant enzymes as well as an increase of ROS and RNS in rupture of redox homeostasis in diabetes were listed in Table 1.

Table 1. Decrease of antioxidant enzymes as well as increase of ROS and RNS in rupture of redox homeostasis in diabetes mellitus.

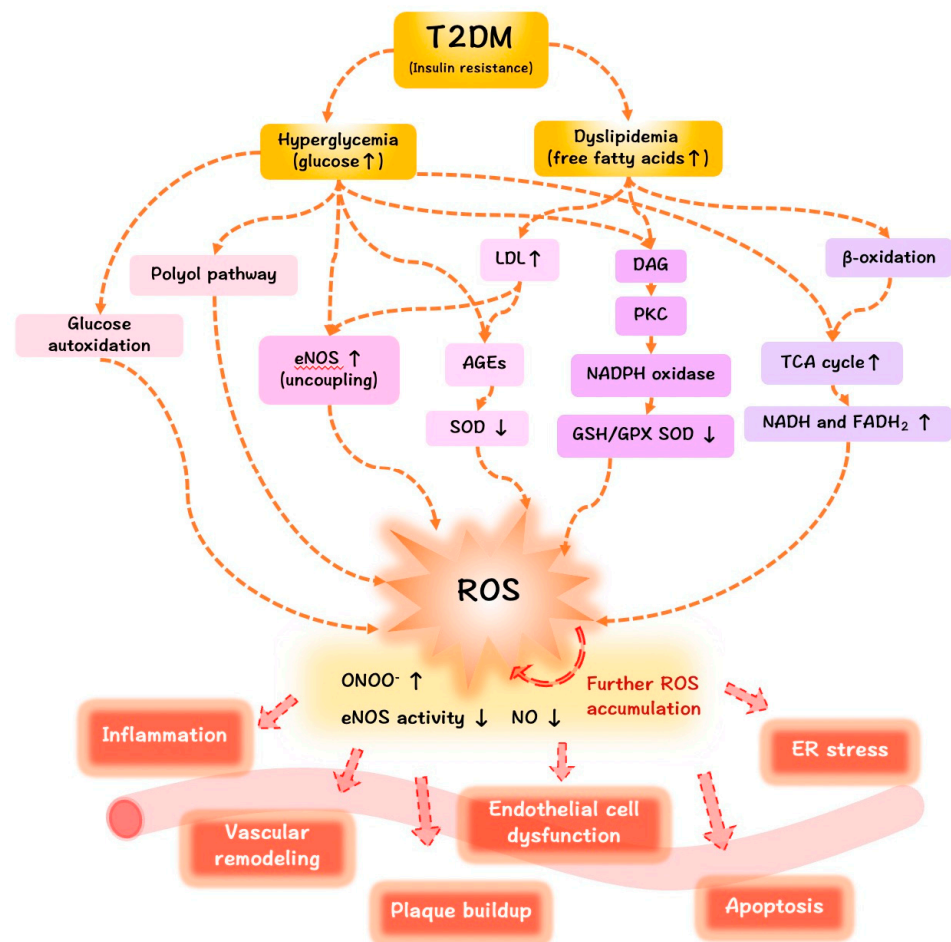| Decreased Antioxidant Enzymes	Type of ROS and RNS Increased
Superoxide dismutases (SODs)	Superoxide ion ($O_2^{\bullet-}$) Peroxynitrite ($ONOO^-$)
Catalase (CAT)	Hydrogen peroxide H_2O_2 Hydroxyl radical $OH^{\bullet-}$
Glutathione peroxidase (GPx)	
Glutathione-S-transferase (GST)	
Myeloperoxidase (MPO)	

Figure 1. The mechanisms of ROS/oxidative stress generation in diabetes mellitus and the effects of ROS release on the vasculature.

4. ROS-Induced Vascular Dysfunction

4.1. Lipid Peroxidation

The increased generation of ROS under diabetes mellitus can induce lipid peroxidation. Cell membrane or organelle membrane is especially sensitive to ROS damage due to its content of high polyunsaturated fatty acids. The process of lipid peroxidation is the oxidative degradation of lipid and the accumulation of peroxidation products is one of the main risk factors of vascular dysfunction [78]. The internalization of LDL in the intima of blood vessel enhances the permeability of endothelium and increases the expression of adhesion molecules; and the aggregated LDLs at the extracellular matrix can be oxidized by ROS to form oxLDLs which could promote the development of plaques [79]. The markers of lipid peroxidation include malonaldehyde (MDA), hydroxynonenal (HNE), and 8-isoprostaglandin F2α [80,81]. 8-isoprostaglandin F2α showed multiple activities to induce vascular dysfunction, including plateles adhesion and aggregation activities as well as vasoconstriction activities. Growing evidence has suggested that oxysterols, which are lipid peroxidation products of cholesterol, are involved in the pathology of diabetes mellitus [82]. Oxysterols were found elevated in the brains in the rodent diabetic models and in the blood of diabetic patients [83]. Increased levels of oxysterols were also found in the plasma and vascular walls of patients with cardiovascular diseases, particularly in atherosclerotic lesions; and can induce cell death, oxidative and inflammatory activities, and phospholipidosis [84]. Macrophages absorb excessive oxysterols in the presence of high peripheral cholesterol level and thereby converse to an inflammatory phenotype. The accumulation of these cholesterol-laden immune cells on blood vessel walls contributes to vascular dysfunction and atherosclerosis [85].

4.2. Protein Carbonylation

Protein carbonylation is one of the most detrimental oxidative protein modifications which cannot be reversed easily [86]. It is also regarded as a crucial biomarker of oxidative stress-related diseases [87]. Under metal ion catalysis, especially Fe^{3+} and Cu^{2+}, ROS can directly oxidize amino acid residue on the protein side-chain to introduce a carbonyl group, which leads to loss of catalytic or structural function of the influenced proteins [88]. It is investigated that carbonylation of actin leads to changes in cytoskeleton dynamics and damage of barrier function of blood vessels [89].

4.3. Glycation

Glycation is also called non-enzymatic glycosylation which is a process of attachment of sugars, generally glucose, fructose, and their derivatives, to protein or lipid [90]. AGEs are glycated proteins or lipids formed after exposure to sugars. AGEs are widely studied in different diseases including vascular complications in diabetes. The amount of AGEs raised under diabetes mellitus is related to hyperglycemia and oxidative stress [91]. The proposed mechanism of AGEs-associated vascular dysfunction includes stimulation of inflammatory response by increasing the release of pro-inflammatory cytokines, promoting the progression of plaque, and enhancing oxidative stress in blood vessels [92–94].

5. Interaction of Oxidative Stress with Various Signaling Pathways

5.1. Keap1-Nrf2-ARE Signaling

Nuclear factor erythroid 2-like 2 (Nrf2) responses to oxidative stress and plays an essential role in preventing endothelium damage and protecting vascular function [95]. Kelch-like ECH-associated protein 1 (Keap1)-Nrf2-antioxidant response element (ARE) signaling pathway participates in the intracellular redox homeostasis of ECs. Nrf2 is the transcription activator that binds to ARE elements in the promoter regions of target genes. Keap1 is not only the negative repressor of Nrf2 but also modulates Nrf2 ubiquitination. Under the normal physiological conditions, Nrf2 is sequestered in the cytosol and maintains at a low concentration; however, the multiple cysteine residues of Keap1 sense the redox state, and it modulates the ubiquitarian level of Nrf2. Under oxidative stress, the chemical modifications of Keap1 relieve Nrf2 from Keap1-directed degradation and translocate it into the nucleus. The binding of Nrf2 to ARE result in the transcription of downstream target genes [96]. In ECs, Nrf2 can be activated by ROS level and phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) signaling pathway [97]. A single-cell sequencing shows that Nrf2 is the key regulating factor of VSMCs transformation [98]. Nrf2 activation suppresses AngII-induced NOX-1/NOX-1/NOX-4 and mitochondrial ROS level, thereby postponing vascular remodeling [99].

5.2. NF-κB Signaling

NF-κB proteins are a transcription factor family critical in inflammation and immunology [100]. ROS and NF-κB signaling pathways can interact in multiple ways. H_2O_2 can affect the activation of the NF-κB pathway by inhibiting the phosphorylation and degradation of IκBα [101–103]; however, the findings on IKK are controversial. Some studies indicated that ROS, especially H_2O_2, can activate IKK in specific cell types whilst some showed that H_2O_2 suppresses IKK [101,102,104]. The activation of the NF-κB signaling pathway leads to the upregulated expression of NF-κB-dependent genes, such as adhesion molecules, cytokines, and growth factors. It has also been demonstrated that the NF-κB is involved in regulating NADPH oxidase subunit p22^{phox} in VSMCs [105].

5.3. PI3K/Akt/AMPK Signaling

The PI3K-Akt signaling pathway plays a critical role in the transduction of mitogenic signals of VSMCs and the proliferative dysfunction of ECs [106–108]. ROS not only activates PI3K to enhance its downstream signaling but also deactivates its phosphatase and tension homolog (PTEN) and then negatively regulates the synthesis of phosphatidylinositol

3,4,5-triphosphate (PIP3), which leads to the inhibition of Akt activation [109]. Akt can significantly enhance the phosphorylation of eNOS. Overexpression of Akt can increase the resting diameter of the blood vessel and blood flow; however, suppressing Akt weakens the EC-dependent vascular relaxation induced by acetylcholine [110]. The endothelial migration induced by vascular endothelial growth factor (VEGF) is also mediated via the PI3K-Akt signaling pathway [111]. Activation of AMP-activated protein kinase (AMPK) is reported to exhibit vascular protective effects [112]. The activity of AMPK can be regulated by multiple stimuli, including low ATP levels, hypoxia, shear stress, exercise, etc. The activation of AMPK leads to the phosphorylation and activation of eNOS [113].

5.4. MAPK Signaling

The Mitogen-activated protein kinases (MAPK, or ERK) pathway, also known as the Ras-Raf-MEK-ERK pathway, includes many proteins, such as MAPK, which is activated by growth neurotrophic factors. There are more than three MAPKs families that have been characterized: p38 MAPKs, c-Jun N-terminal kinases (JNKs), and extracellular signal-regulated kinase (ERKs) [114,115]. The MAPK pathway participates in multiple fundamental cellular processes, including proliferation, differentiation, motility, stress response, apoptosis, and survival. For example, the phosphorylation of MEK and ERK shed the junction protein of VE-cadherin, which results in the opening of junctions and elevation of paracellular permeability [116]. Studies have already shown that ROS induce the activation of MAPK pathways through various routes [117]. H_2O_2 can activate MAPK pathways by the activation of growth factor receptors [118]; or by oxidative modification of intracellular kinases [119]. By inactivating and degrading the MAPK phosphatases (MKPs) through oxidation, ROS can also activate MAPK [120].

5.5. ER Stress

Endoplasmic reticulum (ER) stress has been illustrated to be associated with cardiovascular disease [121]. Three ER stress-sensing proteins, PKR-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol requiring enzyme 1 (IRE1) are activated to induce downstream signaling cascade. More and more studies have investigated the cross-talk between oxidative stress and ER stress. ROS can directly attack the free sulfhydryl groups that are necessary to maintain protein folding, inducing oxidative modification of proteins and triggering ER stress due to the prolonged accumulation of unfolded or misfolded proteins in the ER lumen. At the same time, the expression of glucose-regulated protein 78 (GRP78) increases significantly and unbind from the ER stress-sensing proteins, which results in the activation of ER stress [122]. Studies have already shown that hyperglycemia-induced ER stress can lead to endothelial dysfunction and elevated ROS which can be reversed by ER stress alleviators; nevertheless, ROS scavengers cannot suppress ER stress [123,124].

5.6. Apoptosis

In ECs, the endogenous production of ROS is related to different pro-inflammatory and pro-atherosclerotic factors such as Ang II, oxLDL, or TNF-α, all associated with the apoptosis of cells [125]. The induction of DNA damage by a high concentration of ROS can activate p53 which downregulates Bcl-2 and upregulates Bax [126–128]; however, the reaction of VSMCs to ROS seems to be different from ECs. Ang II and PDGF-induced ROS generation can promote the proliferation and cell growth in VSMCs [129–131].

The aforementioned signaling pathways affecting ROS production in diabetes were summarized in a schematic diagram (Figure 2).
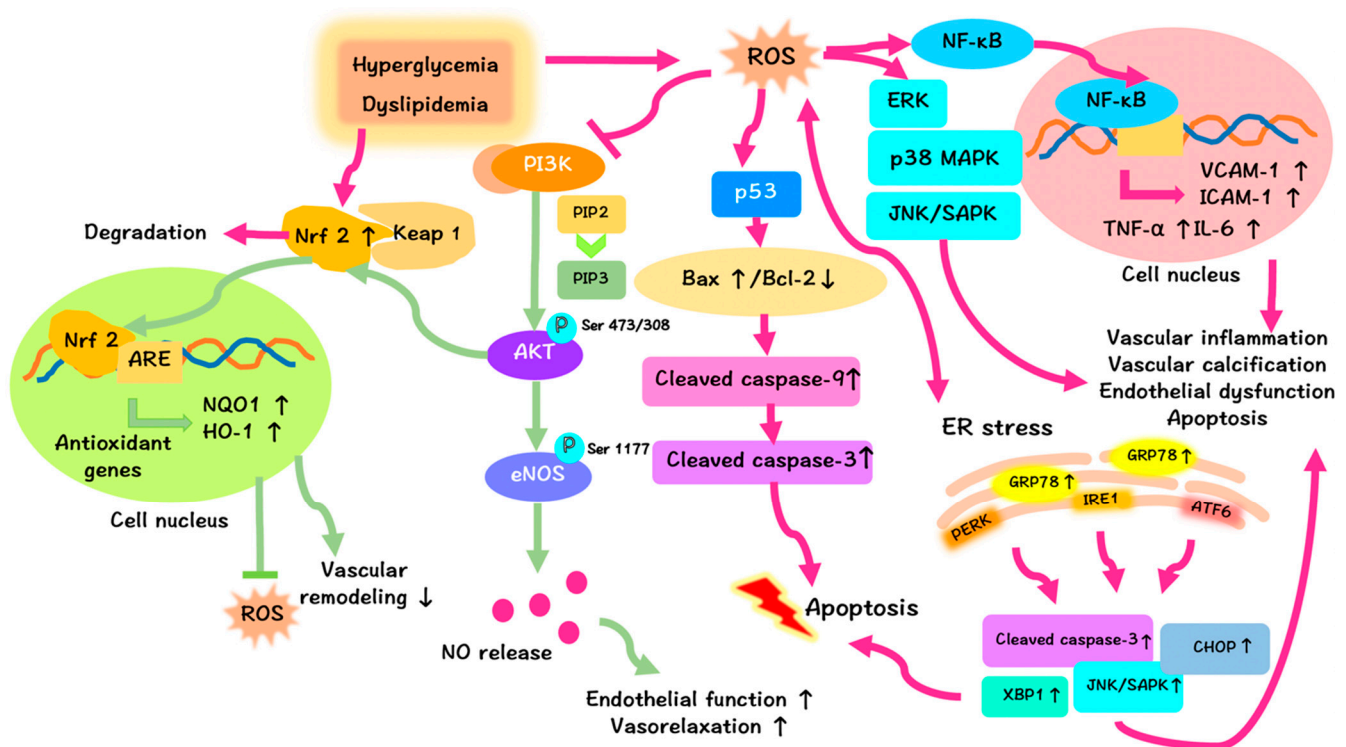
Figure 2. Interaction of oxidative stress with various signaling pathways, leading to vascular dysfunction in diabetes.

6. Antioxidative Effects of Medicinal Plants in Experimental Settings

In order to keep readers abreast of the latest progress in the research on antioxidant effects of medicinal plants and food, we summarized the latest progress in research on antioxidative activity since 2018.

6.1. Salvia miltiorrhiza

Until now, in some countries such as China, India, and Brazil, phytotherapy is still widely used to improve people's health and even treat diseases [132]. *Salvia miltiorrhiza* Bunge, whose root is called DanShen in Chinese medicine, is a golden herbal medicine to treat cardiovascular diseases. Tanshiones and phenolics are considered to be the main bioactive ingredients [133]. A recent study showed that *Salvia miltiorrhiza* Bunge reduced high glucose-induced ROS generation in VSMCs and high-fat diet (HFD)-induced diabetic mice by inhibiting KLF10 expression and upregulating HO-1 [134]. In H9c2 cell and doxorubicin-induced heart failure Wistar rats, its aqueous extract suppressed oxidative stress through the Nrf2/HO-1 signaling cascade and further reduced ROS-dependent apoptosis by amending the ERK/p53/Bcl-xL/caspase-3 signaling pathways [135]; moreover, a similar result of Tanshinone I was attributed to its modulation of Nrf2/MAPK signaling in Nrf2$^{-/-}$ mice [136].

6.2. Panax notoginseng and Panax ginseng

Panax notoginseng, another popular traditional Chinese medicine, has been demonstrated potential antioxidant effects. Its ethanolic extract and total saponin (PNS) activated the AMPK/eNOS pathway to restore acetylcholine-induced endothelium-dependent relaxation in mouse aortas ex vivo and inhibited oxidative stress in high glucose-induced HUVECs and aortas from HFD-induced diabetic mice [137]. PNS protected HUVECs from AGE-induced injury by upregulating the expression of SIRT1 and increasing the SOD level [138]. Keap-1/Nrf2/HO-1 pathway mediated antioxidant activity of 20(S)-Rg3 and 20(R)-Rg3 in H9C2 cells [139]. Similar functions were presented in *Panax ginseng* C.A. Mey; its root, also known as ginseng, has been used to maintain cardiovascular health in Korea

and China [140]. Ginsenoside compound K prevented ox-LDL-induced HUVECs injury by the inhibition of NF-κB/p38/JNK pathways [141]. At the same time, these effects also involved the activation of the Nrf2/HO-1 pathway [142,143]. Even in healthy model rats, ginseng extract increased vasodilation by reducing the level of lysophosphatidylcholine (LPC) that is related to atherosclerosis-induced tissue damage [144].

6.3. Chuanxiong

Ligustrazine (also known as tetra methylpyrazine) is an alkaloid that has been isolated from Chuanxiong (*Ligusticum chuanxiong hort*), and it was reported as a protective ingredient against homocysteine-induced oxidation in HUVECs through improving mitochondrial dysfunction [145]. In addition, Ligustrazine activated PI3K/Akt/eNOS signaling and increased NO release to protect HAECs from damage by oxygen-glucose deprivation, alleviating cerebral ischemia-reperfusion injury in rats [146].

6.4. Astragalus

Astragaloside IV(AsIV) is the main bioactive component of *Astragalus*, a dry rhizome of Astragalus membranaceus, which improves blood circulation, metabolism, and cardiovascular function [147,148]. AsIV reversed upregulated expression of P2X7R and p-p38 MAPK as well as increased the levels of eNOS and NO in glucose-stimulated RAECs and STZ-stimulated SD rats, showing the potential to improve endothelial dysfunction [149]. The same effects of AsIV in RAECs could be achieved by increasing Akt phosphorylation at Ser473, eNOS dephosphorylation at Thr495, and eNOS mRNA expression [150]. In an earlier study (2016), Xu et al. reported that AsIV rose the levels of BH4 and NO, and decreased the generation of anions and $ONOO^-$ in rats with the isoproterenol (Iso)-induced vascular dysfunction, accompanied by inhibition of myocardial hypertrophy in rats [151].

6.5. Carhamus tinctorius L.

Dried flowers (Honghua) and seeds of *Carhamus tinctorius* L. are often used to improve gynecological diseases and have good oxidation resistance [152]. The ethanol extract of flowers of *C. tinctorius* retarded TNF α-stimulated intracellular ROS generation by activating Nrf2/HO-1/CO signaling in HUVECs, followed by inhibiting p65 NF-κB nuclear translocation [153]. In 2K-1C hypertensive rats, the ethanolic extract of *C. tinctorius* suppressed the Ang II-AT1R-NADPH oxidase pathway to reduce O_2^- production in renovascular hypertension while inhibiting aortic gp91^{phox} overexpression as well as increasing NO bioavailability [154].

6.6. Ginkgo biloba L.

With a reputation as "living fossil", *Ginkgo biloba* L. has a great variety of biological activities such as anticancer, antioxidant, and improvement of cognitive function [155]. Ginkgolide B, a natural product from *Ginkgo biloba* L., targeted NOX-4, LOX-1, MCP-1, ICAM-1, and VCAM-1 to abrogate ox-LDL-induced oxidative damage in HUVECs [156,157]. As an HO-1 activator, Ginkgo biloba extract improved vascular repairment by activating PI3K/Akt/eNOS signaling in endothelial progenitor cells [158].

6.7. Coptis chinensi

Coptisine, an isoquinoline alkaloid from *Coptis chinensis* Franch. Is well known for its excellent antibacterial properties and revealed the potential to improve diabetes and cardiovascular disease in vivo and in vitro [159–161]. Coptisine protected endothelium-dependent relaxation in diabetic mice by activating AMPK signaling, further increasing phosphorylation of eNOS and inhibiting ER stress [162]. More antioxidant studies of medicinal plants in cardiovascular disease are supplemented in Table 2.

Table 2. Antioxidant effects of medicinal plants and their bioactive compounds in improving cardio-vascular disease in experimental settings. ↑: upregulation; ↓: downregulation.

Medical Plant	Active Ingredients/Extract	In Vivo/In Vitro Model	Molecular Mechanism	References
Salvia miltiorrhiza Bunge	*Salvia miltiorrhiza* Bunge extract	HG-treated VSMCs and HFD-induced diabetic mice	KLF10 ↓ HO-1 ↑	[134]
		ADR-treated H9c2 cell and Wistar rats	Nrf2/HO-1 ERK/p53/Bcl-xL/caspase-3 ROS ↓	[135]
	Tanshinone I	Nrf2$^{-/-}$ mice	Nrf2/MAPK Signaling	[136]
Panax notoginseng	*Panax notoginseng* extract and PNS	HFD- induced diabetic mice ex vivo mice aorta HG-treated HUVECs	AMPK/eNOS pathway restore relaxations	[137]
	PNS	AGE-induced HUVECs	SIRT1 ↑ SOD levels ↓	[138]
	20(S)-Rg3 and 20I-Rg3	H9C2 cells	Keap-1/Nrf2/HO-1	[139]
Panax ginseng C.A. Mey	Ginsenoside compound K	ox-LDL-induced HUVECs	NF-κB/p38/JNK pathways	[141]
	Ginsenoside Rh1	ox-LDL-induced VEC	Nrf2/HO-1 pathway	[142,143]
	Ginseng extract	Healthy rats	Blood vessel dilation	[144]
	Mountain ginseng Roots extract (including Rb1, Rg1, Rg3, Rg5, and Rk1)	Sprague-Dawley rats and H$_2$O$_2$ -RAECs	Survival rate of RAECs ↑ thrombus formation ↓	[163]
Ligusticum chuanxiong hort	Ligustrazine	Hcy-induced HUVECs	Mitochondrial dysfunction ↓	[145]
		OGD HAECs MI/R injury in rats	PI3K/Akt/eNOS NO release ↑	[146]
Astragalus membranaceus	Astragaloside IV	HG-treated RAECs STZ SD rats	P2X7R, p-p38 MAPK ↓ eNOS and NO ↑	[149]
		RAEC	AMPK/eNOS pathway eNOS mRNA expression	[150]
Carhamus tinctorius L.	The ethanol extract of flowers	TNF α-stimulated HUVECs	Nrf2/HO-1/CO signaling ROS ↓	[153]
		2K-1C hypertensive rats	Ang II-AT1R-NADPH ↓ O$_2^-$ ↓ gp91^{phox} ↓	[154]
Ginkgo biloba L.	Ginkgolide B	LDL-induced HUVECs	NOX-4, LOX-1, MCP-1, ICAM-1, and VCAM-1 ↓	[156,157]
	Ginkgolide K	tMCAO mouse model	JAK2/STAT3 HIF-1α/VEGF	[164]
	Ginkgo biloba extract	EPCs	PI3K/Akt/eNOS signaling	[158]
Coptis chinensis Franch	Coptisine	HFD-induced mice *ex vivo* mice aorta	AMPK signaling phosphorylation of eNOs ↑	[162]
Houttuynia cordata	*Houttuynia cordata* extract	HG-treated ECs	Sirt1/eNOS NO ↑	[165]
		Hyperlipidemia mice and HAEC cultured with PA	FoxO1/p38 MAPK pathway ROS ↓	[166]
Ginkgo biloba	Ginkgolide K	tMCAO mouse model	JAK2/STAT3 HIF-1α/VEGF	[156]
Aralia Elata	*Aralia Elata* extract	HG-treated HUVECs	SIRT/AMPK AKT/eNOS	[167]
Curcuma longa Linn	Curcumin	HFD-induced mice	HO-1 Enzyme Activity ↑ ROS ↓ sirt1 ↑	[168]
Coptis chinensis Franch *and Cortex phellodendri*	Berberine	ApoE−/− mice	Atherosclerotic plaque area ↓ TC, TG, LDL-C, APOB100, VLDL-C ↓	[169]
Allium sativum Linn	*Allium sativum* Linn	Obesity Rats	Aortic wall thickness ↓	[170]
	Allicin	MI/R injury in rats	The activity of SOD, CAT, and GPx ↑ MDA ↓ p38 MAPK signaling pathway	[171]
Ocimum sanctum Linn	*Ocimum sanctum* Linn extract	Sprague-Dawley rats	Cholesterol levels ↓	[172]
		HFD-induced rabbit	Fatty streaks lesion in the artery wall ↓	[173]

7. In Vitro and In Vivo Studies of Food

7.1. Berries

Berries are rich in polyphenols, flavonoids, vitamins, fiber, and minerals [174]. A trial sequence analysis reported berries as a nutraceutical or functional food to prevent and control cardiovascular disease [175]. Blueberry anthocyanins upregulated PI3K/Akt/eNOS/PPARγ signaling pathway to protect HUVECs from high glucose-induced oxidative stress and dysfunction, decreasing the levels of ACE, XO-1, and LDL [176]. Aboonabi et al. (2020) reported a similar result for berry anthocyanins in diabetic human aortic endothelial cells with inhibition of IκB-α and caspase-1 activation [177]. Elderberry extract increased A23187-stimulated eNOS activity in EA.hy926 cells. 20beta-hydroxyursolic acid, a special dihydroxy triterpenoid, was regarded to be a potential active compound of elderberry [178]. Saskatoon Berry which contains anthocyanins and phenolic acids improved cardiovascular function and modulated glucose metabolism in HFD-induced diabetic rats [179].

7.2. Cucurbitaceous Vegetables

Common vegetables of the Cucurbitaceae family include squash, bitter gourd, and cucumber. In bitter gourd, Charantin has been proven to improve blood glucose and blood lipids [180,181]. Meanwhile, Cucurbitaceous vegetables play an enormous role in alleviating oxidative stress-mediated disorders, which are attributed to their nutrient composition: cucurbitacins, carotenoids, phytosterols, antioxidative polyphenols and polyunsaturated fatty acids, etc. [182]. Cucurbitacin I upregulated the expression of NRF-1, PPARα, ERRα, and PGC-1-β to protect H_2O_2-treated H9c2 from mitochondrial dysfunction-induced oxidative stress [183]. The ethanol extract of bitter gourd increased GPx, MDA, and CAT levels. It also avoided the degeneration of the internal elastic lamina of the aorta, showing anti-atherosclerotic potential in cholesterol-fed rats [184]. Recently, pumpkin seed protein was reported to offset high glucose-induced hypertension and hyperlipidemia in rats with metabolic syndrome, which is beneficial for preventing and treating cardiovascular diseases [185]. Cucumis sativus aqueous fraction enhanced NO bioavailability and ICAM-1 expression to inhibit Ang II-induced oxidative stress in HMEC-1 and improved endothelial function [186].

7.3. Cruciferous Vegetables

Common cruciferous vegetables include cauliflower, kale, horseradish, radishes, etc., which contain a variety of nutrients such as carotene, vitamins, folic acid, glucosinolate, and minerals [187]. Earlier studies reported that glucosinolate and its secondary metabolite, Indole-3-carbinol (I3C), have antioxidant and anticancer abilities by increasing Nrf2 nuclear translocation, which induced the expression of downstream antioxidant genes and detoxifying enzymes [188,189]. Recently, Prado et al. reported that I3C increased NO bioavailability and Hsp70 expression to improve hypertension and ischemia-reperfusion arrhythmias in vivo and ex vivo [190]. I3C and its derivate 3,3,'-diindolylmethane inhibited cytokines, ROS production, and thrombus formation [191]. In addition, the benefits of cruciferous vegetables are not limited to being attributed to glucosinolates as the mixtures of compounds mentioned above (such as vitamins K1 and carotene) also play a key antioxidant role [187,192].

7.4. Other Food

Okra (Malvaceae) shows antidiabetic properties that include anti-oxidation, anti-inflammatory, and blood glucose and lipid regulation [193,194]. Okra seed extract reduced TNFα-stimulated VCAM-1 and SELE expression and protected HMEC-1 from H_2O_2 injury, which might be attributed to high concentrations of quercetin 3-O-(malonyl)-glucose, quercetin Cortex-3-O-glucose-xylose and kaempferol-3-O-glucose [195]. In LDLr-KO mice, okra alleviated atherosclerotic lesion development of the aorta [196]. Dietary lycopene presents in fruits and vegetables such as tomatoes, carrots, watermelon, papaya, and guava, has been extensively studied for its role in cardiovascular disease [197]. Lycopene improved

endothelium-dependent vasodilation, through increasing NO bioavailability and reducing mitochondrial damage [197]. In a recent study, lycopene ameliorated atherosclerosis in ApoE$^{-/-}$ mice with a decrease in HNF-1α and NPC1L1 expression [198]. Tea and red wine are considered beverages with antioxidant activity [199]. Green tea extract and epigallocat-echin gallate prevented bisphenol A-induced vascular toxicity by reducing MDA levels in aorta and inhibiting HUVECs apoptosis [200]. Red wine polyphenols prolonged the lifes-pan of SR-B1 KO/ApoER61h/h mice (a model of lethal ischemic heart disease) by reducing atherosclerosis and decreasing MDA level in plasma [201]. On the other hand, resveratrol improved endothelial function by activating the PI3K/Akt/eNOs/PPARγ pathway in HFD-induced diabetic mice, accompanied by up-regulation of PPARδ [202]. In the general diet, arachidonic acid from chicken, milk, fish, and beef is beneficial for improving cardio-vascular function, such as anti-atherosclerosis, regulating blood pressure, and maintaining vasodilation [203]. Omega3 and omega6 are polyunsaturated fatty acids that reported to increase NO availability more than arachidonic acid in HUVECs [204]. Therefore, foods rich in omega3 and omega6 such as salmon, are also beneficial for improving cardiovascular disease [205,206]. Antioxidant studies of functional food and their bioactive compounds in cardiovascular disease are supplemented in Table 3.

Table 3. Antioxidant effects of functional food and their bioactive compounds in improving cardio-vascular disease in experimental settings. ↑: upregulation; ↓: downregulation.

Food and Nutrients	Active Ingredients/Extract	In Vivo/In Vitro Model	Molecular Mechanism	References
Berries (polyphenols, flavonoids, vitamins, fiber and minerals)	Blueberry anthocyanins	HG-induced HUVECs	PI3K/Akt/eNOs/PPARγ signaling pathway ACE, XO-1 and LDL ↓	[176]
	Berry anthocyanins	D-HAEC	IkB-α and caspase-1 activation	[177]
	Elderberry extract (20beta-hydroxyursolic acid)	EA.hy926	eNOS activity ↑	[178]
	Saskatoon Berry extract	HFD-induced rats	Cardiovascular function ↑ glucose metabolism ↑	[179]
Cucurbitaceous vegetables (cucurbitacins, carotenoids, phytosterols, antioxidative polyphenols and polyunsaturated fatty acids, etc.)	Cucurbitacin I	H_2O_2-treated H9c2	NRF-1, PPARα, ERRα, PGC-1-β ↑	[183]
	Bitter gourd extract	Cholesterol-fed rats	GPX and CAT levels ↑	[184]
	Pumpkin seed protein	High-fructose diet rats	TC and TG level ↓ the activity of SOD, CAT, and GPx ↑	[185]
	Cucumis	Angiotensin II-Induced HMEC-1	NO bioavailability ↑ ICAM-1 ↑	[186]
Cruciferous vegetable (carotene, vitamins, folic acid and minerals, glucosinolates, etc.)	I3C	Spontaneously hypertensive rats and Wistar Kyoto rats	NO bioavailability ↑ Hsp70 ↑ ROS ↓	[190,191]

Table 3. *Cont.*

Food and Nutrients		Active Ingredients/Extract	In Vivo/In Vitro Model	Molecular Mechanism	References
Other food	Okra	Okra seed extract (quercetin 3-O-(malonyl)-glucose, quercetin Cortex-3-O-glucose-xylose and kaempferol-3-O-glucose)	H_2O_2-induced HMEC-1	VCAM-1, SELE ↓	[195]
		Okra powder	LDLr-KO mice	The extent of atherosclerosis ↓	[196]
	tomatoes, carrots, watermelon, papaya, and guava	Lycopene	ApoE$^{-/-}$ mice	HNF-1α, NPC1L1 ↓ LDL-C level ↓, HDL-C level ↑ the extent of atherosclerosis ↓	[198]
	abyssal Fish: salmon, trout, anchovies, sardines; Flaxseeds, flaxseed oil, walnuts, soybeans	omega3 and omega6	HUVECs	NO availability ↑	[204]
Drink	Tea	Green tea extract epigallocatechin gallate	Bisphenol A-induced HUVECs	MDA levels ↓	[200]
	Red wine	Resveratrol	HFD-induced mice	PI3K/Akt/eNOs/PPARγ pathway	[202]
		Red wine polyphenols	HFD-induced SR-B1 KO/ApoER61h/h mice	MDA level ↓ atherosclerotic plaque area ↓	[201]

8. Clinical Applications of Antioxidant Treatment

Salvia miltiorrhiza (Danshen) and its compound preparations are widely used in the clinical treatment of angina pectoris, coronary heart disease, ischemic stroke, and diabetes-related cardiovascular diseases [24]. Compound Danshen dripping pills (CDDPs) is commonly used for the treatment of coronary heart disease and angina pectoris in clinical practice in China, consisting of *Salvia miltiorrhiza*, *Panax notoginseng*, and borneol [207]. It is the first traditional Chinese medicine preparation compound that completed the FDA Phase III clinical trial. In a meta-analysis involving 2574 patients with coronary heart disease, compared with percutaneous coronary intervention (PCI) alone, CDDPs combined with PCI more effectively improved blood lipid indexes, vascular endothelial function, inflammation, and cardiac function [208]. Danhong injection (DHI), a Sino Food and Drug Administration (SFDA) approved Chinese traditional medicine, is composed of the water-soluble complex from Danshen and Honghua [209]. A network meta-analysis that compared five Danshen preparations (Danshen injection, Salvianolate injection, compound Danshen injection, and Sodium Tanshinone IIA Sulfonate injection) for clinical improvement (4458 patients) and electrocardiographic improvement (3049 patients) reported that Danhong injection was more effective in treating coronary heart disease than other Danshen preparations [210]. Previously, the hydrophilic extract of Danshen was reported to reduce the levels of VCAM-1, vWF, and oxLDL and increase the activity of antioxidant enzymes (SOD, PONase, GSSG-R) in 62 diabetic patients with a history of coronary heart disease [211,212]. Based on the pharmacological research mentioned above, *Panax notoginseng* preparation was also applied to clinical cardiovascular disease and diabetes therapy in China [213]. Particularly Xuesaitong, which is mainly composed of *Panax notoginseng* saponins (PNS), is a commonly used botanical medicine for the treatment of cardiovascular diseases and diabetic complications [214,215]. Extensive sample data showed that oral administration of PNS improved angina frequency, duration, blood lipids, and cardiac function in patients with unstable angina (UA) [216]. Furthermore, another meta-study

of 1828 patients showed that combined use of *Panax notoginseng* increased the efficacy of conventional drugs in the treatment of UA [217]. It is worth mentioning that coronary artery disease, diabetes, and obesity are the main causes of UA [218]; however, the roles of natural products in the human body are limited. For example, Ginseng effectively ameliorated oxidative stress and vascular diseases in diabetes in vitro and in vivo [219]. In a randomized controlled trial, combined administration of Korean red Ginseng and American Ginseng improved blood pressure in patients with type 2 diabetes but did not affect vascular stiffness or endothelial function [220]. Clinical applications of antioxidant treatment with medicinal plants in cardiovascular disease are supplemented in Table 4.

Table 4. Clinical applications of antioxidant treatment with medicinal plants.

Preparation	Ingredients	Disease	Sample Counts	References
DanshenDuofensuanyan injection and Danshen drop spill	Danshen extract	stable angina pectoris	156 patients	[221]
Compound Danshen dripping pills (CDDPs) combined with PCI	Danshen, Panax notoginseng and borneol	coronary heart disease	2574 patients	[208]
Danhong injection (DHI)	the water-soluble complex from Danshen and Honghua	stable angina	4458 patients	[210]
Xuesaitong (XST)	PNS	unstable angina	1828 patients	[217]
Combined administration of Korean red ginseng and American ginseng	Korean red ginseng and American ginseng	hypertension and type 2 diabetes	80 patients	[220]

9. Conclusions and Future Perspectives

Among the causes of disability and death of diabetics, the most prominent part is the sequelae of vascular dysfunction in various parts of the body. Under the pathological of diabetes, the imbalance between ROS generation and elimination would play a critical role in vascular dysfunction. The progressing injury of ECs and VSMCs would eventually lead to diabetic complications, such as hypertension and atherosclerosis. Therefore, antioxidant treatment against vascular complications in diabetes is worth studying, and compounds from medicinal plants and food are widely studied in this field. Studies showed that the antioxidant effects of natural compounds are synergistic and complicated in many cases, of which the underlying mechanisms still need further study. Foods such as berries, cruciferous vegetables and okra, or drinks such as red wine that people can uptake daily were shown to ameliorate vascular dysfunction. Medicinal plants such as *Salvia miltiorrhiza* and *Panax notoginseng* were also shown to protect against vascular complications in diabetes during the individual or combination treatment with other drugs in clinical studies; it implies that medicinal plants or food can be an adjunct therapy in treatment of vascular complications in diabetes. Some therapeutic effects of medicinal plant treatment are limited or even insignificant. Therefore, clinical trials of medicinal plant treatment on vascular complications in diabetes may need to increase the sample size to better study the efficacy in the human body. The rich resources of bioactive compounds from medicinal plants and food might benefit from reducing the cost and medicinal consumption in the treatment of diabetes and its vascular complications; however, a healthy lifestyle and eating habits are the keys to improving or preventing cardiovascular disease and metabolic syndrome.

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