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Endothelial Cells: From Dysfunction Mechanism to Pharmacological Effect in Cardiovascular Disease

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Abstract

Endothelial cells (ECs) are the innermost layer of blood vessels that play important roles in homeostasis and vascular function. However, recent evidence suggests that the onset of inflammation and the production of reactive oxygen species impair the function of ECs and are a main factor in the development of cardiovascular disease (CVD). In this study, we investigated the effects of inflammatory markers, oxidative stress, and treatment on ECs in CVD patients. This review article is based on the material obtained from PubMed up to 2018. The key search terms used were "Cardiovascular Disease," "Endothelial Cell Dysfunction," "Inflammation," "Treatment," and "Oxidative Stress." The generation of reactive oxygen species (ROS) as well as reduced nitric oxide (NO) production by ECs impairs the function of blood vessels. Therefore, treatment of CVD patients leads to the expression of transcription factors activating anti-oxidant mechanisms and NO production. In contrast, NO production by inflammatory agents can cause ECs repair due to differentiation of endothelial progenitor cells (EPCs). Therefore, identifying the molecular pathways leading to the differentiation of EPCs through mediation of factors induced by inflammatory factors can be effective in regenerative medicine for ECs repair.

Keywords Cardiovascular diseases · Endothelial cell dysfunction · Inflammation · Oxidative stress

Abbreviations

NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
Mo	Monocyte
EC	Endothelial cell
MQ	Macrophage
Plt	Platelet
CVD	Cardiovascular disease
HF	Heart failure
ROS	Reactive oxygen species
NO	Nitric oxide
VEGF	Vascular endothelial growth factor
LDL	Low-density lipoprotein
SCR-A	Scavenger receptor-A
ER	Endoplasmic reticulum

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Introduction

Cardiovascular disease (CVD) is a complex of diseases involving blood vessels and heart, including several complications such as heart failure (HF), atherosclerosis, and cardiomyopathy [1, 2]. Human heart is composed of myocytes, fibroblasts, and an extensive network of blood vessels, each of which is involved in the development of CVD by various molecular mechanisms [3]. Blood vessels are also composed of a number of cells such as smooth muscle and endothelial cells (ECs). The latter are located in the lumen of vessel, have direct contact with cells circulating in blood, and regulate blood pressure as well as leukocyte trafficking [4]. In many diseases (including CVD), the physiological function of blood vessels is disrupted because of inflammatory reactions, oxidative stress, and abnormal expression of some molecules on the surface of ECs [5]. In addition, recent evidence suggests that the use of drugs to treat

CVD can modulate inflammatory responses and reduce the production of reactive oxygen species (ROS) by ECs [6]. Therefore, in this review paper, we examine the molecular mechanism of ECs in pathogenesis of CVD, as well as mechanisms of drugs targeting ECs to improve the function of blood vessels.

Biology of Endothelial Cells in Blood Vessels

ECs constitute a layer between blood and extravascular cells and are responsible for maintaining the structure and regulating the function of blood vessels [7]. Furthermore, ECs produce a series of dilators (such as bradykinin and nitric oxide) and constrictors (like endothelin), preventing platelet aggregation and forming blood clot in addition to regulating the vascular tone [8]. In the heart, ECs and cardiomyocytes interact with each other through the release of a number of cell signaling transmitters, which maintain hemostasis in the vessel and heart tissue [9]. In normal conditions, no adhesion molecules or thrombogenic factors are expressed on the surface of ECs; however, when blood vessels are damaged, vascular endothelial growth factor (VEGF) and stromal-derived factor 1 (SDF-1) are secreted by them, which result in mobilization of endothelial progenitor cells (EPCs) [10]. EPCs are bone marrow (BM)-derived cells involved in the formation of blood vessels, and their proliferation and differentiation can lead to angiogenesis and growth of vascular system [11].

Increased Production of Inflammatory Biomarkers

ECs dysfunction is an important factor in the development and progression of CVD, leading to atherogenesis and plaque formation [12]. Dysfunction of ECs is caused by various stimulants, including inflammatory factors such as IL-6, TNF-α, and intercellular adhesion molecule 1 (ICAM-1), which causes inflammation in blood vessel wall and leads to the development and progression of CVD [13]. Macrophages (MQs) are immune cells contributing to innate immunity. They activate the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-kB) signaling pathway, leading to release of cytokines such as IL-6 and TNF-α [14]. IL-6 leads to the generation of C-reactive protein (CRP), which is an inflammatory biomarker. CRP on the one hand activates FCγRII and causes T helper 1 (Th1) differentiation along with liposomes, and on the other hand activates FCγRI and causes T helper 2 (Th2) differentiation along with phosphatidyl choline (PC). However, as the secretion of inflammatory factors (like cytokines) is increased in CVD, Th1 cells are further differentiated, causing inflammation through the production of inflammatory cytokines and stimulation of immune cells [13, 15]. IL-6, IL-1, and TNF-α also increase the expression of cyclooxygenase (COX) on several tissues and cells, including ECs. COX also activates the prostaglandins (PGs) synthesis pathway, which leads to PGE2 production [16]. PGE2 causes inflammation in ECs by producing inflammatory cytokines and activating platelets [17]. Moreover, inflammation of ECs promotes the expression of CD40 on their surface as well as interaction of CD40 with CD40 ligand (CD40L) on platelets, which leads to the activation of platelets [18, 19]. CD40 decreases NO production and increases ROS production by ECs, suppressing VEGF production and inhibiting angiogenesis, which contributes to the pathogenesis of CVD [20]. Moreover, the activation of platelets leads to their binding with monocytes (Mo) due to the interaction of platelet p-selectin with Mo PSGL-1, which recruits Mo from circulation towards the vessel wall. Additionally, CD40–CD40L interaction increases the production of Von Willebrand factor (VWF) from Weibel–Palade bodies of ECs, forming an appropriate background for Mo and T-cell differentiation on vessel wall and increasing the rate of inflammation [21] (Fig. 1).

Low-density lipoprotein (LDL) is another factor inducing inflammation, which is converted to oxidized-LDL (ox-LDL) due to increased ROS production by ECs. Ox-LDL binds Mo via expression of monocyte chemoattractant protein-1 (MCP-1), causing their differentiation into MQ. Ox-LDL also produces TNF-α and IL-6, which eventually leads to an increase of Mo binding to ox-LDL [22]. CD36 and SCR-A receptors are present on MQs and absorb ox-LDL, after which MQs turn into foam cells [23]. Furthermore, ox-LDL interaction with lectin-type oxidized LDL receptor 1 (LOX-1) on the surface of ECs leads to an increase in ROS production and expression of CD40 as well as vascular cell adhesion molecule 1 (VCAM-1) on the surface of ECs, which increases inflammation and finally causes ECs dysfunction [24]. However, there are other factors in addition to the above-mentioned ones that lead to inflammation and progression of CVD due to ECs dysfunction (Table 1).

Therefore, the identification and measurement of inflammatory factors in CVD patients may be effective in preventing the disease as well as controlling its progression by inhibiting the production and targeting of these factors.

Excessive Production of Reactive Oxygen Species

Oxidative stress is another essential factor in the incidence of CVD, which leads to the generation of ROS such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2) [32]. There are several molecular pathways between inflammation and oxidative stress, so that inflammatory factors causing ECs dysfunction through inflammatory reactions result in ROS generation after inflammation. Also, a number of toxic factors lead to dysfunction of ECs through the induction of inflammation and ROS production (Fig. 2; Table 2).

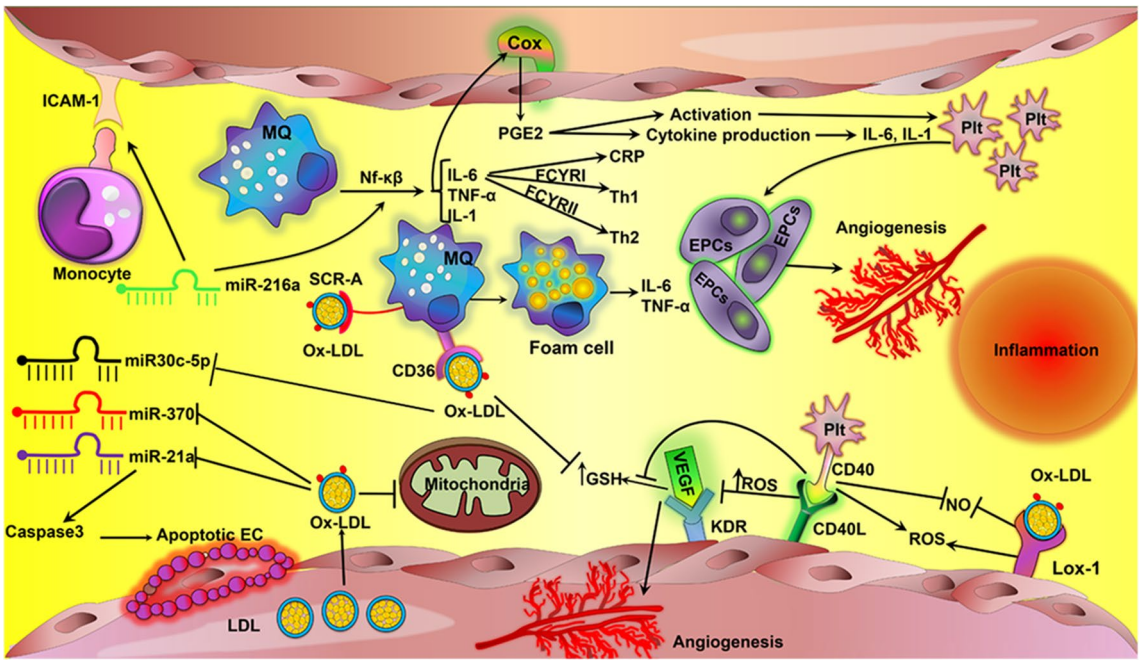

Fig. 1 Inflammatory mechanisms and oxidative stress in cardiovascular disease (CVD). By activating NF-kB pathway, macrophages produce cytokines such as IL-1, IL-6, and TNF-α, which mediate the generation of inflammatory mediators such as CRP that exacerbate inflammatory reactions. On the other hand, macrophages turn into foam cells after interaction with ox-LDL and produce inflammatory cytokines. EC CD40-platelet CD40 ligand interaction inhibits NO production and suppresses angiogenesis. Also, platelets produce a number of factors (such as IL-1 and IL-6) causing differentiation of EPCs that stimulate angiogenesis. They interact through CD40 with CD40 ligand at ECs surface, which prevents angiogenesis by interfering with VEGF/KDR in addition to the production of ROS and the inactivation of GSH. GSH is also inactivated due to intersection of Ox-LDL with CD36, which is expressed on the surface of foam cells. Through interactions with CD36 and SCR-A expressed on the surface of foam cells, OX-LDL leads to the inhibition of some miRs (such as miR-21a and miR-370) in addition to causing inflammation. Furthermore, ox-LDL leads to induction of apoptosis due to mitochondrial dysfunction. *ICAM-1* intercellular adhesion molecule 1; *MQ* macrophage; *COX* cyclooxygenase; *NF-kB* nuclear factor kappa-light-chain-enhancer of activated B cells; *TNF-α* tumor necrosis factor-α; *Th1,2* T helper1,2; *PGE2* prostaglandin E2; *EPCs* endothelial progenitor cells; *SCR-A* scavenger receptor-A; *ox-LDL* oxidized low-density lipoprotein; *EC* endothelial cell; *LDL* low-density lipoprotein; *GSH* glutathione; *ROS* reactive oxygen species; *NO* nitric oxide; *LOX-1* lectin-type oxidized LDL receptor 1; *VEGF* vascular endothelial growth factor; *IL-1,6* interleukin1,6; *Plt* platelet; *miR* MicroRNA; *CRP* C-reactive protein; *KDR* kinase insert domain receptor; *FCγR* FCγ receptor

Table 1 Some of the factors that lead to dysfunction of endothelial cells

Factor	Mechanism	Effect on function or structure of EC	References
Angptl2	Activation of NF-kB signaling and Mo chemotaxis	Reduces NO production by ECs	[25]
RGC32	Causes interaction of Mo with ECs	Through TNF-α, increases ICAM-1 and VCAM-1 expression on ECs	[26]
GPR-124	Induces inflammation by activating NF-kB and NLRP3 signaling	Causes exaggerated nitrosative stress	[27]
TLR 4	Activation of NF-kB signaling and production of inflammatory cytokines	Reduces NO and increases ROS production by ECs	[28]
Endogelin	Activation of NF-kB signaling and production of inflammatory cytokines	Increases leukocyte transmigration through adhesion molecule expression	[29]
Endocan	Inducible inflammatory via production of cytokine	Increases ICAM-1 and VCAM-1 expression on ECS	[30]
Lysophospholipids	Activation of NF-kB signaling and production of inflammatory cytokine by leukocytes	Increases adhesion molecules and chemokine expression on ECs for transmigration of leukocyte	[31]

Angptl2 angiopoietin-like protein 2; *NF-kB* nuclear factor kappa-light-chain-enhancer of activated B cells; *Mo* monocyte; *NO* nitric oxide; *EC* endothelial cell; *RGC32* response gene to complement 32 protein; *TNF-α* tumor necrosis factor α; *ICAM-1* intercellular adhesion molecule 1; *VCAM-1* vascular cell adhesion molecule 1; *GPR-124* G protein-coupled receptor 124; *TLR4* toll-like receptor 4; *ROS* reactive oxygen species

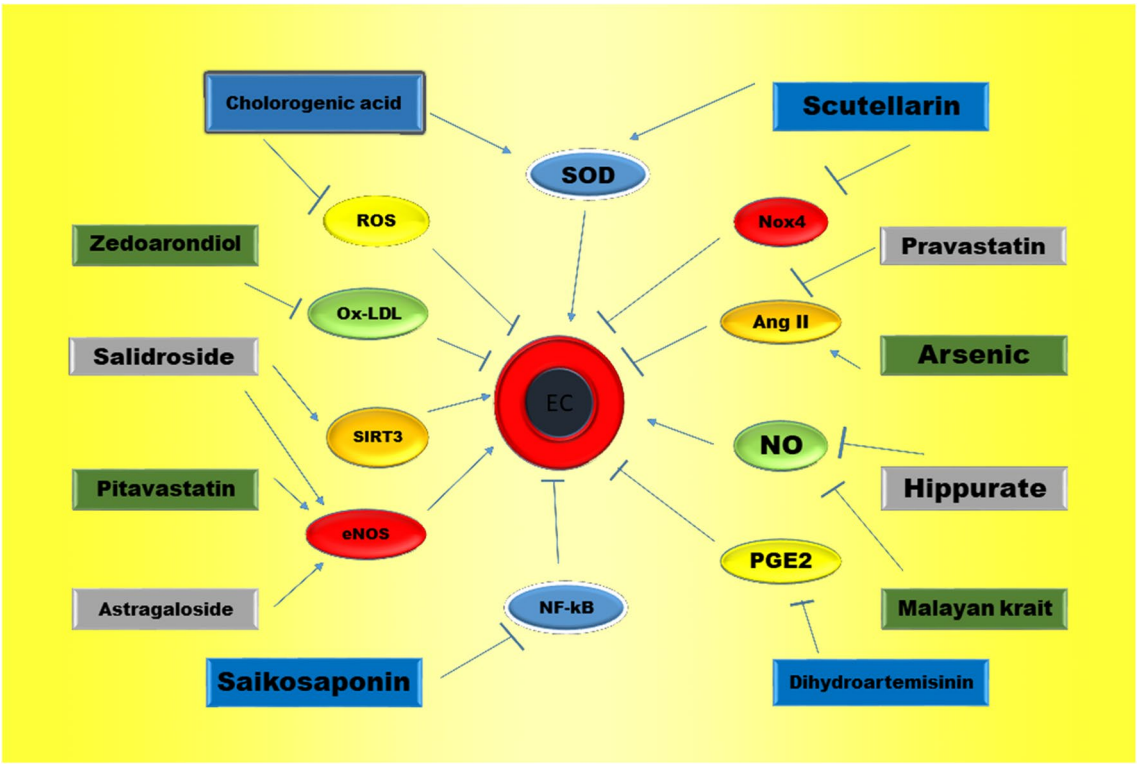

Fig. 2 Effect of drugs and toxic substances on ECs function. Drugs such as chlorogenic acid and Zedoarondiol improve ECs function by controlling ox-LDL and prevent inflammation. Also, chlorogenic acid along with scutellarin leads to the recovery of SOD function, which is an anti-oxidant that prevents excessive ROS production. Salidroside, pitavastatin, and astragaloside also prevent the disruption of ECs through NO production. Due to prevention of inflammation by PGE2 and COX-1 inhibition, DHA counteracts EC dysfunction. Toxic substances also cause CVD due to dysfunction of ECs. For example, arsenic induces the disruption of ECs due to Ang II induction that stimulates inflammatory factors by activating signaling pathways. Malayan Krait venom and Hippurate also cause EC dysfunction by inhibiting NO production. *EC* endothelial cell; *ROS* reactive oxygen species; *NO* nitric oxide; *ox-LDL* oxidized low-density lipoprotein; *COX* cyclooxygenase; *NF-kB* nuclear factor kappa-light-chain-enhancer of activated B cells; *PGE2* prostaglandin E2; *DHA* dihydroartemisinin; *TF* tissue factor; *IS* indoxyl sulfate; *SIRT3* Selective internal radiation therapy 3; *eNOS* endothelial nitric oxide synthase

Table 2 Effect of some toxin factors on function of endothelial cells

Toxin	Target	Mechanism	References
Arsenic	Ang II	Induces inflammation by activation of NF-kB pathway Production of ROS	[33]
Hippurate	NO	Reduces secretion of NO Enhanced ROS production by dysregulation of mitochondrial function	[34]
IS	TF	Increased activation of clot factor, enhanced thrombosis and inflammation in blood vessels	[35]
Malayan krait venom	NO	Leads to dysregulated relaxation of blood vessels	[36]
LPS	*Gch1*	Leads to reduced NO production by increased expression of BH4	[37]
Cigarette smoke	RhoA and FAK	Leads to dysfunction of ECs integrity and enhances the production of ROS	[38]

Ang II angiotensin II; *ROS* reactive oxygen species; *NF-kB* nuclear factor kappa-light-chain-enhancer of activated B cells; *IS* indoxyl sulfate; *TF* tissue factor; *LPS* lipopolysaccharides; *EC* endothelial cell

Mitochondria and NADPH oxidase are two main factors involved in the production of intracellular ROS [39]. In addition to causing inflammation due to the formation of foam cells (MQs that have absorbed excess lipid structures such as cholesterol and LDL), Ox-LDL interacts with LOX-1 on the surface of ECs, reducing NO production and activating the NF-kB signaling pathway [40]. Furthermore, ox-LDL binding to its receptor (LOX-1) expressed on the surface of

ECs connects platelets to ECs and produces endothelin-1, which inhibits NO production by increasing production of ROS [41, 42]. In normal conditions, BH4 or (6R)-5,6,7,8-tetrahydro-L-biopterin is a major co-factor in the pathway of NO generation; however, excessive production of O_2^- causes its reaction with NO and leads to the production of peroxynitrite (ONOO–), which is a free radical causing DNA damage in ECs and disrupts their function [43, 44]. Moreover, reduced NO production leads to the inhibition of VEGF interaction with its receptor (KDR/FLK-1), which prevents the production of glutamate-cysteine glycine (GSH), a tripeptide molecule with anti-oxidant properties [45]. EPCs are ECs precursor cells that differentiate concomitant with the formation of blood vessels. Previous studies have shown that NO production plays a role in the mobilization and differentiation of EPCs. Therefore, reduced NO production can delay or inhibit the repair of ECs [46]. Moreover, NO has been shown to activate AMPK/ERK pathway through secretion of VEGF, which leads to differentiation of EPCs to ECs. Alternatively, it has been shown that adiponectin, which is an anti-inflammatory and anti-oxidant agent, activates the AMPK/AKT pathway, producing NO and differentiating EPCs [47]. Furthermore, studies have indicated that adiponectin prevents CVDs through reduction of ROS, dysregulation of CD36, and inhibition of apoptosis [48, 49]. Therefore, it can be said that since the AMPK pathway plays a major role in EPCs differentiation, its activation may increase patient survival by inhibiting CVDs progression.

Increasing ox-LDL production leads to an increase in the expression of CD36 on the surface of foam cells because of interaction between signal transducer and activator of transcription 1 (STAT-1) with peroxisome proliferator-activated receptor (PPAR-γ) [50]. In addition, this interaction increases the production of ROS by activating NADPH oxidase. Instead, in normal conditions, the expression of CD36 is in equilibrium with GSH, but increasing expression of CD36 due to ox-LDL reduces GSH levels, which leads to an increase in ROS production [51]. Also, ox-LDL production results in the generation of cytochrome C (cyt.c) and activates Caspase 3, eventually disrupting the function of endoplasmic reticulum (ER) and mitochondria by inactivating Wnt/βcatenin pathway, which increases the production of ROS [52, 53]. Therefore, the balance in the expression of CD36 and production of ox-LDL can be important in CVD monitoring and ROS production for CVD progression, and the disruption of this balance can lead to ECs dysfunction.

Effect of MicroRNAs on ECs Function

MicroRNAs (miRNAs) are small non-coding RNAs that play a role in regulating the expressions of genes by targeting mRNAs or preventing their translation [54]. miRNAs are involved in various biological processes, including cell cycle and differentiation, as well as pathological processes like CVD. Recent evidence has shown that miRNAs are implicated in EC senescence by causing inflammation and producing ROSs in the blood vessel wall [55]. For example, miR-216a increases the expression of adhesion molecules (e.g., ICAM-1) on the surface of ECs, increasing the binding of Mo to vessel walls and activating the NF-kB pathway, which increases the rate of inflammation [56]. Ox-LDL also increases the risk of CVD due to decreased or increased expression of miRNAs. For example, ox-LDL reduces miR-370 expression. miR-370 targets TLR-4 and prevents the production of inflammatory cytokines such as IL-6 and IL-1 [57]. Furthermore, ox-LDL decreases the expression of miR-21a, which plays a role in apoptosis of cells by activating caspase 3. Reduced expression of miR-21a is associated with excessive proliferation of ECs and an increasing risk of CVD [58]. Ox-LDL interaction with CD36 leads to the expression of miR-30c-5p, which is involved in preventing the production of inflammatory mediators by MQs [55] (Fig. 1). Conversely, overexpression of a number of other miRs can increase the risk of CVD (Table 3). Although the role of miRNAs in expression regulation of transcription factors and signaling pathways involved in inflammation and RO has been indicated, the identification of miRNAs and their target genes that individually cause inflammation and ROSs can be helpful for researchers to select and target miRNAs in future studies.

Effect of Treatment on Endothelial Cells

Several drugs have been used to treat CVD. However, since inflammation and production of ROS are the main causes of CVD development, the drugs modulating inflammatory reactions and oxidative responses can be more effective in treatment of CVD [68]. Drugs prevent the progression of CVD through various ways. For instance, Zedoarondiol (a drug derived from zedoarae rhizome) increases the expression of Nuclear factor-erythroid2-related factor 2 (Nrf2), which raises the expression of genes encoding anti-oxidant and detoxifying agents such as heme oxygenase-1 (HO-1). In CVD, Zedoarondiol decreases the production of inflammatory mediators and ROS by inhibiting ox-LDL and preventing its binding to CD36 [69, 70]. Astragaloside is another drug enhancing the activity of endothelial nitric oxide synthetase (eNOS) by activating PI3K/AKT signaling pathway as well as increasing NO production, which prevents the accumulation of ROS in the vessels and acts as a vasodilator [71]. Dihydroartemisinin (DHA) is effective in CVD treatment by reducing the expressions of certain molecules. The drug, which plays an anti-inflammatory role, decreases the production of inflammatory cytokines by reducing the expression of COX-1 as well as decreasing PGE2

Table 3 MicroRNAs upregulated in cardiovascular diseases

MiRNA	Disease	Target	Inflammation/ oxidative stress	Mechanism	References
Mir-216a	Atherosclerosis	TERT	Inflammation	Increased polarization of MQ toward to M1	[59]
Mir-146b	Ischemia	CRP,IL-6	Inflammation	Increases inflammatory biomarkers level	[60]
Mir-19b	Atherosclerosis	SOCS3	Inflammation	Increases inflammatory biomarkers level and reduces IL-10	[61]
Mir-92a	MI	Nrf2-KEAP1-ARE signal pathway	Oxidative stress	Increases ROS in ECs	[62]
Mir-181a	Atherosclerosis	BCL-2	Oxidative stress	Increases ROS in ECs and is sensitive to apoptosis	[63]
Mir-1	CAD	SOD1, Gclc, and G6PD	Oxidative stress	Increases ROS and reduces activity of anti-oxidant agents	[64]
Mir-34a	CAD	SIRT1	Oxidative stress	Increases ROS and reduces activity of anti-oxidant agents	[65, 66]
Mir-106a	HF	Mfn2	Oxidative stress	Through mitochondrial membrane depolarization and ROS production	[67]

TERT telomerase reverse transcriptase; *MQ* macrophage; *CRP* C-reaction protein; *SOCS3* suppressor of cytokine signaling 3; *ROS* reactive oxygen species; *EC* endothelial cell; *Nrf2* nuclear factor erythroid 2 p45-related factor 2; *G6PD* glucose-6-phosphate dehydrogenase; *SOD* superoxide dismutase; *SIRT1* silent information regulator 1; *Mfn2* mitofusin 2; *MI* myocardial infraction; *CAD* coronary artery disease; *HF* heart failure

generation [16]. A number of medications improve the CVD treatment process; however, they are associated with a series of side effects. Saikosaponin inhibits and activates NF-kB signaling and superoxide dismutase (SOD), respectively, preventing the progression of CVD. In one study, it was found that Saikosaponin induces ER-stress and generates ROS by releasing human caspase 4 from endoplasmic reticulum (ER). It also induces apoptosis in cells by activating FAS-TRAIL [72, 73]. In addition, chlorogenic acid has been shown to reduce the expression of SOD, which leads to the decrease in ROS production. Nevertheless, the results have shown that the use of this drug results in apoptosis of ECs [74]. Scutellarin is another drug inhibiting NOX4 and increasing the expression of SOD, which prevents ECs from apoptosis due to ROS; however, this drug has been shown to increase platelets interactions with ECs, which can eventually increase the incidence of inflammation [6, 75]. Studies have indicated that atorvastatin reduces inflammation by expressing KLF2 factor as well as inducing ECs apoptosis because of ROS production [76]. Salidroside and Pitavastatin are two drugs that reduce the damage caused by CVD to ECs by producing NO. However, it is known that although this drug may improve CVD, it could lead to CVD progression through the induction of inflammation by activating immune cells (Table 4).

Therefore, although certain drugs target molecules or transcription factors and prevent the progression of CVD, they may activate other molecular pathways that cause further damage to ECs and inactivate ECs over time (Table 4) (Fig. 2).

Discussion and Future Perspective

ECs dysfunction is a main feature of CVD caused by several stimuli, the most important of which are pro-inflammatory cytokines and loss of anti-oxidant mechanisms [94]. Although the production of inflammatory cytokines by different cells is expected to disrupt the hemostasis of blood vessels and aggravate CVD, further investigation has revealed that these cytokines act like a double-edged sword. PGE2 is one of the main factors of inflammation that activates platelets and produces inflammatory mediators [95]. When the platelets are activated, they secrete certain factors through interaction with ECs, including inflammatory factors such as IL-1 and IL-6 as well as angiogenesis mediators like VEGF [96]. Likewise, the number of EPCs in circulation is inversely proportional to ROS generation, so that increasing ROS production is associated with a decrease in circulating EPCs. NO also causes the mobilization, proliferation, and differentiation of EPCs [46] (Fig. 1). Studies have shown that IL-1 and VEGF are among the factors contributing to the differentiation of EPCs and that the level of these factors is higher in hypercholesterolemic patients who are at a higher risk of CVD than healthy subjects [97]. Therefore, although the production of inflammatory factors (e.g., IL-1 and PGE2) can increase inflammation rate, it could play an essential role in EPC-mediated repair of ECs by stimulating angiogenesis.

Table 4 Drugs used for treatment of cardiovascular diseases and related side effects

Drug	Approved by FDA	Mediator(s)	Action mechanism	Possible side effect	References
Chlorogenic acid	Yes (approved only for stroke)	Ox-LDL	Activation of SOD and decreased ROS production	Causes EC death through activation of apoptosis signal pathway	[39, 74, 77]
Scutellarin	Yes (for the pilot phase I clinical trials)	NOX4 AND SOD	Up- and down-regulation of SOD and NOX4, respectively	Causes EC death through activation of apoptosis signal pathway Increases interaction of platelet with ECs	[6, 75, 78]
Salidroside	In phase of clinical trials	SIRT3 and enos	Reduces inflammatory cytokine production and activation of antioxidants	Increases cytokine production by Th1 and Th2 and therefore activates immune response	[79–81]
Pitavastatin	Yes	miR-155 and eNOS	Reduces inflammatory response and increases NO production	Causes EC death through activation of apoptosis signal pathway ROSs production by JNK and p38 MAPK signal activation	[82–84]
Atorvastatin	Yes	KLF2	Reduces inflammatory response	Down-regulation of miR-21 and increased proliferation risk of ECs	[76, 85, 86]
Pravastatin	Yes	Angiotensin II	Reduces ROS production by targeting angiotensin II	May increase endothelin-1 expression that inhibits NO production	[87–89]
Zedoarondiol	Pilot phase I clinical trials	Ox-LDL and Nrf2	Inhibition of inflammation reactions through reduction inflammatory production	–	[70, 90]
Astragaloside	Yes	eNOS	Reduces ROS production	–	[71, 91]
DHA	Yes	COX-1 and PGE2	Reduces inflammatory response	Increased intracellular calcium and induced apoptosis	[16, 92]
Saikosaponin	In phase of clinical trials	NF-kB	Reduces inflammatory responses	May induce apoptosis by production of ROS	[72, 93]

ox-LDL oxidized low-density lipoprotein; *SOD* superoxide dismutase; *ROS* reactive oxygen species; *EC* endothelial cell; *SIRT 3* selective internal radiation therapy 3; *eNOS* endothelial nitric oxide synthase; *Th1,2* T helper 1,2; *NO* nitric oxide; *KLF2* Krüppel-like Factor 2; *DHA* dihydroartemisinin; *Nrf2* nuclear factor-erythroid 2 related factor 2; *COX-1* cyclooxygenase; *PGE2* prostaglandin E2; *NF-kB* nuclear factor kappa-light-chain-enhancer of activated B cells

Conclusion

Today, regenerative medicine plays a significant role relative to other therapies for the treatment of CVD. Considering the dual role of some inflammatory factors in pathogenesis and repair, we can state that the detection of molecular pathways involved in stimulation of inflammation and differentiation of EPCs by inflammatory factors might be used as a therapeutic approach to treat inflammation in CVD patients.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

Research Involving Human Participants and/or Animals This article does not contain any studies with human participants or animals performed by any of the authors.

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