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Exosomes: Potential Player in Endothelial Dysfunction in Cardiovascular Disease

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Abstract

Exosomes are spherical bilayer membrane vesicles with an average diameter of 40–100 nm. These particles perform a wide range of biological activities due to their contents, including proteins, nucleic acids, lipids, lncRNA, and miRNA. Exosomes are involved in inflammation induction, oxidative stress and apoptosis, which can be effective in endothelial dysfunction. Due to the induction of mentioned processes in the endothelial cells, the intercellular connections are destroyed, cell permeability increases and finally cell efficiency decreases and functional defects occur. Cardiovascular disease (CVDs) are of consequences of endothelial dysfunction. Thus by identifying the exosome signaling pathways, which induce inflammation, oxidative stress, and apoptosis, endothelial dysfunction and subsequently CVDs can be reduced; exosomes can be used for appropriate target therapy.

Keywords Exosome · Cardiovascular disease · Endothelial dysfunction · Mechanism

Introduction

Cardiovascular diseases (CVD) are a wide range of disorders, that affect vascular system, heart, brain and other vital organs. CVD is a chronic disease, that begins in childhood, even if the first symptoms appear in the middle age [1]. According to researches, these disorders are more common in patients with chronic kidney disease than general population [2]. A wide range of evidence supports the important role of inflammatory responses in the pathogenesis of CVD through endothelial cell (ECs) dysfunction [3, 4].

In fact, the endothelium creates a barrier due to cell-to-cell attachments, that selectively restricts macromolecules movement [5]. It also has protective effects, anti-apoptotic activity, anti-myocardial fibrosis, as well as vasodilation and immune system regulation [6, 7]. However, ECs with an inflammatory phenotype cause inflammation in the blood vessels, resulting in cardiac dysfunction [8, 9]. In addition, exosome increases the permeability and disrupts the joints by increasing the expression of adhesion molecules; they also decrease nitric oxide (NO) synthesis in ECs, that causes ECs dysfunction and thus increases CVD risk [10, 11].

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In fact, exosome is a largely unknown "cell-to-cell" communication system, that is now increasingly considered for diagnostic and therapeutic use in CVD [12]. As a new type of treatment and diagnostic tool, they are involved in non-invasive assessment of limb response to injury, or in the treatment and development of a reliable treatment method [13–15]. The aim of this study was to evaluate exosomes for the incidence of ECs dysfunction in CVD.

Structure and Function of Exosome

Exosomes are spherical vesicles with a bilayer membrane with an average diameter of 40–100 nm [16]. They form inside secretory cells in endosomal chambers called multivesicular endosomes (MVEs), with a series of precise regulatory processes such as "endocytosis-fusion-efflux" process [17]. Exosomes are secreted out of the cell via exocytosis process; it has three steps, including: exosome biogenesis, transportation of multivesicular bodies (MVBs) to the plasma membrane and MVBs fusion with the plasma membranes. The exosome secretion stage is closely monitored by molecules, such as Rab27a/b, Rab7, Contractin, SNARE and Synaptotagmin-7. Therefore, exosome secretion is monitored by physiological signaling, but some diseases and cancers can affect these regulatory mechanisms and alter exosome secretion [18, 19].

Exosomes can be found in all living cells, especially dendritic, lymphocyte, epithelial and endothelial cells [20]. They do not contain a random array of intracellular proteins, but a specific set of several protein families derived from plasma membranes, intracellular pathways, and cytosols [21]. In fact, exosomes usually contain a variety of biomolecules, including proteins, nucleic acids, lipids, lncRNA and miRNA and even viruses [15, 22]. These particles communicate with recipient cells by three mechanisms; they are absorbed by them. These three mechanisms include: 1- binding of transmembrane proteins from exosome to the existing receptors on the surface of recipient cells, 2-plasma membrane fusion of exosomes with plasma membrane of recipient cells and transfer of their contents to the cytosol of target cells and 3- internalization of exosomes into recipient cells [16].

Exosomes can play an important role in intercellular communications [23]. They are described as new particles in contact with neighboring or distant cells, and binding to membrane proteins, cytoplasm, lipids and nucleotides [24]. Transmission microscopy, possessing a cup-shaped morphology after negative staining and density gradient are used to identify exosomes. CD63, CD9, CD81 and tetraspanin protein markers can also be used to detect exosomes by monoclonal antibodies. Ultracentrifugation, ultrafiltration, size-exclusion chromatography, magnetic beads immunoaffinity, size-based microfluidic, microfluidics separation and dynamic microfluidics techniques are also used to separate exosomes [25].

Nowadays, exosomes are used for diagnosis and treatment of many diseases, including Alzheimer, Parkinson, preeclampsia, gestational diabetes mellitus and infectious diseases such as bacterial infections, sepsis, and COVID-19; they are also used for some cancers, such as breast, cervical, prostate and lung. Therapeutic use of exosomes is based on drug delivery or effective factors on signaling pathways, which are associated with patient's recovery. For example, in the treatment of cancer patients, exosomes can be used to deliver chemotherapeutic drugs such as paclitaxel, cisplatin and doxorubicin. Also, by transmitting chimeric agents such as CAR-T Cell and inducing an effect on the signaling of effector T cells, it is possible to increase exosomes function to eliminate tumor agents; thus, it helps the process of recovery in patients with cancer.

The use of exosomes in the treatment of infectious diseases is another example of the therapeutic use of these particles. In bacterial infections, exosomes can be used to treat patients by transmitting antimicrobial peptides, Hepcidin and beta-defincin-2 to increase the antibacterial function of immune cells. Exosomes containing super-repressor IκB can also be used in people with septic shock; they suppress the induction of septic shock due to IL-6, IL-1 and TNF cytokines by suppressing the NF-Kβ signaling pathway. In addition, recent studies have shown the effective role of exosomes in CVD treating by regulating cellular condition in cardio myocytes [26].

Also due to the transport of protein and functional RNA, exosomes are involved in the pathogenesis of many human malignancies, infectious and degenerative diseases, oncogenesis and tumor metastasis [27].Tumor cells can significantly release more exosomes than healthy ones; this fact suggests, that selective regulation of tumor-derived exosomes (TEXs) is based on their structure and function. TEXs also facilitate tumor growth and metastasis through exosome cross-section [28]. Also in the cardiovascular system, exosomes are related to ECs, cardiac myocytes, vascular cells and stem cells; they play a key role in growth and damage of cardiac muscle and CVD [29]. In fact, lncRNAs and miRNAs contents of exosome provide a potential source of new diagnostic and prognostic biomarkers for CVD. They have many beneficial effects in preventing CVD, and heart repairing [30]. Most importantly, stem cell-derived exosomes will be more effective and safer than stem cell-based alternative therapies for CVDs treatment [31].

The Role of Exosome in Inflammation

Studies show, that inflammatory process induced by exosomes can lead to ECs dysfunction and subsequently CVD. The exosome containing miR-155 can lead to

endothelial dysfunction by inducing inflammation in endothelial cells. miR-155 causes inflammation in ECs by activating the NF-Kβ transcription factor, and subsequently increasing the production of pro-inflammatory cytokines, such as IL-6 and Tumor Necrosis Factor-α (TNF-α). The result is a defect in the function of these cells. On the other hand, miR-155 expression in ECs can also induce inflammation by targeting the two molecules of Src homology 2 (SH2) domain-containing inositol polyphosphate 5-phosphatase 1 (SHIP1) and Suppressor of cytokine signaling 1 (SOCS1) [32–34]. Thus, miR-155 increases the JNK signaling pathway activity by suppressing the SHIP1 molecule activity; the product of this pathway is inflammation induction in ECs through the production of IL-8.

In addition, miR-155 can induce MAPK/STAT1/SATAT3 signaling pathway by suppressing the SOCS1 molecule activity, which can also cause inflammation in ECs by producing Pro-inflammatory cytokines. Subsequently, inflammation in ECs increases cell permeability, which leads to endothelial dysfunction through damage to intercellular connections [35, 36]. Exosome containing Diacyl glycerol (DAG) suppresses the endothelial Nitric Oxide Synthase (eNOS molecule activity, and increases the Egr1 and MMP2 molecules activity in the downstream of PKC-β stimulation pathway, by increasing the level of protein kinase C beta (PKC-β in EC; it results in inflammation induction in EC, endothelial dysfunction and finally CVD [37].

eNOS enzyme incites IL-10 production by producing NO, and induces the HO-1/CO pathway; due to the anti-inflammatory role of this cytokine, it can prevent inflammation. NO-induced HO-1/CO pathway also inhibits signal transmission in the downstream of Toll-like Receptor (TLR), which can also induce an anti-inflammatory effect in ECs [38, 39]. Due to the anti-inflammatory role of eNOS enzyme by NO production, the inflammatory process occurs in ECs by suppressing this enzyme; it results in increased permeability of cells, loss of intercellular connections and consequent defects in EC function.

In addition, PKC-β can upregulate the CD11c, CCL2 and IL-1β inflammatory markers in ECs by activating the ERK1/2 enzyme, thereby inducing inflammation in cells [40]. Expression of CD11c at the ECs level, and then binding to its ligand (ICAM-1) at the immune cell surface results in ERK/c-fos and JNK/C-JUN signaling pathways production in the downstream of this binding; the outcome is IL-8 production [41]. Expressed CCL2 on the ECs surface can also lead to IL-8 production via JNK signaling pathway, which occurs in its downstream in ECs [42]. The produced IL-8 can also induce inflammation through the above pathways and by activating the NF-Kβ transcription factor [43, 44].

Exosome containing C-Reactive Protein (CRP) molecule can also increase the activity of COX1/2 enzymes in ECs by activating the NF-Kβ transcription factor. By producing TXA2/PGH2 in ECs, inflammation and endothelial dysfunction are induced [45]. TXA2 induces inflammation in ECs via the Ca + 2/cnA/NFAT pathway. Prostaglandin (PG) molecule can also induce inflammation in ECs through the G protein-dependent pathway, and induction of the EPAC/Rap signaling pathway [46]. Following the onset of inflammation, by increasing the permeability of ECs, intercellular connections of these cells are destroyed, and consequently ECs malfunction occurs.

Also, exosomes produced from monocytes through Toll-like Receptor 4 (TLR4)/Myeloid Differentiation Primary Response gene 88 (Myd88) pathway can lead to inflammation in ECs and subsequent endothelial dysfunction, which can result in CVD induction [47]. Exosomes containing HMGB1 can also induce a signal in the downstream of the receptor signaling pathway by connecting to its receptor called RAGE. CDC42/RAC1/RH0A/GSK3β/AKT/ROCK signaling in the downstream of RAGE receptor is induced by DIAPH1 mediator, which activates production of SRF transcription factor by increasing the expression of Egr1/C-fos/Tagln genes; finally, it induces inflammation and endothelial dysfunction, and may also contribute to CVD [48].

Downstream activated AKT of exosome containing HMGB can also lead to inflammation in ECs via the mTORC1/4EBP1/P70S6K pathway [49]. In addition, in another pathway induced by AKT, the FOXO1 molecule can induce inflammation in ECs by activating the NF-Kβ transcription factor [50, 51]. Downstream activated GSK3β of this exosome can also activate the TCF transcription factor via the β-Catenin/APC/Axin/CK pathway, which translates IL-1β gene to produce the cytokine; subsequently it generates inflammation [52]. On the other hand, GSK3β can also induce inflammation in ECs via Nrf2/HO1 pathway [53].

Some other pathways induced in the downstream of exosomes containing HMGB1 can have anti-inflammatory effects in ECs. Thus, the Rac1/NADPH oxidase/ROS/p38 signaling pathway in the downstream of this exosome inhibits inflammation in ECs by upregulating the hemeoxygenase-1 (HO-1) molecule. Also in the other pathway, that occurs by RhoA/ROCK signaling pathway in the downstream of this exosome, it can prevent inflammation by inhibiting TNF-α function; thus it prevents permeability increment in ECs, and consequent endothelial dysfunction. So, HMGB1 exosome can have dual effects on ECs following the onset or absence of inflammation [54–56].

Exosome containing Free Fatty acid (FFA) can lead to inflammation in ECs via the NF-Kβ and JNK pathways. This exosome can also induce endothelial dysfunction by reducing NOS enzyme activity, and consequently reducing NO production. This defect in the function of ECs along with causing an inflammatory condition in these cells causes CVD [57, 58]. The NF-Kβ transcription factor, in addition

to inflammation induce endothelial dysfunction by inducing miR-31-5P, and subsequently inhibiting the eNOS enzyme; the result is an increased risk of developing CVD [59].

Contrary to the above findings, some other studies have shown that exosomes can prevent inflammation induction in endothelial cells and subsequent endothelial dysfunction, so these exosomes can be used as therapeutic targets in CVD [60]. Thus, exosomes containing Small Nuclear RNA host gene 9 (SNHG9) lncRNA act as a CeRNA by targeting mRNA of TNF receptor type-1 associated death domain protein (TRADD); it can prevent inflammation in ECs and subsequently endothelial dysfunction [61]. Some exosomes can also reduce NF-Kβ acetyl P65 transcription factor activity by increasing the SIRT1 expression in ECs, which in turn reduces inflammation. Finally, it increases ECs function and reduces CVD incidence [62].

The Role of Exosome in Oxidative Stress Induction

Studies show that exosomes can lead to ECs dysfunction through oxidative stress and induce CVD [63]. The exosome can activate the ROS/NOS signaling pathway by suppressing miR-223 in ECs. Downstream of this activated pathway, Grb/shc/MAPK/ET1 signaling leads to endothelial dysfunction and subsequently induces CVD [63, 64]. Other exosomes can also suppress eNOS enzyme by increasing Reactive Oxygen Species (ROS) production and consequently reducing NO production [65]. Since, the produced NO by eNOS enzyme can be Guanylate enzyme cofactor to produce cGMP, and the produced cGMP molecule through RAC-1/CORTACTIN/ARP2/3 signaling pathway leads to ECs function maintenance, the NO molecule by affecting cGMP production, indirectly affects ECs performance [66]. Therefore, with the reduction of NO production by ROS, ECs function is impaired; one of the consequences can be CVD development [67, 68].

In addition, exosome-induced oxidative stress with ROS production can activate NF-Kβ signaling pathway in ECs. Epigenetic changes resulting from activation of NF-Kβ transcription factor in the downstream of this pathway, increase the expression of VCAM, MCP-1, VEGF and MMP molecules on the ECs surface. Increased expression of these molecules reduces endothelium-dependent vasodilation, which can impair ECs structure and affects CVD development [69–71]. MCP-1/ICAM-1 molecules, which are expressed by increasing ROS production and subsequent epigenetic changes are associated with NF-Kβ signaling on ECs surface; they can alter ECs structure by increasing monocyte-endothelial adhesion, and subsequently induce atherosclerosis and other CVDs [72, 73].

Exosome-induced ROS can also increase contraction in ECs by activating the two signaling pathways of MLCK/MYPT1/MLC and Rho/Rho Kinase. By inducing this action in ECs, the structure of these cells is altered and lead to CVD, such as aortic aneurysm [74]. As it was mentioned before, exosomes are involved in endothelial dysfunction, and CVD induction by inducing oxidative stress by RNS. Thus, RNS molecules can lead to up regulation of endothelin-1 molecules. Following this action, Protein Kinase C is activated and the signaling pathway resulting from PKC activation can lead to vasoconstriction, thereby inducing a number of CVDs such as coronary spasm [75].

Also, exosomes containing High-Mobility Group Protein-1 (HMGP-1), miR-15-b-5p and miR 378-3P, which are produced from active platelets can induce Neutrophil Extracellular Trap (NET) formation by activating the Akt/mTOR signaling pathway [76]. Subsequently, the Rac2 molecule from the NET network can activate NADPH oxidase enzyme via the MAPK signaling pathway. This enzyme can also produce a type of ROS by converting O_2 to its free radical (O_2^-), which leads to endothelial dysfunction by damaging endothelial cells [77]. In addition, HMGB1 binding to TLR4 can activate the RIPK3/p-DRP1 signaling pathway, which results in ROS production by mitochondrial fission [78]. On the other hand, miR-15b can also regulate ROS production via Sirtuin 4 Pathway [79]. Therefore, produced exosomes from platelets can have different effects on ROS production and regulation.

Despite the role of some exosomes in inducing oxidative stress and subsequent endothelial dysfunction and CVD, some studies have shown that these exosomes can have adverse effects on oxidative stress; they prevent CVD, and can be used as a treatment strategy [80]. Thus, SRT 1720 exosome can increase antioxidant enzymes production by expressing SIRT1 molecule in ECs, and subsequently suppress oxidative stress in ECs; it results in homeostasis induction in ECs, cell function increment, and finally reduces CVD incidence.

In addition, the aforementioned exosomes through the expression of SIRT1 molecule can increase COX-2 expression, and induce homeostasis in ECs by increasing COX2-mediated vasodilation; this homeostasis can also neutralize the adverse effects of ROS and RNS molecules, that are involved in oxidative stress [62].

The Role of Exosome in Apoptosis

In addition to inflammation and oxidative stress induction, exosomes can induce endothelial dysfunction by causing apoptosis in ECs, and subsequently induce CVDs. Thus, the exosome containing HMGB1 can induce apoptosis in ECs via RAGE/Bax/Bcl-2/Caspase 3 pathway; it results in

cell apoptosis, endothelial dysfunction and ultimately CVD induction [81–83]. In addition, another study showed that an exosome treated with Advanced Glycation End products (AGEs) could lead to apoptosis in ECs via the RAGE/NADPH/ROS/p-JNK pathway [84, 85]. Exosomes containing Protein Disulfide Isomerase (PDI), which is produced from active platelets can also activate Bip molecules in ECs by binding to Calnexin. This molecule can also induce apoptosis in ECs through the ASK 1/TRAF 2/JNK/Caspase 3 pathway, and subsequently induces endothelial dysfunction [50, 51, 63]. In addition, the Bip molecule, which is activated in downstream of the PDI exosome activation pathway, can lead to Cytochrome C exit from the mitochondria via the eIF2/ATF4/CHOP/Bcl 2/Bax/Bak pathway [86].

On the other hand, the exosome containing Amyloid-β (Aβ) can send out Cytochrome C to the mitochondria by binding to the DR4/5 receptor in ECs via the FADD/Caspase 8/Bid/Bax/Bak signaling pathway; by cytochrome C removal from the mitochondria, apoptosis is induced in ECs [87]. The exosome containing TNF-α can also induce apoptosis in ECs via the FADD/Caspase 8/Bid/Cytochrome C and TRAF2/TRADD/Caspase 1/Caspase 3,6,7 signaling pathways [88]. On the other hand, exosomes containing FFA can also induce apoptosis in ECs via GSK-3β/Wnt/β-Catenin signaling pathway and p38MAPK [89, 90].

In addition, exosomes containing ox-LDL induce apoptosis in ECs by inducing the NADPH oxidase/ROS/p38 MAPK signaling pathway, thereby causing endothelial dysfunction [91]. Defect in ECs performance may lead to CVDs creation.

Some studies have shown that exosomes containing Growth Factor (GF) can also activate NADPH oxidase via the PKC/PI3K/Src/MAP Kinase/PAK signaling pathway. This enzyme can lead to ROS production. ROS is produced by NADPH oxidase, which is induced through the exosome containing GF; it can induce Redox signaling event by inhibiting PTEN, MKP-1 and PTP proteins. This signaling pathway contains Akt, c-Src, p38 MAPK, JNK, SAPK, ERK, PKC and ASK-1 signaling, which can activate Redox sensitive transcription factors such as NF-Kβ, AP-1, P53, Ets and HIF-1α. Consequently, these transcription factors can lead to ECs apoptosis by transcribing genes, called Redox sensitive genes, which include P21, SOD, and TRPM 2 [92]. On the other hand, exosomes containing GF can lead to Cytochrome C removal from the mitochondria via the PI3K/AKT/BAD/BAX pathway. Consequently, Caspase 3 and Caspase 9 are activated, which start apoptosis in ECs [93].

In addition, the exosome containing Rac-1 via the NOX 2/ROS/P38MAPK signaling pathway can lead to mitochondrial dysfunction, which is followed by caspase activation; it can induce apoptosis in ECs [94]. The exosome containing miR-122 can also play effective role in apoptosis induction in ECs by regulating the XIAP/ERK/Caspase8/Caspase3, GATA4/Bax/Bcl-2 and PTEN/PI3K/Akt signaling pathways [95].

Therefore, exosomes microRNAs are effective in CVDs; by designing appropriate target therapies, these exosomes can be used as a treatment strategy (Table 1). As explained in the text, in addition to miRNA, exosomes also contain other contents such as proteins, lipids and enzymes, which can be effective in inducing CVD or cardioprotection. Therefore, identifying the signals resulting from these contents can also be effective for CVD treating, by designing appropriate target therapies (Table 2).

As explained above, endothelial dysfunction occurs by apoptosis induction in ECs, which can be effective in causing CVD. Therefore, by identifying the effective signaling pathways, in which exosomes can induce apoptosis in ECs, endothelial dysfunction and CVDs can reduce mentioned consequences.

Table 1 Association between miRs and cardiotoxicity

miR	Target	Potential mechanism	Ref
miR-143	IGF-IR	miR-143 overexpression inhibits angiogenesis in cardio myocytes via the IGF-IR/NO pathway, and subsequently induces MI	[96, 97]
miR-21	PTEN	miR-21 can play an effective role in the formation of atherosclerotic plaques by inhibiting induced PTEN from AKT pathway	[98]
miR-21-3P	SORBS2/PDLIM5	miR-21-3P can play an important role in inducing hypertrophy in cardio myocytes by inhibiting the activity of the two molecules, SORBS2 and PDLIM5	[99]
miR-126	PI3K/AKT	miR-126 can inhibit apoptosis induction in vascular endothelial cells by targeting the PI3K/AKT signaling pathway	[84, 85, 98]
miR-210	ISCU/SIRT3	miR-210 can indirectly prevent apoptosis induction and oxidative stress damage in cardio myocytes by inhibiting the expression of the two molecules, ISCU and SIRT3	[100, 101]
miR-30a	Beclin-1/ATG-12	miR-30a can regulate autophagy in cardio myocytes by affecting Beclin-1 and ATG-12 molecules	[30, 102]

miR microRNA, *IGF-IR* insulin-like growth factor 1 receptor, *NO* Nitric oxide, *MI* myocardial infarction, *PTEN* phosphatase and tensin homolog, *SORBS2* sorbin and SH3 domain-containing protein 2, *PDLIM5* PDZ and LIM domain 5, *PI3K* phosphatidylinositol 3-kinase, *ISCU* iron-sulfur cluster assembly scaffold protein, *SIRT3* Sirtuin-3, *ATG-12* Autophagy related 12

Table 2 Role of other exosome contents (excluding miRNA) in Cardiovascular Disease and Cardiotoxicity

Exosome contents	Target	Potential mechanism	Ref
HSP90	Akt signaling	HSP90 through the Akt signaling pathway can activate the Caspase-9 molecule; it induces apoptosis in cardio myocytes and plays an important role in heart failure	[103, 104]
HSP75	TAK/p38, JNK and Akt signaling pathways	HSP75 can reduce hypertrophy and fibrosis in cardio myocytes by suppressing the activation of TAK/P38, JNK, Akt signaling pathways	[105]
HMGB-1	PI3K/Akt/mTOR pathway	HMGB-1 can induce the growth and proliferation of cardio myocytes in CVD by activating the PI3K/Akt/mTOR pathway	[15]
CXCR4	IGF-1α/Akt/Caspase3	Exosome containing CXCR4 improves cardio myocyte function after MI through upregulation of IGF and AKt molecules and downregulation of caspase3	[106]
PAPP-A	Akt and ERK1/2 phosphorylation	Exosome containing PAPP-A activates the Akt/ERK1/2 pathway through IGF-1 secretion; it stops apoptosis in cardio myocytes by suppressing caspase activity	[107]
TNF-α	Sirt1/AMPKα2/eNOS and RAC1/PAK2 pathways	TNF-α containing exosomes can inhibit angiogenesis and MI induction by inhibiting the sirt1/AMPKα2/eNOS and RAC1/PAK2 pathways	[108]
Mst1	Hippo pathway	Mst1 through the Hippo pathway can inhibit autophagy and induce apoptosis in cardio myocytes in diabetic patients	[109]
NOX4	ROS	NOX4 via the ROS/Akt/mTOR/NF-Kβ pathway can induce hypertrophy in cardio myocytes, and subsequently induce heart failure	[6, 7]
NOX2	PTEN/BCL-1	NOX2 increases Bcl2 expression and inhibits PTEN by activating the PI3K/Akt pathway, and subsequently inhibits apoptosis induction	[110]
LDL	TLR4/NF-Kβ	Oxidized LDL induces apoptosis in cardio myocytes by regulating the TLR4/NF-Kβ pathway	[57, 58]
LDL	Akt/FGF2 pathway	Oxidized LDL via the Akt-FGF2 pathway leads to DNA methylation; subsequently it induces coronary toxicity	[111]
LDL	LOX-1	Oxidized LDL induces oxidative stress in vascular endothelial cells by increasing LOX-1 expression and regulating the PI3K/Akt/eNOS pathway	[112]

HSP heat shock protein, *JNK* Jun N-terminal Kinase, *HMGB-1* high mobility group box 1, *PI3K* phosphatidylinositol-4,5-bisphosphate 3-kinase, *mTOR* mammalian target of rapamycin, *CVD* cardiovascular disease, *CXCR4* CXC chemokine receptor, *IGF-1* insulin-like growth factor-1, *MI* myocardial infarction, *PAPP-A* pregnancy-associated plasma protein-A, *ERK* extracellular signal-regulated kinase, *TNF-α* tumor necrosis factor-alpha, *Sirt1* sirtuin (silent mating type information regulation 2 homolog) 1, *AMPK* adenosine monophosphate-activated protein kinase, *eNOS* endothelial nitric oxide synthase, *RAC1* Ras-related C3 botulinum toxin substrate 1, *PAK2* p21 (RAC1) activated kinase 2, *Mst1* macrophage stimulating 1, *NOX* NADPH oxidase, *NF-Kβ* nuclear factor kappa-beta, *PTEN* phosphatase and TENsin homolog deleted on chromosome 10, *BCL2* B-cell lymphoma 2, *LDL* low-density lipoprotein, *TLR4* toll-like receptor 4, *FGF2* fibroblast growth factor 2, *LOX-1* lectin-like ox-LDL receptor

Conclusion

Studies have shown that exosomes can lead to endothelial dysfunction by inducing inflammation, oxidative stress, and apoptosis in ECs. With the induction of dysfunction in ECs, one of the consequences of this event is CVDs occurrence. Thus, by identifying signaling pathways, in which exosomes induce inflammation, oxidative stress and apoptosis in ECs, can prevent endothelial dysfunction and CVDs; CVDs can be reduced by designing appropriate target therapies and can be used as a treatment strategy (Table 3).

Table 3 Therapeutic effects of exosomes in Cardiovascular Diseases

Source	Type of disease	Target	Mechanism	Ref
MSC	MI	NF-Kβ/TNF-α	The lncRNA MALAT1 in the derived exosome from MSC cell can prevent cardiac dysfunction by inhibiting the NF-Kβ/TNF-α signaling pathway	[113, 114]
MSC	MI	Sirt1	The lncRNA KLF3-AS1 in the derived exosome from MSC cell can reduce cellular apoptosis in MI by regulating the Sirt1 molecule expression	[115]
MSC	MI/RI	PI3K/AKT	The MSC-derived exosome can reduce oxidative stress by increasing ATP levels, and activating the PI3K/AKT signaling pathway; thereby it prevents I/R damage	[116]
iPSC	MI	Caspase3/7	iPSC-derived exosome can inhibit apoptosis induction and oxidative stress, following MI in myocardial cells by inhibiting Caspase 3/7 activity	[117]
CPC	MI	ephrin A3/PTP1b	CPC-derived exosome can inhibit apoptosis in cardio myocytes, following MI by downregulation of ephrin A3 and PTP1b molecules	[118]
CDC	MI	Irak-1/Traf6	The CDC-derived exosome can inhibit TLR signal transduction by downregulation of Irak-1 and Traf6 molecules, thereby preventing pro-inflammatory cytokines production in cardiac muscle cells and MI-induced damages	[119]
DC	I/RI	PI3K/mTOR	The DC-derived exosome contains HSP70 can induce balance between Treg and TH17 cells by stimulating the PI3K/mTOR signaling pathway, thereby reducing I/RI damages	[120, 121]

MSC mesenchymal stem cell, *MI* myocardial infarction, *NF-Kβ* nuclear factor kappa B, *TNF-α* tumor necrosis factor-α, *lncRNA* long non-coding RNA, *MALAT1* metastasis-associated lung adenocarcinoma transcript 1, *Sirt1* silent mating type information regulation 2 homolog-1, *KLF3-AS1* KLF3 Antisense RNA 1, *MI/RI* myocardial ischemia/reperfusion (I/R) injuries, *ATP* adenosine triphosphate, *PI3K* Phosphatidylinositol 3-kinase, *iPSC* induced pluripotent stem cell, *CPC* cardiovascular progenitor cell, *PTP1b* protein-tyrosine phosphatase 1b, *CDC* cardiosphere-derived cell, *Irak-1* interleukin 1 receptor-associated kinase 1, *Traf6* TNF receptor-associated factor 6, *TLR* toll-like receptor, *DC* dendritic cell, *I/RI* ischemia/reperfusion injuries, *mTOR* mammalian (or mechanistic) target of rapamycin, *HSP70* heat shock protein 70

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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