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microRNAs shuttled by mesenchymal stromal cell-derived exosomes in coronary artery disease: A systematic review of preclinical studies

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Abstract

Introduction: Coronary artery disease (CAD) is a life-threatening cardiac condition with high morbidity and mortality worldwide. This systematic review article highlighted the therapeutic roles of mesenchymal stromal cells (MSCs)-derived exosomal microRNAs (exo-miRs) in preclinical models of CAD.

Methods: A comprehensive search was conducted on PubMed, Web of Science, Scopus, and Google Scholar to identify relevant publications until 04 Apr 2025. The literature review focuses on the origin of MSCs, the technique employed for exosome extraction and identification, the route and frequency of exosomal administration, the mechanisms through which exo-miRs regulate paracrine activity, and their impact on cardiac outcome.

Results: After meticulous evaluation, fifty-six studies were deemed eligible for inclusion in this systematic review. Bone marrow-derived MSCs were the most commonly utilized cell type in the preclinical studies. The majority of studies employed the ultracentrifugation method for exosome isolation from MSCs. The administration of exosomes was primarily achieved through a single intramyocardial injection, utilizing a wide range of exosome concentrations (ranging from 0.02-400 μg/μL).

Conclusion: The included studies predominantly have reported the anti-inflammatory, anti-apoptotic, angiogenic, antifibrotic, and reparative effects of MSC-exo-miRs, especially under hypoxic conditions. These findings support the capacity of MSC-exo-miRs to regulate the immune system and facilitate cardiac recovery following an injury.

Introduction

Coronary artery disease (CAD), also called ischemic heart disease, is a life-threatening cardiac condition characterized by impaired blood flow in the coronary arteries, primarily due to atherosclerosis. This process leads to the narrowing and stiffening of the arteries, limiting oxygen-rich blood supply to the heart muscle and potentially causing myocardial ischemia, angina, myocardial infarction (MI), or ultimately heart failure. Despite advances in medical and surgical therapies, the burden of CAD continues to rise,[1] necessitating the exploration of new therapeutic strategies and biomarkers for both early diagnosis and effective treatment.

The role of multipotent mesenchymal stromal cells (MSCs) in preventing and treating CAD has become more prominent. MSCs can self-renew and differentiate into various types of cells thanks to their multipotency. Clinical studies have shown that MSC therapy can compensate for the limitation of the repair ability of myocardial cells. These cells promote angiogenesis and neovascularization, limit the infarcted area, regulate the immune system, and prevent fibrosis. Moreover, these cells can differentiate into smooth muscle cells, endothelial cells, and pericytes, generally improving heart function.[2-5]

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MSCs secrete many paracrine factors, including growth factors, cytokines, chemokines, and extracellular vesicles (EVs), mainly exosomes, having multiple implications in regulating key biological processes. These effects include the modulation of immune responses, migration and proliferation of effector cells, and inhibition of apoptosis. Various components, such as proteins, nucleic acids [DNA, mRNAs, non-coding microRNAs (miRs/miRNAs), long non-coding RNAs (LncRNAs)], lipids, and enzymes are encapsulated within exosomes and contribute to preserving and mediating the functional effects of their parent cells.[6] MSCs-derived exosomes are advantageous over parental MSCs due to lower immunogenicity, better crossing of membrane barriers, not being trapped in capillary beds, a higher safety profile, and less possibility of ectopic tumor formation. By transferring the contents of stromal cells to nearby or distant cells, exosomes present their biological effects and play a vital role in disease processes. These properties make MSC exosomes more favorable compared to the original cells.[7]

microRNAs have crucial functions in regulating gene expression.[8] Dysregulation of miR expression has been implicated in the pathophysiology of CAD,[9,10] causing inflammation, vascular remodeling, and endothelial dysfunction. As a result, miRs have garnered significant interest as potential diagnostic and therapeutic targets in cardiovascular diseases. Integrating findings from the study on human epicardial adipose tissue-exos-miRs profiles provides deeper insights into their roles in CAD pathophysiology and highlights their diagnostic and therapeutic potentials,[11] which can complement preclinical studies on MSC-exos-miRs. The shuttling of miRs via MSC-derived exosomes represents a critical mechanism through which these stem cells exert their beneficial effects, particularly in the context of tissue repair and regeneration in CAD. This systematic review article highlights the therapeutic roles of MSC-exosomal miRs in CAD. Primary outcomes were cardiac function, apoptosis, inflammation, and fibrosis.

Methods

Search strategy and selection of papers

This systematic review was conducted on studies reporting the impact of exosomal miRs derived from MSCs (MSC-exos-miRs) on *in vivo* and *in vitro* cardiovascular models. This study was designed following PRISMA. A librarian searched PubMed, Web of Science, Scopus, and Google Scholar until 04 April 2025. Table S1 (Supplementary file 1) presents the terms and MeSH-based keywords used for the search strategy.

Inclusion and exclusion criteria

Original research articles in English describing preclinical *in vitro* and animal models with CAD using exosomes of MSCs as experimental intervention were included. MSC-derived exosomal miRs used for the regeneration and treatment of cardiovascular injuries, such as myocardial ischemia-reperfusion (I/R) damage, MI, acute coronary syndromes (ACS), vascular calcification, and atherosclerosis were included since they are either causes, complications, or related conditions to CAD. Coronary artery disease is the overarching term that includes the long-term pathological process and risk factors, while ACS is a critical and acute manifestation of CAD. Therefore, CAD is the most appropriate term to encompass the entire spectrum of related conditions. Review articles, abstracts, and articles written in a language other than English were excluded. Moreover, retracted articles and the ones with low quality were excluded. Two separate researchers (S.M, A.A) reviewed all the records from the primary search of the databases. The included studies by two researchers were matched and compared, and the third researcher controlled the controversial studies.

Extracting data

Two researchers (S.M and S.M.M.M) independently reviewed the included studies. They extracted the articles' data regarding the type of study, animal/cellular CAD models, sample size, the source and origin of MSCs, the technique employed for exosome extraction and identification, the route, frequency, and dosage of exosomal administration, the mechanisms through which exo-miRs regulate paracrine activity, and their impact on cardiac outcome, and therapeutic potential. These data were controlled by the other researchers. The detailed extracted data of the included studies are presented in Tables 1 and 2.

Assessment of the quality of studies

The quality of the included studies was assessed based on the ARRIVE guidelines 2.0.[12] Besides, the risk of bias in studies was evaluated by SYRCLE's risk of bias tool.[13]

Results

Included studies

The primary database search resulted in 1300 articles, out of which 578 were eliminated due to duplicate records. Some studies (n = 565) were excluded based on the subject and abstract screening. Forty-seven studies were excluded due to the unavailability of the full text. One hundred and ten full texts were reviewed and screened to finalize the included studies. A total of 56 studies were included in the review. Fig. 1 shows the detailed PRISMA flow diagram of the literature search.

Characteristics of the included studies

Preclinical models of CAD were MI (n = 23),[14-36] I/R (n = 17),[37-53] ischemia (n = 4),[54-57] hypoxia (n = 1),[58] hypoxia/reperfusion,[59] ischemia/hypoxia,[60] atherosclerosis

Table 1. Therapeutic role of MSC-derived exosomal microRNAs in CAD models

Authors	Model	CAD	Animals	Cells	Sample size & groups	MSC donor organism	Source of MSCs	MSCs preconditioning	Outcome	Therapeutic potential
Yang et al (2021)[14]	*In vitro, In vivo*	MI	SD male rats	Rat primary CMECs under hypoxia (0.3% O2)	Sham/ MI/ MI + hMSCs- Exo	Human	American Type Culture Collection (ATCC, USA	Transfection with miR-543 inhibitor, pCDNA3.1-COL4A1, and their negative controls	↑LVEF ↓LVEDD ↓Infarct size	Diminished infarction size attenuated MI-induced injuries ↑Ki-67 expression
Wang et al (2023)[15]	*In vitro, In vivo*	MI	C57BL/6J mice	HUVECs	30: Sham/ MI/ MI + ADSC-Exo	Mice	AD-MSCs	Transfected with a miRNA-205 inhibitor	↑EF and FS ↓Cardiomyocyte apoptosis ↑Number of neo-vessels	↑Angiogenesis ↑cardiac function ↓Fibrosis
Sun et al (2022)[16]	*In vitro, In vivo*	MI	C57BL/6J male mice	Neonatal mouse ventricle myocytes	30: Sham/ MI/ MI + exosome	Male C57BL/6J mice	BM-MSCs	Transfection with miR-182-5p mimics and control	↓LVEDD and LVESD ↑LVEF and LVFS	Anti-inflammatory on MI
Pu et al (2021)[17]	*In vivo*	MI	Male SD rats	H9c2 cells	36: PBS/ Exo/ Exo-NC/ Exo-miR-30e	Tibia and femur of healthy rats	BM-MSCs	Infected with LV-miR-30e-5p or empty vector with a MOI of 20	↑LVEF and LVFS ↓LVEDD, LVESD, LVVs, and LVVd	↓Heart failure in rats with MI
Wang (2017)[18]	*In vitro, In vivo*	MI	Male C57BL/6J mice	Human fibroblasts and HUVECs	Sham/ control/ fibroblast-EV/ MSC-EV/MSC- scramble-EV/ MSC-siR210-EV	C57BL/6 mice	BM-MSCs	-	↑LVEF and LVFS ↑Capillaries in peri-infarct regions	Angiogenesis on MI
Xiao et al (2018)[19]	*In vitro, In vivo*	MI	Male C57BL/6J mice	Neonatal mouse ventricle myocytes	27: Sham/MI/MI + MSC	-	BM-MSCs	-	↓Autophagic Flux	Cardioprotective effects: ↓Inflammation in the myocardial repair process
Peng et al (2020)[20]	*In vitro, In vivo*	MI	BALB/c mice	Primary cardiomyocytes from adult BALB/c mice	50: sham, I/R I/, I/R + EXO, I/R + EXO/inhibitor NC,I/R + EXO/miR-25 inhibitor	BALB/c mice	BM-MSCs	-	↓Infarct area ↓Upregulation of IL-1β, IL-6, and TNF-α	Cardioprotective effects: ↓inflammation in the myocardial repair process
Zheng et al (2022)[21]	*In vivo*	MI	SD rats	-	100: sham/ MI/ Blank-Ex/ mimic-NC-Ex/miR-29b-3p mimic-Ex/ oe-NC / oe-ADAMTS16/ miR-29b-3p mimic-Ex + oe-NC/ miR-29b-3p mimic-Ex + oe- ADAMTS16	Femur and lumen bone of rats	BM-MSCs	-	↑Cardiac hemodynamic function	↑Angiogenesis and ventricular remodeling MI
Xiong et al (2022)[22]	*In vitro, In vivo*	MI	SD rats	H9c2 cells	Sham/AMI/ MSCs-Exo/ MSC^{TXL}-Exo	Tibia and femur of male SD rats	BM-MSCs	Transfected with miR-146a-5p inhibitors or its negative control	↓Apoptotic cardiomyocytes ↓Levels of pro-apoptotic Bax and cleaved-Caspase 3 and inflammatory cytokines ↑LVEF ↓Infarct size	Cardiac repair after MI

Table 1. continued

Authors	Model	CAD	Animals	Cells	Sample size & groups	MSC donor organism	Source of MSCs	MSCs preconditioning	Outcome	Therapeutic potential
Wang et al (2021)[23]	*In vitro, In vivo*	MI	C57BL/ 6JNifdc mice	Cardiomyocytes	32: Sham/ MI group/ Exo-NC/ Exo-inhibitor	Mouse	AD-MSCs	Transfected with NC inhibitor or miR-671 inhibitor	↓Myocardial fibrosis ↓Concentrations of IL-6 and TNF-α in the MI model mice	MI
Li et al (2019)[24]	*In vivo*	MI	Male SD rats	-	20: Sham/ Model/ BMSC-Exos/ BMSC-301- Exos	Male SD rats	BM-MSCs	Transfection with miR-301 mimics	↑LVEF and LVFS ↓LVESD and LVEDD	↓Myocardial autophagy protects against MI
Zhu et al (2022)[25]	*In vitro, In vivo*	MI	Male C57BL/6 mice	HMVEC transduction with Lenti/ F1H1 and a corresponding control	66: PBS, Exo, Exo/ anti-miR-Con, Exo/ anti miR-31	Human	UC-MSC	Transduced with a lentiviral antimiR-31	↑Cardiac function	↓MI
Wan et al (2022)[26]	*In vivo*	MI	c57BL/6 mice	-	198: PBS, MSCs-EVs, EVs-NC, EVs-miR-200b-3p, MSCs-EVs + lentivirus-expressing control short hairpin RNA, MSCs-EVs + lentivirus-expressing BCL2L11 short hairpin RNA, MSCs-EVs + overexpressed-negative lentivirus, MSCs-EVs + BCL2L11-overexpressing lentivirus, EVs-miR-200b-3p + Neg, EVs-miR-200b-3p + BCL2L11	-	MSCs (Shanghai Zhongqiao Xinzhou Biotechnology Co.)	Transfected with miRNA mimic NC or miR-200b-3p mimic	↓LVEDD and LVESD ↑LVEF and LVFS	↓MI-induced apoptosis of cardiomyocytes and inflammation
Xuan et al (2019)[27]	*In vitro, In vivo*	MI	NOD/SCID mice C57/B6 mice	Human dermal fibroblast cell line (CC-2511) and lung fibroblast cell line (CC-2512)	9: PBS, EV-hiPSC, or EV-CPC^{ISX-9}	Human	iPSC cell line	Transfected with 25 nM miR-373 mimic, anti-miR-373, negative controls, and RNAiMAX	↑CM Proliferation and angiogenesis Reversed Ventricular Remodeling in Mice Post MI	↓Fibrosis ↑Angiogenesis in Infarcted Heart
Fu et al (2020)[28]	*In vitro, In vivo*	MI	Female SD rats	H9c2 cells	40: Sham/ PBS/ EXO-control/ EXO-338 mimic	Rat femur and tibia	BM-MSCs	Transfection of miR-338 mimics or negative control	↓LVESD and LVEDD ↑EF and FS	↓Cardiomyocyte apoptosis in MI
Ma et al (2018)[29]	*In vitro, In vivo*	MI	Female C57BL/6J mice	HUVECs	Saline control/ miR-132/ Exo-null/ Exo-132	Bone cavity of mouse femurs and tibias	BM-MSCs	-	↑LVEF	↑Angiogenesis in MI
Huang et al (2020)[30]	*In vitro, In vivo*	MI	Male SD rats	H9C2 cells under hypoxia	105: AMI + PBS, AMI + hucMSC-exo, AMI + in-NC/hucMSC-exo, AMI + in-miR-19a/hucMSC-exo, AMI + NC/hucMSC-exo, and AMI + miR-19a/hucMSC-exo	Human	hUC-MSCs	Transfected with miR-19a mimic, miR-19a inhibitor, and NC vectors	The cardiomyocytes are arranged regularly	↓Acute MI

Table 1. continued

Authors	Model	CAD	Animals	Cells	Sample size & groups	MSC donor organism	Source of MSCs	MSCs preconditioning	Outcome	Therapeutic potential
Yang et al (2022)[31]	*In vitro, In vivo*	MI	SD rats	Rat cardiomyocyte H9c2 cells	60: Sham /MI + PBS/ MI + Vs-NC/MI + EVs-miR-223/ MI + EVs-miR-223 + pcDNA3.1-P53/ MI + EVs-miR-223 + pcDNA3.1-S100A9	Human	hUC-MSCs	Transfection with miR-223 mimic or NC mimic	↑Cardiac function	↓Fibrosis and inflammation of cardiomyocytes ↑Angiogenesis
Pu et al (2023)[32]	*In vitro, In vivo*	MI	SD rats	HUVECs	20: Sham/MI/M-EVs/N-EVs	Human	hUC-MSCs	-Incubation with 2.25 μM NMN for 48 h -Transfected with miR-210-3p inhibitor or negative control	↓Fibrosis size and cell apoptosis in infarcted hearts	↑Angiogenesis MI
Ji et al (2024)[33]	*In vitro, In vivo*	MI	Male SD rats	H9c2 cells	40: Sham/ AMI/ Control-Exo/ miR-21-5p-Exo	Rat	MSCs (CP-R131)	Transfected with miR-21-5p inhibitor or NC inhibitor	↓Myocyte apoptosis and fibroblast proliferation Reverse ventricular remodeling	RNA-based therapies in cardiovascular disease
Wang et al (2024)[34]	*In vitro, In vivo*	MI	Mice	Cardiac muscle cells	-	-	BM-MSCs	-	↓Expression of inflammatory cytokines	↑Cardiac function ↓Expression of inflammatory cytokines
You et al (2024)[35]	*In vivo, in vitro*	MI	C57B/6 male mice	H9C2 cells under hypoxia (1% O_2)	Sham/MI/ MI + exos/ MI + exos + miR-let-7i-5p inhibitor/ MI + exos + miR-let-7i-5p inhibitor NC	SD mice	BM-MSCs	Transfected with MiRNA-let-7i-5p mimic, miRNA-let-7i-5p mimic NC, miRNA-let-7i-5p inhibitor, or miRNA-let-7i-5p inhibitor NC	↓Myocardial apoptosis ↓Infarction progression	↓Myocardial apoptosis ↓MI progression ↓MI
Zhu et al (2022)[36]	*In vitro, In vivo*	MI	Male C57BL/6 J mice	HUVECs	10: PBS, Exo, Exo/ antimiR-Cont, Exo/ antimiR-31	Human	hAD-MSC	Transduction with a lentiviral antimiR-31 or antimiR-control	↑Cardiac function ↓Infarct size ↑Angiogenesis	Angiogenesis on MI
Zhao et al (2019)[37]	*In vivo*	I/R	C57BL/6 mice	RAW264.7 cells or peritoneal macrophages	Untreated/ LPS/ LPS + NC-mimic/ LPS + miR-182-mimic	Mouse	BM-MSCs	Transfection with miR-182 inhibitor NC inhibitor	↑EF and FS	Anti-inflammatory on MI
Chen et al (2020)[38]	*In vitro, In vivo*	I/R	Male SD rats	I/R myocardium cells	20: Sham, I/R, Exo-67, Exo-125b	Femur and tibia of 2 male SD rats	BM-MSCs	Transfected with Lv-cel-miR-67 or Lv-miR-125b	↑LVEF, LVFS, and LVSP ↓LVESD, LVEDD, and LVEDP	Protects against myocardial I/R
Mao et al (2022)[39]	*In vivo*	I/R	Male SD rats	-	Sham, I/R, I/R ± Exo, I/R ± NC-Exo, I/R ± miR-183-5p-Exo, I/R ± anti-miR-183-5p-Exo	6 male SD rats	BM-MSCs	Transduction with LV-miR-183-5p, LVanti-miR-183-5p, or NC	↓MI size	↓Apoptosis and oxidative stress in I/R cardiomyocytes ↑Cardiac function Protecting against MI/R injury

Table 1. continued

Authors	Model	CAD	Animals	Cells	Sample size & groups	MSC donor organism	Source of MSCs	MSCs preconditioning	Outcome	Therapeutic potential
Chen et al (2021)[40]	*In vitro, In vivo*	I/R	SD rats	H9c2 cells	Control, I/R, I/R + exosome, I/R + miR-143-3p KD exosome, I/R + miR-143-3p OE	Femur and tibia of SD rats	BM-MSCs	Transfection with NC mimic, miR-145-5p mimic, NC inhibitor, or miR-145-5p inhibitor	↓Apoptosis and autophagy of rat cardiomyocytes	Myocardial I/R injury regulating autophagy
Wang et al (2022)[41]	*In vitro, In vivo*	I/R	Male SD rats	H9c2 cells under H/R or transfection	30: Sham group, Exo-miR-455-3p, I/R, I/R + Exo-miR-455-3p	Rats	BM-MSCs	-Stimulated with H/R (O_2 < 1%, hypoxia 48 h, reoxygenation 24 h) -Transfection with MEKK1 overexpression plasmid, miR-455-3p mimics, or miR-455-3p inhibitor	↓Myocardial cell apoptosis	Myocardial I/R damage
Zhang et al (2021)[42]	*In vivo*	I/R	SD rats	-	120: Sham, model, normal BMSC-exos, Hypoxic exos, exos-miR-98-5p Antagomir, miR-98-5p Agomir, miR-98-5p Agomir NC, miR-98-5p Agomir + oeTLR4	6 male SD rats	BM-MSCs	-Stimulated by hypoxia (1% O_2 for 24 h) -Transfected with miR-98-5p antagomir	↓LVEDP ↑LVSP	↓Myocardial I/R injury
Li et al (2020)[43]	*In vitro, In vivo*	I/R	Male C57BL/6 N mice	Neonatal rat cardiomyocyte transfected with miR-NC or miR-29c mimic	I/R + PBS, I/R + Nor-exo, and I/R + Hypo-exo	Mouse	BM-MSCs	H/R (O_2 < 1%, hypoxia 48 h, reoxygenation 24 h)	↓Infarcted size	↓Excessive Autophagy ↓Cardiac I/R Injury
Gao et al (2023)[44]	*In vitro, In vivo*	I/R	Female C57BL/6 mice	-Murine macrophage RAW 264.7 cells stimulated with 100 ng/mL LPS -Primary neonatal mouse cardiomyocytes, cardiac fibroblasts, and endothelial cells isolated from C57BL/6	18: Sham, I/R control, MSC, MSC-Exo, NC agomir, miR-125-5p	Mouse	BM-MSCs	Transfected with mmu-miR-125a-5p antagomir and NC antagomir for 24 h	↑Cardiac function on day 28 post-myocardial I/R	↑Recovery from myocardial I/R injury
Zou et al (2020)[45]	*In vitro*	I/R	-	H9c2 cells transfected with 10 pmol/mL miR-149, let-7c, or control mimics	Control, H/R, H/R + Exo, H/R + NC,H/R + mimics-149, H/R + mimics-7c	Rat	BM-MSCs	H/R (Hypoxic atmosphere for 4 h followed by reoxygenation for another 24 h)	↓H/R-induced apoptosis	Cardiomyoblast H/R injury
Wei et al (2019)[46]	*In vitro, In vivo*	I/R	C57BL/6 male mice	PBMCs transfected with the miRNA-181a precursor, NC, mimic inhibitor, or inhibitor NC	12: Sham /PBS/ WT-EXO, miRNA- 181a-EXO	Human	UC blood-MSCs	Transduction with GV309-neg-EGFP-LV or GV309-miRNA-181a-EGFP-LV	↑EF and FS	Influenced the inflammatory response after myocardial I/R injury
Yue et al (2022)[47]	*In vitro, In vivo*	I/R	Male C57BL/6 mice	-H/R-exposed myocardial cells co-incubated with Exo-mimic-NC, exo-miR-182-5p mimic, Exoinhibitor-NC, or exo-miR-182-5p inhibitor -HUVECs	30: Sham, I /R, I/ R + Exo-mimic-NC, I/ R + Exo- miR-182-5p mimic	Well-grown C57BL/6 mice	BM-MSCs	Treated with 10% GW4869 or 0.005% DMSO	↓MI size and recovery of cardiac function	↓I/R-evoked inflammation, apoptosis, and injury

Table 1. continued

Authors	Model	CAD	Animals	Cells	Sample size & groups	MSC donor organism	Source of MSCs	MSCs preconditioning	Outcome	Therapeutic potential
Ou et al (2020)[48]	*In vitro, In vivo*	I/R	Male SD rats	Neonatal cardiomyocytes under hypoxia (1% O_2) and transducted with 1000 ng/ mL $EV^{agomir\text{-}NC}$, $EV^{miR\text{-}150\text{-}5p\text{-}agomir}$, $EV^{antagomir\text{-}NC}$, or $EV^{miR\text{-}150\text{-}5p\text{-}antagomir}$	72: I/R,I/R + sh-NC, I /R + sh-TXNIP, I/ R + EVmiR-150-5pagomir, I/ R + EVagomir-NC, I/ R + EVmiR-150-5p-agomir + oeTXNIP	Healthy SD rats	MSCs	Transduction with agomir-NC (50 nM), miR-150-5p-agomir (50 nM), antagomir-NC (100 nM), or miR-150-5p-antagomir (100 nM)	↓LVEDV, LVEDD, LVESV, and LVESD ↑LVEEF and LVEFS	↓Apoptosis and myocardial I/R injury
Tang et al (2020)[49]	*In vitro, In vivo*	I/R	Male SD rats	Primary cardiomyocytes under H/R for 18 h	Sham, I/R, I/R + PBS, I/R + exosome	Human	MSCs	miR-320b mimic and its control	-	Anti-pyroptosis ↓I/R Injury
Chen et al (2024)[50]	*In vivo, in vitro*	I/R	SD rats	H9c2 cells under H/R (95% N_2 and 5% CO_2 for 3 h) and 100 nM miRNA/NC inhibitor	Control /model/ BMSC exo/ BMSC exo + anti-miR-93-5p /BMSC exo + DSD/BMSC exo + DSD + anti-miR-93-5p	Rat	BM-MSCs	H/R Pretreated with DSD or miRNA inhibitor	↓Cardiac damage	↓Activation of the TXNIP/NLRP3/ Caspase-1 signaling pathway and cardiomyocyte pyroptosis
Du et al (2024)[51]	*In vivo, in vitro*	I/R	SD male rats	H9C2 cells under hypoxia (95% N_2 and 5% CO_2)	40: Sham, I/R + PBS, I/R + BMSC- Exo, I/R + BMSC-Exo-25-3p	20 male rats	BM-MSCs	-	↓Cardiac infarct size ↓Incidence of malignant arrhythmias ↓Myocardial enzyme activity	↓Inflammatory response ↓Myocardial I/R injury
Gu et al (2024)[52]	*In vivo, in vitro*	I/R	Male C57BL/6 mice	H9c2 cells under hypoxia (5% CO_2 and 95% N_2 for 6 h) pretreated with DSPE-PEG-CMP, DSPE-PEG-CMP-EXO, DSPE-PEG-CMP-miR302-EXO, or miR302	30: Control / model/ DSPE-PEG-CMP/ DSPE- PEG- CMP-EXO/ DSPE- PEG-P- miR302-EXO/ miR302	Tibia and femur of C57BL/6 mice	BM-MSCs	-	↓Myocardial I/R injury	↓Cell apoptosis, inflammation ↑Cardiac function
Lee et al (2025)[53]	*In vivo, in vitro*	I/R	C57BL/6J mice	Embryonic rat cardiomyocyte-derived H9c2 cardiac myoblasts exposed to PM (10 µg/ mL or 50 µg/mL) for 6 h, H/R (hypoxia (1% O_2) for 6 h followed by reoxygenation for 12 h), and transfected with miR-221 and miR-222 mimics or inhibitors (100 nM/well)	Control, PM + I/ R, PM + I/ R + ADSC-Exo, PM + I/ R + miR-221 miR-222 mimics	Human	AD-MSCs	-	↓Cardiomyocyte mitophagy and apoptosis	↓Cardiac damage caused by PM + I/R
Du et al (2017)[54]	*In vitro, In vivo*	Ischemia	Transgenic mice expressing VEGFR2-Luc	HUVECs with NO stimulation (with chitosan NO-releasing polymer and β-galactosidase)	60: PBS/EXO/NO EXO	Human	P-MSCs	Transfected with 100 nmol/L miR-126 inhibitor and a NC inhibitor	↓PIK3R2/↑Level of AKT phosphorylation ↑Angiogenic processes	↑Angiogenesis

Table 1. continued

Authors	Model	CAD	Animals	Cells	Sample size & groups	MSC donor organism	Source of MSCs	MSCs preconditioning	Outcome	Therapeutic potential
Feng et al (2014)[55]	*In vivo*	Ischemia	C57BL/6J mice	-	48: microRNA Scramble / siRNA-Mecp2/miR-22-mimic/ $Exo^{non\text{-}IPC}$, Exo^{IPC}/ $Exo^{IPC + miR\text{-}22 Inhibitor}$	C57Black -6 mice	BM-MSCs	-Starved overnight of glucose followed by ischemia (Repeated cycles of anoxia (30 min) with intermittent reoxygenation (10 min) for two cycles in an anoxic chamber) -Transfected with miR-22 mimics FOR 24 h	↓Fibrotic area	Anti-fibrotic
Sánchez-Sánchez et al (2021)[57]	*In vitro, In vivo*	Ischemia	Nude rats	Neonatal rat cardiomyocytes and HUVECs transfected with 20 nM miR-4732-3p for 6 h	70: Control /glucose deprivation/ glucose deprivation + EVs /glucose deprivation + miR-NC/glucose deprivation + miR-4732	-	Immortal MSC-TERT line	-	Recovery of systolic function	↑Angiogenic and cardioprotective responses
Luo et al (2017)[56]	*In vitro, In vivo*	Ischemia	Male SD rats	H9c2 cells under hypoxia (93% N2, 2% O2 and 5% CO2) for 24 h	Normal/AMI + PBS/ AMI + Exosome /AMI + miR-126-Exosome	-	AD-MSCs	Transfection of miR-126 mimics or miR-126 NC for 48 h	↓Cardiac fibrosis ↑Cell proliferation in the border zone	Protecting myocardial cells: ↓Apoptosis, inflammation, fibrosis, and ↑angiogenesis
Yu et al (2015)[58]	*In vitro, In vivo*	Hypoxia	Female SD rats	Primary rat neonatal cardiomyocytes under hypoxia (1% O_2, 5% CO_2, and 94% N_2)	Sham / Saline control / $Exo^{GATA\text{-}4}$/ Exo^{Null}	Femurs and tibias of SD rats	BM-MSCs	Transduction with recombinant GATA-4	↓Infarct size in heart tissue	Anti-apoptotic MI
Zhao et al (2024)[59]	*In vitro*	Hypoxia/ reperfusion	-	H9c2 rat cardiomyocytes under H/R (incubated in 3.3 mmol/L H_2O_2 for 10 min followed by reoxygenation for 30 min)	-	Femur and tibia of SD rats	BM-MSCs	-	↑Cardiomyocyte apoptosis	↓Pik3c3 expression and phosphorylation of AKT/mTOR
Sun et al (2019)[60]	*In vitro, In vivo*	Ischemia, Hypoxia	Male SD rats	H9C2 cells under H/R (hypoxia (95% N_2 and 5% CO_2 for 16 h, followed by reoxygenation for 3 h) and transfection with pre-miRNA of miR-468-5p andanti-miR-486-5p	28: H/R, BMSC-exo, exo-miR-486-5p, exo- anti-miR-486-5p	Femur and tibia of SD rats	BM-MSCs	-	↓Area of MI	↓Myocardial I/R injury
Yang et al (2021)[61]	*In vitro, In vivo*	Atherosclerosis	ApoE−/− female C57BL/6J mice	HUVECs	Blank, AS model, AS model + miR- 145 exosome	Human	hUC-MSCs	Transfected with 10 nM Cy3-labeled miR-145 mimic	↓Atherosclerotic plaques	↓Atherosclerosis
Ma et al (2021)[62]	*In vitro, In vivo*	Atherosclerosis	ApoE−/− mice	RAW264.7 cells transfected with miR-21a-5p inhibitor or inhibitor NC	20: PBS/MSC-exo	Male C57BL/6 J mice	BM-MSCs	Transfection with miR-21a-5p mimic, mimic NC, miR-21a-5p inhibitor, or inhibitor NC	↓Plaque area and macrophage infiltration in AS mice	↑M2 macrophage polarization ↓Macrophage infiltration

Table 1. continued

Authors	Model	CAD	Animals	Cells	Sample size & groups	MSC donor organism	Source of MSCs	MSCs preconditioning	Outcome	Therapeutic potential
Wang et al (2015)[63]	*In vitro, In vivo*	Sepsis	Male WT C57BL/6 mice	RAW264.7 cells Primary cardiomyocytes isolated from adult rat hearts	40: sham, CLP + PBS control, CLP + PBS, WT- MSC, miR- 223-KO-MSC	Mouse tibia and femur	BM-MSCs	-	↑Survival rate ↑Values of left ventricular EF and FS	Anti-inflammation, Cardioprotection in polymicrobial sepsis
Pei et al (2021)[64]	*In vitro, In vivo*	Sepsis	Male KM mice	Mouse primary cardiomyocytes transfected with miR-141 mimic or miR-141 inhibitor	31: control, CLP, exo, exo- NC, exo- knockout, PBS	Mouse	BM-MSCs	Transfection with miR-141 inhibitor	↓Number of apoptotic cells in mouse myocardial tissues	↓Myocardial injury in septic mice
Luo et al (2022)[65]	*In vitro*	Calcification	-	Human aortic vascular smooth muscle cells	-	Human	BM-MSCs	Transfection with hsa-miR-15a-5p mimics/inhibitors, hsa-miR-15b-5p mimics/inhibitors, hsa-miR-16-5p mimics/ inhibitors, or mimics NC/inhibitors NC	↓HA-VSMCs osteogenic transdifferentiation	↓Atherosclerosis
Chen et al (2021)[66]	*In vitro*	Endothelial dysfunction	-	Primary EC cells from male C57BL/6 mice transfected with Keap1 overexpressed and knockdown plasmids and NC	Untreated /ox-LDL/ ox-LDL + EXO- miR-NC/ ox-LDL + EXO- miR-512-3p	Bilateral leg bones of mice	BM-MSCs	Transfection with miR-512-3p mimics and miR-NC	↓EC cell apoptosis and inflammatory Response ↑Proliferation	↓Apoptosis and inflammatory response ↓Atherosclerosis
Lei et al (2021)[67]	*In vitro, In vivo*	Myocardial toxicity	Healthy SPF SD female rats	H9c2 cells	85: normal/ doxorubicin/ Exo/ Exo + mimic NC/ Exo + miR-96 mimic/ Exo + inhibitor NC/ Exo + miR-96 inhibitor	Rats	BM-MSCs	Transfected with miR-96 mimic, mimic NC, miR-96 inhibitor or inhibitor NC	↓Proinflammatory cytokines (TNF-α, IL-1β, and IL-6) and collagen fibers	↓Doxorubicin-Induced Myocardial Toxicity
Wang et al (2021)[68]	*In vitro, In vivo*	Chronic heart failure	Male SD rats	H9C2 cells and HUVECs treated with OGD/R for simulating myocardial and under H/ R (hypoxia (5% CO_2 and 95% N_2 for 3 h), followed by reoxygenation (5% CO_2 for 48 h) injury	20: Sham/LAD /LAD + PBS/ LAD + hucMSC-Exo	Human	UC-MSCs	Transfected with miR-1246 inhibitor or the corresponding NC	↓LVSD, IVSS, LVIDD, and LVIDS ↑EF	Hypoxia-induced myocardial tissue damage in chronic heart failure
Yan et al (2022)[69]	*In vitro, In vivo*	Heart failure	Male C57BL/6 J mice	Mouse cardiomyocytes HL-1	24: Sham/HF /HF + PBS/ HF + MSC-Exos	Mouse	BM-MSCs	Transfection with miR-129-5p inhibitor, small interfering RNA (si)-TRAF3, or negative controls for 24 h	↑Level of stroke volume	↓Apoptosis and Oxidative Stress in Heart Failure

ADAM19: A Disintegrin and metalloproteinase 19, ADAMTS16: A disintegrin and metalloproteinase with thrombospondin motifs 16, AD-MSCs: Adipose derived mesenchymal stem cells, AKT: protein kinase, B, BCL2L11: Bcl-2-like protein 11, BM-MSCs: Bone marrow derived MSCs, Bnip3: B-cell lymphoma 2–interacting protein 3, DAAM1: Disheveled-associated activator of morphogenesis 1, DSD: Danshen decoction, EMT: Epithelial–myofibroblast transdifferentiation, ESRK1/2: Extracellular signal-related kinases 1 and 2, Faslg: Fas ligand gene, FG: Fractional shortening, FIH: Factor-inhibiting HIF, GDF11: Growth differentiation factor 11, GSDMD: Gasdermin D, HDAC2: Histone deacetylase 2, HIF: Hypoxia-inducible factor, H/R: Hypoxia-reperfusion, HUVECs: human umbilical vein endothelial cells, IMI: Intramyocardial injection, I/R: Ischemia-reperfusion, IRAK: Interleukin-1 receptor-associated kinase, IV: Intravenously injection, JAM-A: Junctional adhesion molecule A, JNK: c-Jun NH2-terminal kinase, Keap1: Keleh-like ECH-associated protein 1, KLF-6: Kruppel-like factor 6, LVD: LV diastolic dimension, LVEDD: Left ventricular end-diastolic diameter, LVEDV: LV enddiastolic volume, LVEF: LV ejection fraction, LVESD: LV end-systolic diameter, LVESV: LV end-systolic volume, MAPK: Mitogen-activated protein kinase, Mecp2: Methyl CpG binding protein 2, MI: Myocardial infarction, NAT1: N-Acetyltransferase 1, NFAT: Nuclear factor of activated T cells, NLRP3: NLR Family pyrin domain containing 3, NO: Nitric oxide, Nrf2: NF-E2-related factor 2, P53: Tumor protein 53, PDK4: Pyruvate dehydrogenase kinase 4, PI3K: Phosphatidylinositol 3 kinase, PM: Particulate matter, P-MSCs: Placenta-derived MSCs, PRSS23: Protein serine protease 23, PTEN: Phosphatase and tensin homolog, RASA1: RAS P21 protein activator 1, ROCK2: Rho associated coiled-coil containing protein kinase 2, SD: Sprague-dawley, SMAD: Suppressor of mothers against decapentaplegic, SNRK: Sucrose non-fermenting-1 related kinase, S100A9: S100 calcium-binding protein A9, SOX6: Sry-related high-mobility group box6, TERT: Telomerase reverse transcriptase, TGF-β: Transforming Growth Factor beta, TGF-βR: TGF-β receptor, TLR4: Toll-like receptor 4, TRAF6: Tumor necrosis factor receptor-associated factor 6, TXNIP: Thioredoxin interacting protein, UC-MSCs: Umbilical cord derived MSCs, VEGFA: Vascular endothelial growth factor A, YAP1: Yes-associated protein 1.

Table 2. Characteristics of MSCs and their exosomal microRNAs in CAD models

Authors	Exosome isolation	Characterization	Exosome markers	Exosome concentration	miRs	Deliver target miRs into exosomes/ cell lines	Administration routes	Treatment route/ time	miRNA Targets
Yang et al (2021)[14]	Exosome extraction kit (Sigma-Aldrich, Merck KgaA, Darmstadt, Germany)	Particle size analysis TEM Western blotting	TSG101, HSP70, and CD63	0.13 µg/µl	miR-543		IV	40 µg protein in 300 µl PBS per rat	Downregulating COL4A1 expression
Wang et al (2023)[15]	ExoQuick-TCTM kit	TEM NTA Bradford assay Western blotting	CD63 and CD9	100 µg protein, 50 µL	miR-205		Intramuscularly / IV	Five locations along the anterior wall of the left ventricle's border zone	Cardiac function and HIF-1a and VEGF increased expression
Sun et al (2022)[16]	Ultracentrifugation method	TEM NTA Western blotting	CD9, CD63 and Alix	5 µg	miR-182-5p		IMI	several sites around the infarct region	TLR4/NF-κB signaling pathway
Pu et al (2021)[17]	Ultracentrifugation method	TEM NTA Western blotting	TSG101, Alix, and CD81	20 µg/mL	miR-30e		IV	Exosomes were injected via the tail vein for 3 consecutive days 7 days after MI surgery	LOX1/ NF-κB p65/ Caspase-9 axis
Wang (2017)[18]	Ultracentrifugation method	TEM Western blotting	LAMP-1, CD44, CD105, and TSG 101	-	miR-210		IV	MSC-EVs in mice subjected with MI injury	Efna3
Xiao et al (2018)[19]	Ultracentrifugation method	Electron microscopy and immunoblotting	CD63, CD9, and Alix	0.2 µg/µl	miR-125b		IMI	Injection of 5 µl exosomes into 5 sites at the border of the infarct 30 min after ligation	p53-Bnip3 signaling
Peng et al (2020)[20]	Total Exosome Isolation Reagent	TEM NanoSight NS500 Western blotting	HSP70, CD63, and CD9	0.05 µg/µl	miR-25-3p		IMI	5 µg in 100 µL PBS injected into the border zone of the infarcted heart at three sites 30 min after ligation	Pro- apoptotic genes FASL and PTEN
Zheng et al (2022)[21]	Ultracentrifugation method	Western blotting TEM NTA	CD81 and TSG101	-	miR-29b-3p		Injection		ADAMTS16
Xiong et al (2022)[22]	Ultracentrifugation method	Micro BCA protein assay TEM NTA Western blotting	CD63, TSG101, and Alix	0.2 µg/µl	miR-146a-5p		IMI	20 µg exosomes in 100 µL PBS injected into the border zone of the infarcted heart at three sites	IRAK1/ NF-κB p65 pathway
Wang et al (2021)[23]	Total Exosome Isolation Reagent	TEM NTA Western blotting	CD63 and CD81	100 µg	miR-671		IMI	100 µg Exo-NC or Exo-inhibitor was dissolved in PBS and injected in the boundary area of the infarcted cardiac near the ligation site	TGFBR2/ Smad2 Axis
Li et al (2019)[24]	Exosomes isolation kit	TEM Western blotting	CD81, CD63, and CD9	-	miR-301		IMI	30 min after LAD artery ligation, BMSCExos were injected at 5 points in the peripheral area of the MI	-
Zhu et al (2022)[25]	Ultracentrifugation method			2 µg/µl	miR-24-3p		IMI		Plcb3 and NF-κB pathway ↑M2 Macrophage Polarization

Table 2. Continued

Authors	Exosome isolation	Characterization	Exosome markers	Exosome concentration	miRs	Deliver target miRs into exosomes/ cell lines	Administration routes	Treatment route/ time	miRNA Targets
Wan et al (2022)[26]	Ultracentrifugation method	TEM NTA Western blotting	CD9, CD81, and GRP94	6.66 μg/μl	miR-200b-3p		IMI	EVs (100 μg) or recombinant lentivirus (5×10^7 viral genome particles per mouse heart) injection around the infarct area (anterior wall, lateral wall, and apical area) after LAD artery ligation	BCL2L11
Xuan et al (2019)[27]	Ultracentrifugation method	TEM TRPS Western blotting	Tsg101, CD9, Hsp70, and flotillin-1	10^{12} particles/ ml	miR-373		IMI	10 mins after LAD ligation, EVs (1 × 1012/ml) were injected into the myocardium along the border zone with a total of 20 μl	GDF-11 and ROCK-2
Fu et al (2020)[28]	Exosome Isolation Reagent	TEM Western blotting	CD9,CD63, and CD81	-	miR-338		IMI	50 μL of exosome were injected before the chest was closed	Regulate the JNK pathway via targeting MAP3K2
Ma et al (2018)[29]	Total exosome isolation reagent	TEM Western blotting	CD63 and CD9	30 μg/μl	miR-132	Loading miR-132 via electroporation	IMI	Injection of exosome (600 *μg*) after LAD ligation	↓The expression level of its target gene RASA1
Huang et al (2020)[30]	Ultracentrifugation method	TEM NTA Western blotting	CD9, CD63, Alix 3, and GM130	400 μg/g	miR-19a	-	IV	400 μg/g exosome injection	SOX6
Yang et al (2022)[31]	Ultracentrifugation method	BCA assay TEM Western blotting	CD9, CD81, and CD63	50 μg/mL	miR-223	Transfection of EVs with miR-223 mimic or NC mimic	IMI	EV injection (50 μg/mL) after the ligation at three different sites around the infarcted area	Modulate the P53/S100A9 axis
Pu et al (2023)[32]	Ultracentrifugation method	TEM NTA Western blotting	TSG101and CD63	4×10^7 particles/ μl	miR-210-3p		IMI	EVs (50 uL or 2×10^9 particles) were injected in the border zone of the infarction area 30 min after ligation	EphrinA3
Ji et al (2024)[33]	Ultracentrifugation method	TEM NTA Western blotting	CD81 and TSG101	100 μg	miR-21-5p		IV	100 μg of exosomes suspended in 100 μL sterile PBS via tail vein injection	YAP1 signaling pathway
Wang et al (2024)[34]	-				miR-223-3p		IMI	Peri-infarct myocardial region was injected	↓NLRP3
You et al (2024)[35]	Ultracentrifugation method	TEM Western blotting BCA assay	CD63, CD81, and TSG101	0 or 50 μg/ml	miR-let-7i-5p		IMI	Immediately after ligation, the peri-infarct myocardial region was injected at three different points with a total of 10 uL of exosomes	Bcl-2

Table 2. Continued

Authors	Exosome isolation	Characterization	Exosome markers	Exosome concentration	miRs	Deliver target miRs into exosomes/ cell lines	Administration routes	Treatment route/ time	miRNA Targets
Zhu et al (2022)[36]	Ultracentrifugation method	NTA TEM Western blotting BCA assay	CD9 and TSG101	5 µg (IM) 100 µg (IV)	miR-31		IMI, IV	IMI: Exosomes (5 µg, 2.2×10^7 particles) were injected in the infarct border area two times on each side of the ligation IV: Exosomes (100 µg, 4.3×10^8 particles) were injected at the tail vein at 7, 14, and 21 days post-surgery	FIH1/ HIF-1α pathway
Zhao et al (2019)[37]	Ultracentrifugation method	NTA TEM Western blotting BCA assay	CD9, CD63 TSG101, and Alix	-	miR-182		IMI	Exosomes (5, 30, or 50 ug) 3 days following myocardial I/R injury	TLR4 signal
Chen et al (2020)[38]	ExoQuick-TC kit	TEM Western blotting	CD9 and CD63	50 µg	miR-125b		IMI	After LAD, exosomes (50 µg) were injected into the ligation zone adjacent to the left anterior free wall after left ventricle exposure	Sirtuin7
Mao et al (2022)[39]	Ultracentrifugation method	NTA TEM Western blotting	CD9, CD63, and CD81	2 µg/µl	miR-183-5p		IV	Exosomes (400 µg in 200 µL PBS) were injected via the tail vein within 5 min of the beginning of reperfusion	FOXO1
Chen et al (2021)[40]	Hieff ™ Quick exosome isolation kit	NTA TEM Western blotting	CD63 and CD81	0.5 µg/µl	miR-143-3p		IMI	Exosomes (200 µg suspended in 400 µl PBS) were injected into the myocardium	CHK2- Beclin2 pathway
Wang et al (2022)[41]	Ultracentrifugation method	TEM Western blotting	CD63, CD9, and Alix	10 µg	miR-455-3p		IMI	Exosomes (10 µg) were transfused into the left ventricular wall of rats	MEKK1- MKK4-JNK signaling pathway
Zhang et al (2021)[42]	Ultracentrifugation method	TEM BCA assay Western blotting	CD63 and CD9	1 µg/µl	miR-98-5p		IMI	100 µL exosomes (1 µg/µL) were injected into 4 different sites of the anterior wall of the left ventricle	↓TLR4 and activating the PI3K/ Akt signaling pathway
Li et al (2020)[43]	Ultracentrifugation method	Western blotting	CD9, CD63, and Alix	1 µg/µl	miR-29c		IMI	Exosomes (20 µg resuspended in 20µL PBS) were injected in 2 sides of the border zones right after LAD coronary ligation	PTEN/ Akt/ mTOR Signaling Pathway
Gao et al (2023)[44]	Ultracentrifugation method	NTA TEM BCA assay Western blotting	CD63, CD9, TSG101, and Alix	0.66 µg/µl	miR-125a-5p		IMI	10 µg exosomes or 20 nmol miR-125a-5p agomir into the border zone at the onset of reperfusion	Klf13, Tgfbr1, and DAAM1
Zou et al (2020)[45]	Ultracentrifugation method	TEM Western blotting	CD63, ALIX, and TSG101	-	miR-149	-	-	-	Faslg and w/β-catenin signaling pathway

Table 2. Continued

Authors	Exosome isolation	Characterization	Exosome markers	Exosome concentration	miRs	Deliver target miRs into exosomes/ cell lines	Administration routes	Treatment route/ time	miRNA Targets
Wei et al (2019)[46]	Ultracentrifugation method	NTA TEM Western blotting	CD9, CD63, TSH, and ALIX-101	200 µg	miR-181		IMI	200 µg of exosomes suspended in PBS were injected before the chest was closed	T-cell receptor signaling and TGF-β signaling
Yue et al (2022)[47]	Ultracentrifugation method	NTA TEM Western blotting	CD63, HSP70, TSG 101, Alix, and Calnexin	1 µg/µl	miR-182-5p		IMI	10 µg exosomes dissolved in 10 µL PBS injected at the front and outside of the visible injury area	GSDMD
Ou et al (2020)[48]	ExoQuick-TC EV purify reagent	NTA TEM BCA assay Western blotting	CD9, CD63, Alix, and GRP94	10^7 U/µl	miR-150-5p		IMI	EVs (10 µL per injection, 5.8 × 10^{12} particles) were injected 5 times 10 min before perfusion	TXNIP
Tang et al (2020)[49]	Ultracentrifugation method	NTA TEM Western blotting	CD9, CD81 and TSG101	-	miR-320b		-	Exosomes (50µg/25µL PBS)	NLRP3 protein
Chen et al (2024)[50]	Ultracentrifugation method	TEM NTA PKH67 staining miRNA sequencing	TSG101, CD63, and calnexin	20 µg	miR-93-5p		IMI	20 µl of exosomes (50 µg) were injected in situ into the original location of the infarcted myocardium	TXNIP/ NLRP3/ Caspase-1
Du et al (2024)[51]	Ultracentrifugation method	NTA TEM Western blotting	CD63 and CD9	-	miR-25-3p	Electroporation of 100 µg of miR-25-3p in 500 µl BMSC-Exo (250 µM)	IV	Exosomes (100 µg/kg) were injected through the tail vein 2 h before I/R surgery	JAK2 / STAT3 signaling pathway
Gu et al (2024)[52]	Exosome isolation reagent kit	NTA TEM Flow cytometry	CD29 and CD44	2.5 to 40 µM	miR-302	-4 µL ethanolic solution (100 nM) including DSPE-PEG-CMP was incubated with the exosomes (200 µL, 1 × 10^{10} particles) -electroporation of exosomes via miR302 mimic	IV	Engineered exosomes were injected via the tail vein (0.25 µg/100 µL PBS/ mouse) 12 h after reperfusion after coronary artery ligation every 2 days for 4 weeks	Cardiomyocyte specific peptide
Lee et al (2025)[53]	ExoQuick-TC Exosome Precipitation Solution	NTA TEM BCA assay Western blotting	CD9 and CD63	-	miR-221- and miR-222		Intratracheally, intraperitoneally, and intramuscularly injection	Exosomes (100 µg of protein in 50 µL) were uniformly injected into the left ventricular marginal zone	BNIP3-MAP1LC3B-BBC3/ PUMA pathway
Du et al (2017)[54]	Ultracentrifugation method	ELISA TEM BCA assay	-	-	miR-126	-	IMI	Exosomes (100 µg in 100 µl PBS) were immediately injected post-ischemia at 3 sites in the right adductor muscle adjacent to and within 1 mm proximal or distal to the ligation site	VEGF

Table 2. Continued

Authors	Exosome isolation	Characterization	Exosome markers	Exosome concentration	miRs	Deliver target miRs into exosomes/ cell lines	Administration routes	Treatment route/ time	miRNA Targets
Feng et al (2014)[55]	ExoQuick + Ultracentrifugation	TEM Western blotting Bioanalyzer for RNA	CD63	1 µg	miR-22	-	IMI	1 mg exosomes were injected along the border between the infarct zone and normal myocardium after LAD	MeCP2
Sánchez-Sánchez et al (2021)[57]	Ultracentrifugation method	NTA TEM BCA assay Western blotting EVs Small RNA Sequencing	ALIX, HSP70, TSG101, and CD9	3.5×10^9 EVs/ µl	miR-4732-3p	Electroporation of miR- 4732-3p (40 nM) into EVs	IMI	EVs (3.5×10^{10} per animal) were transplanted immediately after permanent LAD artery ligation in two injections of 10 mL, at two discrete locations of the infarct border zone	SMAD2 and SMAD4 components of the TGF-β pathway
Luo et al (2017)[56]	ExoQuick-TC	NTA TEM Western blotting	CD63, CD9, and TSG101	2 µg/µl	miR-126	-	IV	Exosomes (400 µg of protein suspended in 200 µl PBS) were injected at the tail vein immediately after the ligation operation	-
Yu et al (2015)[58]	ExoQuick-TC kit	TEM Western blotting	CD9, CD63, and HSP70	-	miR-19a	-	IMI	Exosomes (harvested from 4×10^6 MSCs in 50 µl saline) were injected after LAD coronary artery	PTEN/ Akt/ ERK signaling pathways
Zhao et al (2024)[59]	Exo Quick-TC kit	NTA TEM Western blotting	CD63, CD9, and CD81	-	miR-101a-3p	Transfected with miR- 101a- 3p inhibitor (2 µg/ mL)	-	-	PIK3-Akt signaling pathway
Sun et al (2019)[60]	Total Exosome Isolation kit	NTA TEM Western blotting	CD9, CD63, ALIX, and TSG101	2 µg/µl	miR-486-5p	-	IV	rats with exosomes (400 µg in 200 µL PBS) were injected into the tail vein at the beginning of the reperfusion and 3 h later coronary artery was re-ligated	PTEN/ PI3K/ AKT signaling pathway
Yang et al (2021)[61]	Total exosome isolation reagent	NTA TEM Western blotting	CD63 and CD9	0.932×10^3 copies/µL	miR-145	-	IV	Exosomes (80 mg) were injected every week, one week after carotid atherosclerotic plaque induction in the right common carotid artery	JAM-A
Ma et al (2021)[62]	Total Exosome Isolation Reagent Kit	NTA TEM	-	0.5 mg/ml	miR-21a-5p	-	IV	Exosomes (200 µl, 0.5 mg/ml) were injected into the caudal vein once a day for 2 weeks	KLF6 and ERK1 /2 signaling pathways

Table 2. Continued

Authors	Exosome isolation	Characterization	Exosome markers	Exosome concentration	miRs	Deliver target miRs into exosomes/ cell lines	Administration routes	Treatment route/ time	miRNA Targets
Wang et al (2015)[63]	Ultracentrifugation method	NTA TEM BCA assay Western blotting	CD63 and CD81	-	miR-223miR-233SEMA3A; STAT3	-	IV	Exosomes (2μg/g body weight in 150 μl of incomplete culture medium) were injected through the tail or jugular vein, 1 hour after CLP surgery	SEMA3A, STAT3
Pei et al (2021)[64]	Ultracentrifugation method	NTA TEM Western blotting	CD63 and CD9	-	miR-141	-	IV	Exosomes (2 μg/g) were injected through caudal veins 1 hour after CLP	PTEN and activates β-catenin
Luo et al (2022)[65]	Complete exosome isolation kit	NTA TEM Western blotting	CD9, CD81, Tsg101, and Histone H3	-	miR-15a/15b/16	-	-	-	NFAT-3
Chen et al (2021)[66]	Ultracentrifugation method	TEM Western blotting	CD63, CD81, and CD9	-	miR-512-3p	-	-	-	Keap1/ Nrf2 signaling pathway
Lei et al (2021)[67]	Ultracentrifugation method	BCA assay NTA TEM Western blotting	CD63 and CD81	3×10^{11} particles/ml	miR-96	-	IV	2 doses of exosomes (3×10^{10} particles suspended in 0.1 mL PBS) were injected into the tail vein of the rats on days 5 and 11	Inhibiting the Rac1/Nuclear Factor-κB Signaling Pathway
Wang et al (2021)[68]	Gradient centrifugation	NTA TEM Western blotting	CD63, PDCD6IP, TSG101, and LC3A	1 μg/μl	miR-1246	-	IMI	Exosomes (20 μg in 20 μl PBS) were directly injected into two lesions of the infarcted myocardial boundary area	Targeting PRSS23 ↓Activation of the Snail/alpha-smooth muscle actin signaling
Yan et al (2022)[69]	Ultracentrifugation method	BCA assay DLS TEM Western blotting	CD81 and TSG101	0.1 μg/μl	miR-129-5p	-	IV	Exosomes (50 μL, 100 μg/mL) were postoperatively injected through the tail vein once a week for 3 times	TRAF3, NF-κB signaling

ADAM19: A Disintegrin and metalloproteinase 19, ADAMTS16: A disintegrin and metalloproteinase with thrombospondin motifs 16, AKT: protein kinase, B, BCL2L11: Bcl-2-like protein 11, Bnip3: B-cell lymphoma 2–interacting protein 3, DAAM1: Disheveled-associated activator of morphogenesis 1, DSPE-PEG-NHS: 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine*N*-[hydroxysuccinimidyl polyethylene glycol-2000], EMT: Epithelial–myofibroblast transdifferentiation, ESRK1/2: Extracellular signal-related kinases 1 and 2, Faslg: Fas ligand gene, FG: Fractional shortening, FIH: Factor-inhibiting HIF, GDF11: Growth differentiation factor 11, GSDMD: Gasdermin D, *HDAC2*: Histone deacetylase 2, HIF: Hypoxia-inducible factor, H/R: Hypoxia-reperfusion, HUVECs: human umbilical vein endothelial cells, IMI: Intramyocardial injection, I/R: Ischemia-reperfusion, IRAK: *Interleukin-1 receptor-associated kinase*, IV: Intravenously injection, JAM-A: Junctional adhesion molecule A, JNK: c-Jun NH2-terminal kinase, Keap1: Keleh-like ECH-associated protein 1, KLF-6: Kruppel-like factor 6, LVD: LV diastolic dimension, LVEDD: Left ventricular end-diastolic diameter, LVEDV: LV enddiastolic volume, LVEF: LV ejection fraction, LVESD: LV end-systolic diameter, LVESV: LV end-systolic volume, MAPK: Mitogen-activated protein kinase, Mecp2: Methyl CpG binding protein 2, MI: Myocardial infarction, NAT1: N-Acetyltransferase 1, NC: Negative control, NFAT: Nuclear factor of activated T cells, NLRP3: NLR Family pyrin domain containing 3, NMN: Nicotinamide mononucleotide, Nrf2: NF-E2-related factor 2, P53: Tumor protein 53, PDK4: Pyruvate dehydrogenase kinase 4, PI3K: Phosphatidylinositol 3 kinase, PRSS23: Protein serine protease 23, PTEN: Phosphatase and tensin homolog, RASA1: RAS P21 protein activator 1, ROCK2: Rho associated coiled-coil containing protein kinase 2, SD: Sprague-dawley, SMAD: Suppressor of mothers against decapentaplegic, SNRK: Sucrose non-fermenting-1 related kinase, S100A9: S100 calcium-binding protein A9, SOX6: Sry-related high-mobility group box6, TERT: Telomerase reverse transcriptase, TGF-β: Transforming Growth Factor beta, TGF-βR: TGF-β receptor, *TLR4:* Toll-like receptor 4, TRAF6: Tumor necrosis factor receptor-associated factor 6, TRPS: Tunable resistive pulse sensing, TXNIP: Thioredoxin interacting protein, VEGFA: *Vascular endothelial growth factor A,* YAP1: Yes-associated protein 1

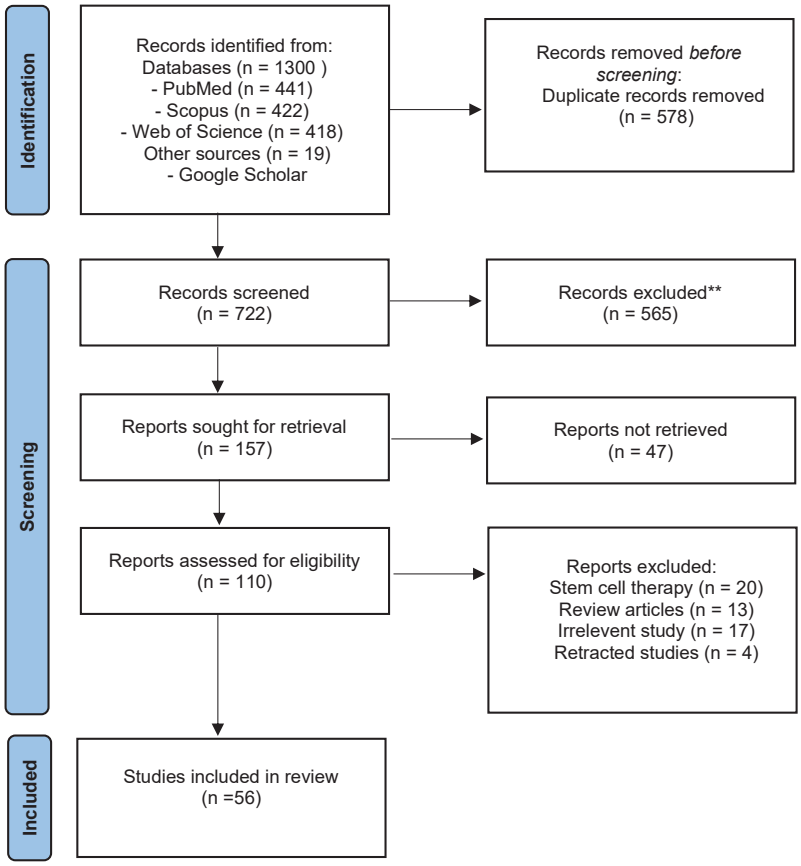

Fig. 1. PRISMA flow diagram of literature search and selection process.

(n = 2),[61,62] sepsis (n = 2),[63,64] calcification (n = 1),[65] endothelial dysfunction,[66] myocardial toxicity,[67] and heart failure.[68,69]

Of the 56 included studies, 44 articles had a mixed methodology (*in vitro* studies were followed by *in vivo* studies),[14-16,18-20,22,23,25,27-36,38,40-54,56-58,60-64,67-69] 8 were i*n vivo*,[17,21,24,26,37,39,42,55] and 4 were *in vitro*[45,59,65,66] studies. Mice were the model animals in 18 *in vivo* studies,[15,16,18-20,23,25,26,29,33-37,43,44,46,47,52,53,55,61-64,66,69] and the rest of the articles used rats as their study models. Most *in vitro* studies utilized animal model cardiomyocytes [neonatal rat cardiomyocytes or H9C2 cells (a rat cardiomyoblast cell line)]; however, 9 studies examined human umbilical vein endothelial cells (HUVECs)[15,29,32,36,47,54,57,61,68] and 1 article studied both human fibroblasts and HUVEC.[18]

Sources of MSCs and their preconditioning methods

The included studies utilized a diverse range of MSCs, including bone marrow-derived MSCs (BM-MSCs), umbilical cord MSCs (UC-MSCs), placenta-derived MSCs (P-MSCs), and adipose-derived MSCs (AD-MSCs). Specifically, BM-MSCs were the most prevalent source being used in 37 studies (66.07%), followed by UC-MSCs in 6 studies (10.71%),[25,30-32,61,68] AD-MSCs in 5 studies (8.92%),[15,23,36,53,56] and human placenta-derived MSCs (hP-MSCs) in one study.[54] Cell lines (Shanghai Zhongqiao Xinzhou Biotechnology Co.),[26] immortal MSC-TERT lines,[57] human MSC (American Type Culture Collection),[14,49] and rat MSCs (CP-R131)[33] along with induced pluripotent stem cell (iPS)[27] were also applied. The tissue of origin was unspecified in a minority of studies.[48] Nineteen, eighteen, and fourteen articles used rats,[17,21,22,24,28,33,38-42,45,48,50,51,58-60,67] mice,[15,16,18,20,23,29,35,37,43,44,47,52,55,62-64,66,69] and human-derived tissue,[14,25,27,30-32,36,46,49,53,54,61,65, 68] respectively, as a donor of MSC organism. The donor organism of MSCs was not defined in 5 studies[19,26,34,56,57] (Table 1). Regarding preconditioning methods, the majority of studies did not employ specific techniques. However, 6 studies (10.71%)[41-43,45,50,55] utilized a hypoxic environment to precondition MSCs before exosome isolation, and 16 studies (28.57%)[14,30,35,41,47-53,56,58-60,68] used preconditioning for H9c2, HUVEC, myocardial, and cardiomyocyte cells (Table 1).

For exosome isolation, ultracentrifugation was the dominant method used in 34 out of 56 studies (60.71%). Other methods included the use of exosome extraction kits such as ExoQuick (used in 7 studies, 12.5%),[15,38,48,53,56,58,59] the Total/complete Exosome Isolation Reagent Kit (10 studies, 17.85%),[20,23,24,28,29,52,60-62,65] Hieff Quick (used in 1 study, 1.78%),[40] Sigma (1 study, 1.78%),[14] and Gradient centrifugation (1 study, 1.78%).[68] ExoQuick and

ultracentrifugation were employed in one study.[55] The isolation method of one study was not defined.[34]

The identification of exosomes primarily relied on transmission electron microscopy (TEM) to examine their morphology. Western blotting and Flow cytometry were used to detect specific biomarkers. Other techniques, such as dynamic light scattering (DLS), and nanoparticle tracking analysis (NTA) were employed to characterize and analyze the size, distribution, and concentration of exosomes. In terms of miRNA insertion, transfection into MSC cells was used in 31 out of 56 studies (55.35%)[14,16,22-24,26-28,30-33,35,37,38,40-42,44,49,54-56,61,62,64-69] and 5 studies of 56 studies used transduction (8.92%).[25,36,39,46,48] On the other hand, 2 studies used transfection to insert microRNAs into exosomes (3.57%) and 4 of them used electroporation for this approach (7.14%)[29,51,52,57] to deliver target miRs into exosomes and cell lines. For more details, see Table 2.

Route and frequency of MSC-exosomal miR administration

In 31 *in vivo* studies,[16,19,20,22-29,31,32,34,35,37,38,40-44,46-48,50,54,55,57,58,68] the exosomes were injected intramyocardially around the infarct area, and in 16 studies,[14,17,18,30,33,39,51,52,56,60-64,67,69] the intravenous route was used for exosome administration. Interestingly, one study used both intramyocardial and intravenous routes for their experiment,[36] one study used both intramuscular and intravenous routes,[15] and another study used simultaneous intratracheally, intraperitoneally, and intramuscularly injection.[53] Two studies did not explain the exact route of administration in the methodology.[21,49] Most studies used a single intramyocardial injection of exosomes after surgical I/R induction. Studies used a broad spectrum of exosome concentrations varying from 0.02 μg/μL to 400 μg/μL. In some studies, the exosome concentration was not declared, and the total amount of injected exosomes was just mentioned.

Improvement/outcomes

In vitro studies focused on the anti-inflammatory and anti-apoptotic effects of exosomes under hypoxic conditions.[14,30,35,41-43,45,47-53,56,58-60,68] On the other hand, the *in vivo* studies mainly focused on cardiac function improvement (increased left ventricular ejection fraction and fractional shortening (LVEF and LVFS), decreased end-diastolic and systolic diameter of the left ventricle (LVEDD and LVESD), and the reduction in the infarct area size and fibrosis.[14-18,22,24,26,28,29,37,38,42,46,48,50-52,58,63,68,69] Exosomal miRNAs derived from various MSC sources have been shown to play beneficial roles in targeting dysregulated signaling in CAD. These roles include anti-apoptotic effects,[26,28,35,39,47,48,52,56,58,66,69] anti-inflammatory actions,[16,19,20,26,31,37,46,47,51,52,56,63,66] promotion of differentiation, anti-fibrotic activity,[15,27,31,55,56] pro-angiogenic effects.[15,18,21,27,29,31,32,36,54,56,57] To a lesser extent, MSC-exos-miRs were involved in reducing calcification,[65] suppressing autophagy,[24,40,43] and enhancing cell viability. The detailed results of each study are summarized in Table 1 and Fig. 2.

Quality and risk of bias assessment

According to the ARRIVE guidelines 2.0 evaluations, the selected studies have had an appropriate quality to be included in the review. The main risk of bias in the included studies was the lack of clear information about the blinding and randomization process in the performance and detection phases. However, due to the small sample size of most of these animal studies, researchers assessed all the target animals instead of randomization. There was no significant risk of bias in the included studies regarding the SYRCLE's risk of bias tool (Figs. 3 and 4).

Discussion

Recent studies support that MSC-exosomal miRs are the most functional factors regulating the regeneration of the cardiovascular, offering a multifaceted strategy to combat CAD by addressing cellular dysfunction, apoptosis, and inflammation while promoting angiogenesis and tissue repair and suppressing fibrosis.

Both MI and I/R injury are downstream effects of CAD. Myocardial ischemia occurs when the coronary artery is partially or totally occluded, resulting in the functional loss of cardiomyocytes. After an MI and performing reperfusion treatments by fibrinolytic or angioplasty, the re-establishment of blood supply causes cell damage, called I/R injury. Although reperfusion is crucial to preventing more damage, it leads to further injury due to oxidative stress, inflammation, and an overload of calcium. The pathophysiology of maladaptive cardiac remodeling after MI is the early inflammatory response, apoptosis, and the succeeding longer-term scar alteration.

Inflammation plays a central role in the development and progression of CAD by contributing to immune cell recruitment, endothelial dysfunction, and atherosclerotic plaque formation and destabilization. The result of this review indicated that MSC-exos-miRs can decrease inflammation in MI,[19,20,23,26,31,34] I/R,[47,52,56] and sepsis[63] models. MSCs exosomes carrying miR-25-3p,[20] miR-125b,[19] miR-200b-3p,[26] and miR-223[31] have anti-inflammatory and cardioprotective effects after MI. Moreover, in I/R models, miR-126,[56] miR-182-3p,[47] and miR-302[52] could diminish inflammation. Surprisingly, as an effective agent, miRs can target the inflammatory signaling pathways through several mechanisms, such as the TLR/NF-κB pathway, NLRP3[34] inflammasome, PI3K/AKT pathway, and JAK/STAT pathway. Reducing macrophage infiltration and promoting the M2 macrophage phenotype is another anti-inflammatory role of MSC-exos-miRs.[62] Likewise, BM-MSCs-Exos diminish the inflammatory response by miR-302d and controling

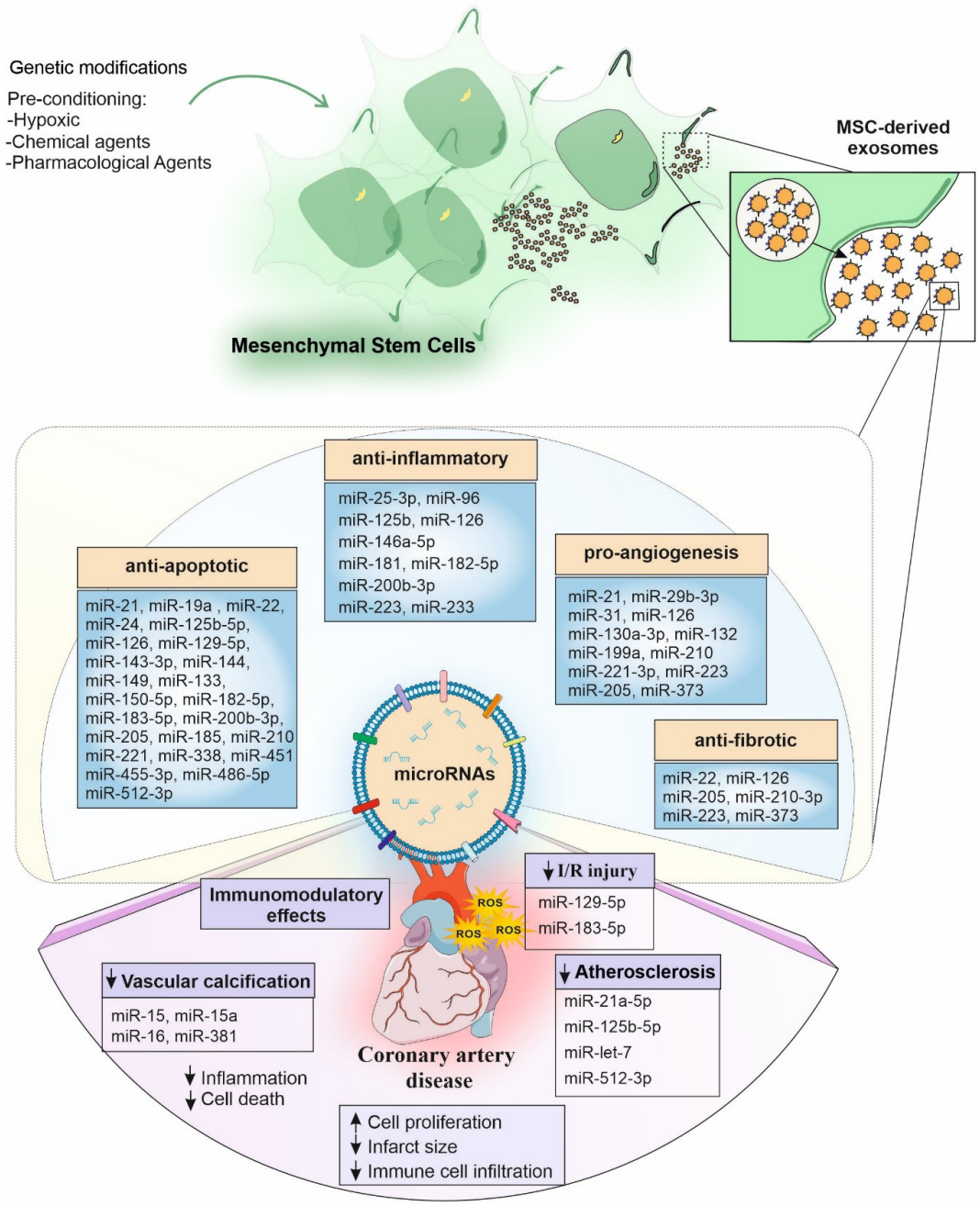

Fig. 2. The effect of exosomal miRs derived from mesenchymal stromal cells on coronary artery disease. Exosomal miRs derived from Mesenchymal stromal cells (MSCs) could have anti-inflammatory, anti-apoptotic, pro-angiogenesis, and anti-fibrotic effects on patients with coronary artery disease. Besides, some miRs could have immunomodulatory effects, and reduce ischemia-reperfusion (I/R) injury, vascular calcification, atherosclerosis, infarct size, and immune cell infiltration.

the BCL6/MD2/NF-κB signaling pathway in cardiac regeneration after AMI.[70]

The main features of acute MI include elevated oxidative stress, loss of NADH and ATP, and cell death, all connected directly to cellular bioenergetics. MSC-exosomal miRs can preserve cardiac cells by suppressing oxidative stress and cell apoptosis and promoting cardiac regeneration and repair. In this review, an important group of MSC-exo-miRNAs was identified in CAD models that present antiapoptotic effects by targeting different pathways. This antiapoptotic miRNA group includes let-7i-5p,[35] miR-21-5p,[33] miR-101a-3p,[59] miR-129-5p,[69] miR-143-3p,[40] miR-149,[45] miR-150-5p,[48] miR-182,[47] miR-183-5p,[39] miR-200b-3p,[26] miR-205,[15] miR-210-3p,[32] miR-221 and miR-222,[53] miR-302,[52] miR-338,[28] miR-455-3p,[41] miR-512-3p,[66] and miR-4732-3p.[56]

Shuttled miR-486-5p, miR-144, and miR-21[71] from MSC-exos can prevent cardiomyocyte apoptosis by targeting the PTEN/PI3K/AKT pathway.[60,72] miR-21a-5p participates in cell survival/death pathways, presenting

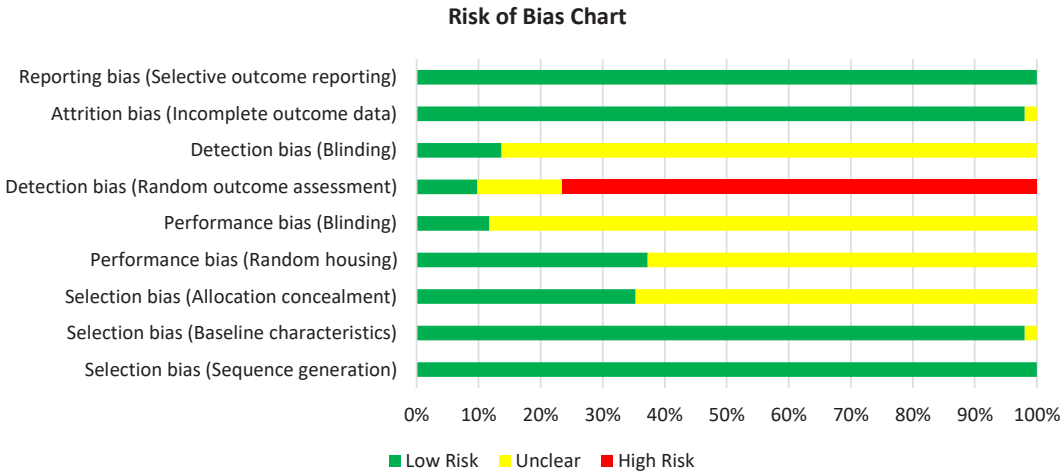

Fig. 3. Risk of bias chart based on the SYRCLE tool.

Item	1	2	3	4	5	6	7	8	9
Type of bias	Selection bias	Selection bias	Selection bias	Performance bias	Performance bias	Detection bias	Detection bias	Attrition bias	Reporting bias
Domain	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete outcome data	Selective outcome reporting
Yang (2021)	+	+	?	?	?	-	?	+	+
Wang (2023)	+	+	?	?	?	-	?	+	+
Sun (2022)	+	+	?	?	?	-	?	+	+
Pu (2021)	+	+	?	?	?	-	?	+	+
Wang (2022)	+	+	+	+	?	-	?	+	+
Wang (2017)	+	+	?	+	?	-	?	+	+
Feng (2014)	+	+	?	?	?	-	?	+	+
Zhao (2019)	+	+	?	?	?	-	?	+	+
Wang (2015)	+	?	?	?	?	-	?	+	+
Xiao (2018)	+	+	?	?	+	-	+	+	+
Peng (2020)	+	+	+	+	+	-	+	+	+
Yu (2015)	+	+	?	?	?	-	?	+	+
Chen (2020)	+	+	+	+	?	-	?	+	+
Luo (2017)	+	+	+	?	?	-	?	+	+
Zheng (2022)	+	+	+	+	?	?	?	+	+
Xiong (2022)	+	+	+	+	?	-	?	+	+
Mao (2022)	+	+	?	?	?	-	?	+	+
Wang (2021)	+	+	+	+	?	-	?	+	+
Wang (2021)	+	+	?	?	?	-	?	+	+
Chen (2021)	+	+	+	+	?	-	?	+	+
Li (2019)	+	+	+	+	?	+	?	+	+
Yan (2022)	+	+	+	+	?	+	?	+	+
Zhang (2021)	+	+	?	?	?	+	?	+	+
Lei (2021)	+	+	?	?	?	-	?	+	+
Li (2020)	+	+	+	+	?	-	?	+	+
Pei (2021)	+	+	?	?	?	-	?	+	+
Zhu (2022)	+	+	+	+	?	-	?	+	+
Gao (2023)	+	+	?	?	?	-	?	+	+
Wan (2022)	+	+	?	?	?	?	?	+	+
Xuan (2019)	+	+	?	?	?	+	+	+	+
Zilun (2019)	+	+	+	+	?	-	?	+	+
Sánchez (2021)	+	+	?	?	?	-	?	+	+
Fu (2020)	+	+	?	?	?	-	?	+	+
Ma (2018)	+	+	?	?	?	-	?	+	+
Yang (2021)	+	+	?	?	?	-	?	+	+
Ma (2021)	+	+	+	+	?	-	?	+	+
Yue (2022)	+	+	?	?	?	?	?	+	+
Huang (2020)	+	+	?	?	?	-	?	+	+
Yang (2022)	+	+	?	?	?	-	?	+	+
Pu (2023)	+	+	?	?	+	-	+	+	+
Ou (2020)	+	+	+	+	?	+	?	+	+
Sun (2019)	+	+	?	?	?	-	?	+	+
Zhu (2022)	+	+	?	?	?	-	?	+	+
Tang (2020)	+	+	?	?	?	-	?	+	+
Chen(2024)	+	+	?	?	+	-	?	+	+
Du(2024)	+	+	+	?	?	?	?	+	+
Gu(2024)	+	+	+	+	+	?	+	+	+
Ji(2024)	+	+	?	?	+	-	+	!	+
Lee(2024)	+	+	?	+	?	?	+	+	+
Wang(2024)	+	+	?	+	?	-	?	+	+
You(2024)	+	+	+	+	?	?	?	+	+

Based on the evaluated risk of bias, studies were divided into + : Low risk, ! : Unclear, and - : High-risk studies.

Fig. 4. Risk of Bias in the included studies.

cardioprotective effects after MI by targeting PTEN, FasL, PDCD4, and Peli1.[73] Likewise, in ischemic human cardiomyocytes, it is found that human BM-MSCs-exosomal miR-21-5p could enhance cardiac tissue's calcium handling gene and contractility.[74] Moreover, miR-22 (by targeting methyl CpG binding protein 2),[55] miR-24,[75] miR-125b-5p (by interaction with SMAD4),[76] miR-221,[77] and miR-451 (by targeting TLR4/NF-κB pathway) hinder apoptosis. AD-MSCs-derived exosomal miR-221/222 and miR-146a can reduce MI-induced myocardial injury by targeting PUMA and EGR1 (early growth response factor 1), respectively.[78,79] Similarly, exosomal miR-25-3p alleviates MI by targeting a histone-lysine N-methyltransferase EZH2 (Enhancer of zest homolog 2) that promotes the formation of heterochromatin and thereby represses gene expression.[60] Cardiomyocytes are protected after reperfusion with the help of the miR149/let-7c/Faslg pathway.[45] Moreover, these exosomes can reduce myocardial cell damage through the HAND2-AS1/miR-17-5p/Mfn2 pathways.[45] Some other MSCs-exosomal miRs such as miR-338,[28] miR-133,[80] miR-210,[81] and miR-126[82] could improve cardiac function, diminish infarct size, and prevent cardiomyocyte apoptosis by targeting different pathways. Other exosomal miRs, such as miR-132, miR-223, miR-19a, and miR-22 have also been reported to have cardioprotective effects.[55,58,83] miR-125b-5p derived from MSC exosomes can regulate the infarct size of mice and cardiac function by reducing autophagy through the p53-BNIP3 signaling pathway.[19]

A plethora of reports support that the paracrine activity of ischemic preconditioning MSCs can improve their therapeutic effect on MI in primates.[84] Hypoxia-conditioned BM-MSCs,[76] ischemic pre-conditioned BM-MSCs,[55] and GATA-4-overexpressing MSCs that were enriched in exosomal miR-125b, miR-22, and miR-19a,[58] respectively, could enhance the apoptosis of cardiomyocytes, decrease cardiac fibrosis, and ease cardiac repair. Besides, MSCs, grown under hypoxic conditions, secret exosomal miR-19a, that acts as anti-apoptotic. These exosomes with a high concentration of miR-19a can reduce apoptosis and increase mitochondrial membrane stability, increasing rat cardiomyocytes' survival rate.[58]

One of the important complications after MI is cardiac fibrosis and scarring. Therefore, a critical principle following MI is preventing fibrosis and reducing its progression. Scar repair, which includes angiogenesis and activation of myofibroblasts (MFBs), is responsible for cardiac structural recovery at the early stages of MI. On the other hand, insufficient repair can cause thinning and eventual rupture of the heart wall. Therefore, a precise mechanism in scar repair should be established to balance maintaining the heart's function and creating resistance of the walls.[85] Based on the results of this systematic review, MSC-exos carrying miR-22, miR-126, miR-205, miR-210-3p, miR-223, and miR-373 exert antifibrotic effects on CAD preclinical models.[15,23,27,31,32,55,56] AD-MSC-derived exosomal miR-671 attenuates myocardial fibrosis by hindering the TGFBR2/Smad2 signaling pathway.[23]

After MI, the angiogenesis of the myocardium is critical for stimulating the function of the ischemic heart.[86] MCSs-exosomal miRs can induce the formation of new blood vessels[87] by penetrating the endothelial cells to increase cell proliferation and help re-endothelialize blood vessels.[88] The proliferative and angiogenic effects of MSC-derived exosomes can be primarily attributed to specific miRs, including miR-199a and miR-130a-3p.[71] miR-126 enhanced the VEGF signaling pathway by downregulating the expression of PI3KR2 and SPRED1. Moreover, miR-126 targeting VCAM1, PIK3R2, and SPRED1 presents anti-inflammatory effects.[82] miR-210 found in the exosomes derived from BM-MSCs can improve the angiogenesis of the repair process by affecting the EFNA3 gene. Likewise, MSC can preserve myocytes against stress *in vitro* and *in vivo* by overexpressing exosomal miR-210. It is important to note that both exogenous and endogenous miR-210 have similar therapeutic effects.[81] MiR-21 is also associated with the property of neovascularization and angiogenesis by the PTEN/Akt pathway in preventing MI complications.[18,89] It should be noted that inflammatory factors (IL-6 and TNF-α) and miR-dysregulated angiogenesis-related miRs (miR-320, miR-21-3p, miR-146b-5p, miR-17-5p, and 196a-5p) impair the MSCs-exo ability to stimulate angiogenesis. Those proinflammatory cytokines also decrease VEGF, MAPK, and PI3K-AKT signaling pathways related to angiogenesis.[90] Nevertheless, alternative results indicate that inflammatory mediators could enhance the capacity of MSC-derived exosomes to facilitate angiogenesis.[91]

Atherosclerosis is the underlying cause of CAD and is involved in the development of both CAD and ACS. Coronary atherosclerosis, progressively narrows the coronary arteries' lumen, leading to reduced blood flow and myocardial ischemia. Exosomes that contain miR-512-3p have a protective role against oxidized low-density lipoproteins-induced vascular damage. This miR inhibits the destructive effect of Keleh-like ECH-associated protein 1 (Keap1) to cause endothelial damage.[66] Vesicles containing miR-21a-5p stimulate M2 macrophage polarization and reduce the infiltration of macrophages through ERK1/2 and KLF6 signaling pathways, thus diminishing atherosclerosis.[62] In addition, macrophage accumulation is suppressed through the miR-let7/IGF2BP1/PTEN pathway. MSC-exos also exerts atherosclerosis inhibitory properties by inhibiting miR-342-5p.[79] MSC-derived miR-145-rich exosomes can downregulate junction adhesion molecule A, prevent cell migration *in vitro*, and diminish atherosclerotic plaque.[61] On the other hand, exosomes derived from BM-MSCs carrying miR-223 stabilize atherosclerotic plaques by suppressing the expression of NLRP3.[92]

Differential expression of epicardial adipose tissue-exos-miRs was found in CAD patients compared to patients without CAD, providing hints for further mechanisms of atherosclerosis. Among 53 uniquely identified miRs, 21 miRs were downregulated and 32 miRs were upregulated in CAD patients. Seven differentially expressed miRs (miR-485-3p, miR-382-5p, miR-429, miR-205-5p, miR-200a-5p, miR-183-5p, and miR-141-3p) were involved in cell proliferation, survival, differentiation, and apoptosis.[11]

Vascular calcification (VC), a common cardiovascular problem in chronic kidney disease (CKD) cases, is caused by irregular inflammation, metabolism of phosphate and calcium, and other factors. Vascular calcification is often associated with atherosclerosis and CAD. Gau et al. found that miRs derived from BM-MSCs-exosomes can diminish calcium deposition in the human aorta's vascular smooth muscle cells (VSMCs) by affecting the central pathways.[93] Later, this team found that BM-MSCs-exosomes play a role in inhibiting VC by transferring miR-16/-15a/-15 and hindering nuclear factors of activated T cells 3 (NFAT-3). This target gene can prevent the osteogenic trans-differentiation of VSMCs in the aorta by downregulating the osteocalcin expression.[65] Moreover, Liu et al. indicated that BM-MSCs-derived exosomes exert anti-apoptosis and anti-calcification roles in CKD by transferring miR-381. This miR directly downregulates NFAT-5, reducing VSMC apoptosis and VC.[94]

Conclusion

Cell-free therapy using MSC-exos-miRs demonstrates remarkable potential in cardiology, particularly through its ability to mitigate inflammation, apoptosis, and fibrosis, prevent tissue damage, promote angiogenesis, and protect against I/R injury. Exosomes derived from MSCs play a pivotal role in regulating physiological and pathological processes by transporting bioactive molecules such as miRs to recipient cells. These exosomal miRs contribute significantly to the therapeutic effects of MSCs by influencing cell proliferation, differentiation, and migration. However, challenges remain due to the heterogeneity of MSC sources, preconditioning methods, and exosome extraction protocols. These variations complicate the assessment of therapeutic efficacy and hinder clinical translation. Standardized protocols for preparing and evaluating MSC-exosomal miRs are crucial to ensuring reproducibility in clinical trials. Additionally, optimizing therapeutic parameters such as exosome extraction,[95] content, concentration, administration frequency, and delivery routes are vital for enhancing their efficacy in treating CAD. Developing universally accepted methods for isolating and characterizing MSC-derived exosomes is essential to ensure homogeneity and reproducibility in clinical applications. Future studies should focus on identifying optimal therapeutic concentrations, dosing regimens, and delivery routes to maximize the cardioprotective effects of MSC-exosomal miRs.

Review Highlights

What is the current knowledge?

- MSC-exosomal miRs have positive effects in preclinical models of cardiovascular disease.

What is new here?

- MSC-exosomal miRs are emerging as key regulators in CAD, influencing atherosclerosis progression, plaque stability, and post-ischemic cardiac repair.
- MSC-exosomal miRs offer dual diagnostic and therapeutic potential in CAD, modulating inflammation, apoptosis, and tissue repair.
- The cardioprotective properties MSC-exosomal miRs could play a role in the management of CAD patients.

Authors' Contribution

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Investigation: Amin Arasteh, Seyedeh Mina Mostafavi Montazeri, Sepideh Zununi Vahed.
Methodology: Sepideh Zununi Vahed, Soroush Mostafavi, Amin Arasteh.
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Competing Interests

The authors declared that there was no conflict of interest in this study.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Data Availability Statement

Data will be made available upon a reasonable request.

Ethical Approval

This study was ethically approved via Tabriz University of Medical Sciences (Ethical code: IR.TBZMED.VCR.REC.1402.231).

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Supplementary files

Supplementary file 1 contains Table S1.

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