



MINI-REVIEW

Role of Adipose-Derived Stem Cells Therapy in Heart Failure

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ABSTRACT: Adipose-derived stem cells (ADSCs) therapy has emerged as a promising strategy for treating degenerative, inflammatory, and cardiometabolic diseases. In addition to their higher bioavailability in adipose tissue, ADSCs demonstrate superior activity in producing specific immune modulators and growth factors when compared to other stem cell types. The detrimental impact of heart failure (HF)—a condition that still lacks a fully effective therapy—has driven significant interest in the therapeutic potential of ADSCs. This interest is supported by robust evidence from experimental studies employing HF animal models. Accordingly, this review aims to explore the cardioprotective mechanisms through which ADSCs may exert beneficial effects in the context of HF.

KEYWORDS: Cardiac remodeling; heart failure; stem cell

1 Introduction

Reports on stem cell therapy date back to the 1960s [1–3], and data have highlighted its capacity to stimulate and regulate mechanisms that treat diseases rather than merely alleviating symptoms [4]. Mesenchymal stem cells (MSCs) are the most commonly used adult stem cells and are found in various niches, including bone marrow, umbilical cord, and adipose tissue [5]. MSCs exhibit immunosuppressive properties, significantly reducing the incidence and severity of graft-vs.-host disease [6]. Moreover, MSCs suppress T-cell activity through both direct contact and the release of soluble molecules, such as interleukin-10 (IL-10), transforming growth factor- β (TGF- β), hepatocyte growth factor (HGF), prostaglandin E2, nitric oxide (NO), and human leukocyte antigen (HLA)-G5, which safeguard MSCs from lysis mediated by natural killer cells [6–8].

Adipose MSCs (ADSCs) have garnered considerable attention due to their versatility across a range of applications, including metabolic [9,10], musculoskeletal [11,12], and cardiovascular diseases [13–17], as well as their reproducible and minimally invasive isolation process. ADSCs can differentiate into various cell lineages, making them suitable for both allogeneic and autologous therapies [18–20]. ADSCs also exhibit immunomodulatory effects, primarily attributed to their ability to secrete interleukin-6 (IL-6) and TGF- β 1. Additionally, the absence of HLA-DR expression further underscores their immunological versatility [21,22]. Clinical studies have explored transplantation strategies using stromal vascular fraction—a component of adipose tissue isolated prior to cell culture—as well as ADSCs, ADSC sheets, and ADSC-derived exosomes, to investigate various bioactive molecules involved in tissue regeneration [23,24].

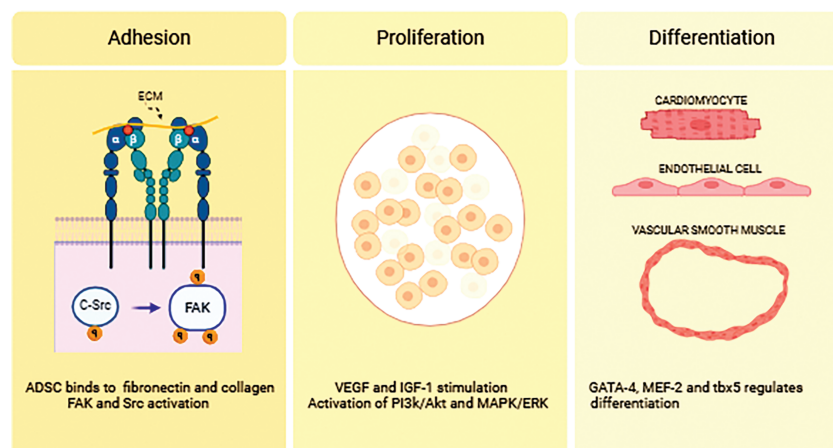
The heart is a key target for ADSCs therapy, given its limited regenerative capacity [25]. Evidence suggests that ADSCs possess the potential to differentiate into cardiomyocytes, endothelial cells, and



vascular smooth muscle cells [26–28]. These properties have supported the application of ADSCs in treating both ischemic and non-ischemic HF. Accordingly, this review will delve into the molecular mechanisms underlying the cardioprotective effects of ADSCs in HF.

2 Mechanisms of ADSCs Action in the Myocardium

ADSCs can be isolated from subcutaneous lipoaspirates to establish a rich cell culture in Dulbecco's modified Eagle's medium [29]. These cells express surface markers, such as CD90, CD29, CD44, and CD105, while lacking markers associated with hematopoietic lineage. In culture, ADSCs display a fibroblast-like morphology [30,31] and play a beneficial role in injured tissue by promoting adhesion, proliferation, and differentiation [32]. Following cardiac injury, chemotactic signaling stimulates stem cell migration via regulation of stromal cell-derived factor-1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4) axis [33]. Notably, integrin $\alpha 5 \beta 1$ —a key cellular receptor—facilitates the binding of ADSCs to fibronectin and collagen in injured myocardial tissue, which in turn promotes tissue regeneration [34]. Thereby, extracellular matrix (ECM) changes in a way that promotes the interaction of ADSCs and their exosomes with specific ECM components, particularly fibronectin, tenascin-C, and type III collagen. This process activates intracellular signaling pathways, including focal adhesion kinase (FAK) and steroid receptor coactivator (Src), promoting cell survival and anchorage [35,36]. Growth factors, including vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1), activate signaling pathways such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK). This activation leads to enhanced clonal expansion of ADSCs, potentially contributing to improved cardiac function [37,38]. The differentiation of ADSCs into cardiomyocytes or endothelial cells is regulated by transcription factors, such as GATA-4, MEF-2, and Tbx5. These factors modulate the expression of specific genes, including α -actinin and cardiac troponin (Fig. 1) [39,40].



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Figure 1: The adhesion, proliferation, and differentiation of adipose-derived stem cells (ADSCs) are orchestrated by various signaling pathways and growth factors. Initiates with adhesion to the extracellular matrix (ECM), and prominent molecules involved in these processes include focal adhesion kinase (FAK), steroid receptor coactivator (Src), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IGF-1). Integrin α and β denote subunits of integrin receptors, such as $\alpha 5 \beta 1$, which mediate ADSC binding to ECM components like fibronectin and collagen. The symbol "q" refers to Gaq, a subunit of G-proteins involved in intracellular signaling cascades related to ADSC-mediated cardioprotection

A myocardial microenvironment rich in cytokines and paracrine factors drives the differentiation of ADSCs [29,41]. Common strategies to induce cardiomyocyte differentiation include the use of growth factor-enriched culture media, dimethyl agents, and cardiomyocyte co-cultures [42]. However, preserving the functional capacity of harvested cardiac cells remains a significant challenge. Basic fibroblast growth factor (bFGF)-based cultures have demonstrated a synergistic effect with VEGF and are hypothesized to generate endothelial cells from ADSCs by modulating miRNA/mRNA interactions [43,44]. Moreover, Rangappa et al. [45] reported that ADSCs can differentiate into cardiomyocytes when incubated with 5-azacytidine (9 $\mu\text{mol/L}$ for 24 h), a cytidine analogue that promotes CpG (cytosine followed by a guanine) base-pair demethylation, expressing sarcomere protein markers such as α -actinin, myosin heavy chain, and troponin I.

A pivotal mechanism underlying ADSC therapy is their paracrine effect, which modulates the cardiac microenvironment. ADSCs have been demonstrated to support regeneration in ischemic disease by secreting VEGF and IGF-1 [44]. ADSCs also stimulate the upregulation of endothelial cell-specific molecule-1 (Esm1) and stanniocalcin-1 (Stc1) mRNA expression [46]. This process enhances the binding of VEGF to its receptor VEGFR2, thereby amplifying VEGF signaling and promoting angiogenesis [46–48]. The pro-angiogenic potential of ADSCs appears to persist even when collected from elderly individuals. Additionally, ADSCs have been shown to reduce tumor necrosis factor alpha (TNF- α) protein secretion by type 1 (M1) macrophages. These findings suggest that ADSCs may offer protection against atherosclerosis by targeting M1 macrophage foam cells through the regulation of the nuclear factor kappa B (NF- κ B)/TNF- α signaling pathway [49].

ADSC-derived exosomes have been shown to mitigate cardiac injury in infarcted mice by inhibiting apoptosis and promoting angiogenesis through the miRNA-205 signaling pathway [50]. These exosomes contain miRNAs such as miRNA-21 and miRNA-210, along with their associated proteins. miRNA-21 plays a crucial role in suppressing apoptosis and enhancing cell survival, while miRNA-210 facilitates angiogenesis and strengthens the cardiac response to hypoxia [51,52]. Exomes derived from ADSCs also facilitate macrophage M2 polarization and contribute to the attenuation of post-infarct myocardial (IM) injury by activating the sphingosine-1-phosphate/sphingosine kinase-1/sphingosine-1-phosphate receptor (S1P/SK1/S1PR1) signaling pathway. These exosomes have been shown to downregulate the expression of fibrotic proteins, including collagen I, collagen III, and α -SMA [53].

Despite their therapeutic potential, the efficacy of ADSCs can be constrained by limited viability and differentiation following transplantation. This challenge has driven research into strategies aimed at enhancing ADSCs resilience. One promising approach involves platelet-derived extracellular vesicles, which have been shown to augment the pro-angiogenic properties of ADSCs. This enhancement leads to improved vascularization, increased blood flow, and greater capillary density, while also mitigating tissue degeneration in ischemic environments [35]. Moreover photobiomodulation has been shown to enhance the metabolic activity and paracrine signaling of ADSCs, while also increasing their resistance to doxorubicin-induced toxicity [14,54–56].

3 Evidence of ADSCs in the HF

HF remains a significant global disease burden [57–59]. Several experimental studies have demonstrated that ADSCs can enhance cardiac function, mitigate fibrosis, and stimulate angiogenesis [60]. Yan et al. [61] found that ADSCs overexpressing N-cadherin exhibited improved myocardial retention, increased cardiomyocyte proliferation and angiogenesis, reduced fibrosis, and enhanced left ventricular systolic performance. ADSCs have been observed to persist at the infarct site for at least two weeks, secreting angiogenic factors such as Esm1 and Stc1, which contribute to cardioprotection and neovascularization [46]. Furthermore, even under hypoxic conditions, the upregulation of α 1-adrenergic receptors

and VEGF enhanced new vessel formation and reduced cardiomyocyte apoptosis in ADSC sheet-based therapy following myocardial infarction (MI). Notably, the α 1-adrenergic antagonist doxazosin abolished this regenerative effect, highlighting the critical role of α 1-adrenergic receptors in promoting angiogenesis in ADSC-based post-MI therapy [62].

Wang et al. [63] examined the therapeutic potential of ADSC-derived exosomes in a rat model of doxorubicin-induced HF. The exosomes boosted ATP synthesis and reduced myocardial apoptosis, culminating in improved cardiac performance. Furthermore, ADSCs were found to regulate key apoptosis-related proteins, including Bax, caspase-3, and p53. In humans, the SCIENCE study demonstrated that ADSCs therapy had no significant impact on cardiac function or myocardial miRNA expression, as assessed by extracellular vesicle analysis. The only observed change was a slight increase in miRNA-126 expression. These findings suggest that, while ADSCs are safe, they did not confer substantial clinical benefit in patients with ischemic HF [64].

ADSCs therapy in ischemic and non-ischemic HF exhibits a consistent safety profile, although clinical efficacy outcomes remain heterogeneous. The SCIENCE II trial showed that intramyocardial injections of allogeneic ADSCs in patients with non-ischemic HF significantly reduced left ventricular end-systolic volume (LVESV) and improved left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, and quality of life, suggesting clinical benefit [65]. In contrast, the Danish trial involving patients with ischemic HF found that ADSCs did not induce significant improvements in cardiac parameters or clinical symptoms, despite being well tolerated [66]. Complementary studies, such as that by Kawamura et al. [67], which applied ADSCs in spray form during coronary artery bypass grafting (CABG), demonstrated enhanced ventricular function and alleviation of HF symptoms, possibly due to angiogenesis induction and microvascular regeneration.

Kastrup et al. [68] further evaluated intramyocardial ADSCs delivery in ischemic HF patients, reinforcing the safety use of ADSCs and reporting a trend toward improved LVEF and functional capacity. Although no relevant immunological reactions were observed, four patients developed donor-specific anti-HLA antibodies without clinical manifestations. The absence of significant adverse effects supports clinical feasibility, in which ADSCs benefits appears more consistent in patients with active inflammation and less irreversible structural damage. However, the discrepant outcomes across HF phenotypes underscore the need to better identify patient subgroups most likely to benefit, as well as to standardize dosing, delivery methods, and clinical response criteria.

Evidence suggests that ADSCs promote regeneration and neovascularization, mitigate fibrosis, and regulate apoptosis, potentially making them a viable alternative to conventional HF treatments. However, no single molecular mechanism has been identified as responsible for their protective effects (Table 1) [69]. Moreover, according to clinicaltrials.gov, only ten ongoing clinical trials are currently evaluating the safety and efficacy of ADSCs (clinical trial IDs: NCT02387723; NCT03092284; NCT06840275; NCT01502514; NCT02673164; NCT01502501; NCT03797092; NCT03746938; NCT02052427; NCT01556022).

Table 1: ADSCs evidences in HF. ↑ = increase, ↓ = decrease

Author	ADSCs therapy	Subjects	HF phenotype	Results
Wang et al. (2023) [63]	ADSCs exosomes	Exosomes from mice; Wistar rats (control, HF, ADSC-exosomes groups)	Doxorubicin for 6 weeks; LVEF < 45%	↑ATP level; ↓apoptosis; ↓Bax, caspase-3 and p53; ↑Heart function in the HF group
Watanabe et al. (2021) [46]	ADSCs sheets and cell transplant	Lewis rats and transgenic (Sham, control MI, WT-ADSCs, TG-ADSCs groups)	After 5 weeks of MI (ligation of the left anterior descending artery); LVEF < 40%	ADSCs sheets: ↓Fibrosis; ↑Vasculogenesis; ADSCs transplant: ↑Esm1 and Stc1; ↑Cardiac function
Traxler et al. (2023) [64]	Allogeneic ADSCs transplant (healthy donors)	Small extracellular vesicles from patients with symptomatic HFrEF. Lewis rats allogeneic ADSCs and NaCl (placebo group)	HF with reduced ejection fraction (HFrEF); LVEF < 45%	↓miR-126
Qayyum et al. (2023) [66]	Allogeneic ADSCs intra-myocardial injection	Chronic HFrEF patients (ADSCs and placebo groups)	Chronic ischemic HFrEF; LVEF ≤ 45%	↓NT-ProBNP (only 6 months, not 1 year follow up)
Kawamura et al. (2024) [67]	ADSCs spray therapy	Ischemic cardiomyopathy + CABG patients (ADSCs and placebo groups)	Ischemic HF; LVEF ≤ 40%	↑NYHA class; ↓LGE-MRI volume; ↑LVEF
Kastrup et al. (2017) [68]	Allogeneic ADSCs intra-myocardial injection	Chronic ischemic HF patients (all received intervention)	Ischemic HF; LVEF ≤ 45%	No-significant results at 6 months: ↓LVESV; ↑LVEF
Qayyum et al. (2024) [65]	Allogeneic ADSCs intramyocardial injection	Non-ischemic HFrEF patients (ADSCs and standard care)	Non-ischemic HFrEF; LVEF < 40%	↓LVESV; ↑LVEF; ↑NYHA class
Horie et al. (2022) [62]	ADSCs sheets (<i>in vivo</i>) and ADSCs culture (<i>in vitro</i>)	ADSC from Lewis rats; Rats with MI (MI, ST, and ST + Dox groups) (<i>in vivo</i>)	Chronic HF (4 weeks after MI); LVEF-NA	↑Angiogenesis; ↓Cardiac dysfunction; ↓Cardiac remodeling (via α1-adrenergic receptor)
Yan et al. (2020) [61]	ADSCs transplant	Mice (Sham, MI + Vehicle, MI + ADSCs-con, MI + ADSCs-Ncad, MI + ADSCs-Tcad, MI + ADSCs-WT-Ncad groups)	Ischemic HF (4 and 8 weeks after MI); LVEF < 40%	↑Angiogenesis; ↑Cardiomyocyte proliferation; ↑MMP-10/MMP-13/HGF

Note: ADSCs: adipose-derived stem cells; HF: heart failure; MI: myocardial infarction; MMP: matrix metalloproteinases; HGF: hepatocyte growth factor; CABG: coronary artery bypass graft; NYHA: New York Heart Association functional class; HFrEF: heart failure with reduced left ventricular ejection fraction; LGE-MRI: Late gadolinium enhancement magnetic resonance imaging, NT-proBNP: N-terminal pro-b-type natriuretic peptide, NA: not available, Ncad: N-cadherin, Tcad: T-cadherin. 4 ADSCs cardioprotective mechanisms.

Multiple mechanisms have been implicated in the cardioprotective effects of ADSCs (Fig. 2). Angiogenic factors, including Esm1 and Stc1, activate the VEGF/VEGFR2 signaling pathway, enhancing endothelial cell migration and survival [46]. ADSC-derived exosomes contain regulatory miRNAs, such as miR-126 and miR-210, that enhance the angiogenic response by suppressing pathways antagonistic to VEGF signaling [70]. ADSCs regulate apoptosis by increasing the Bcl-2/Bax ratio, suppressing caspase activation, and inhibiting the intrinsic apoptotic pathway [63]. An increased Bcl-2/Bax ratio, combined with miRNA-21 in ADSC-derived exosomes, suppresses the expression of phosphatase and tensin homolog (PTEN), a negative regulator of the PI3K/Akt pathway. PTEN inhibition triggers Akt activation, subsequently promoting cell proliferation and survival [71,72].

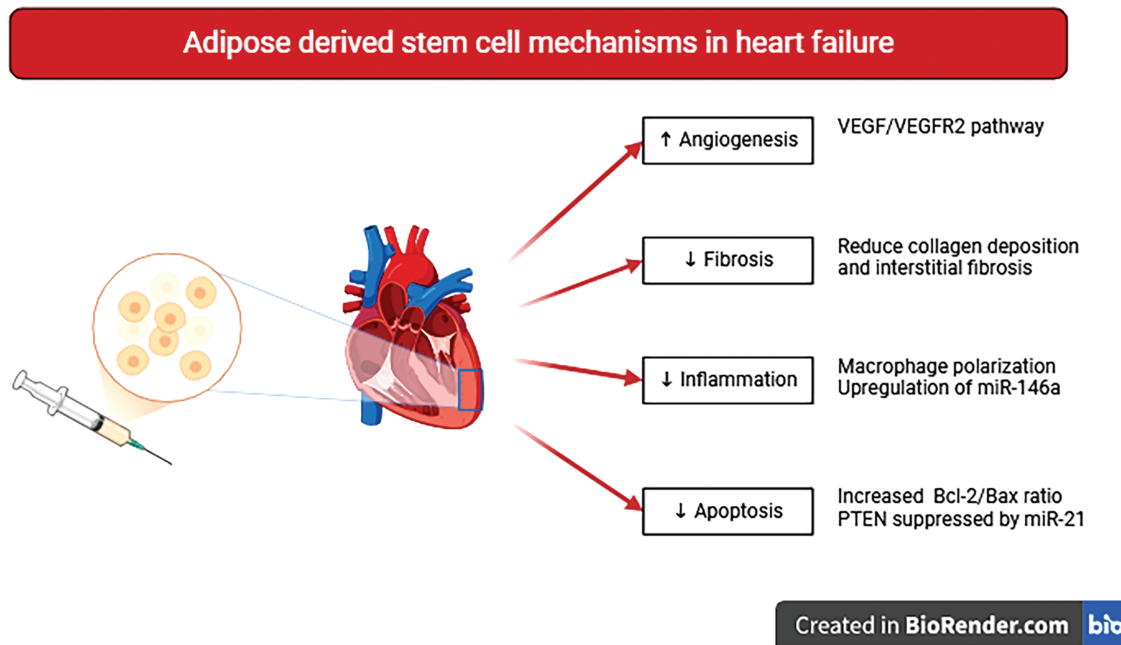


Figure 2: Putative molecular mechanisms underlying ADSCs therapy are based on paracrine effects. The key therapeutic outcomes include pro-angiogenic, antifibrotic, anti-inflammatory, and antiapoptotic cardioprotective actions

Myocardial fibrosis is a common consequence of HF, contributing to impaired contractility and myocardial relaxation. ADSCs have been shown to reduce collagen deposition and interstitial fibrosis [46]. Our previous studies demonstrated that ADSCs inhibited myocardial hypertrophy and fibrosis while improving inflammatory cytokine levels in infarcted rats [16]. These findings were linked to enhanced myocardial contractility as well as capillary density, and reduced apoptosis [73]. In H9c2 cardiomyocytes co-cultured with ADSCs, there was a decrease in fibrosis markers (e.g., MMP-2 and MMP-9) alongside the suppression of apoptotic markers (t-Bid and caspase-3) and hypertrophic markers (NFAT3, ANP, and BNP) [74].

ADSCs plays a central role in post-MI immune modulation by promoting the polarization of macrophages from M1 to the M2 phenotype, contributing to tissue regeneration. ADSC-derived exosomes activate the S1P/SK1/S1PR1 pathway, promoting this phenotypic transition and attenuating myocardial damage [53]. Furthermore, in diabetes wound model, these exosomes carry miRNA-146a, which inhibits the NF- κ B inflammatory pathway [75]. This may contribute to attenuating local inflammation and fostering a more favorable microenvironment in the injured myocardium, however, more evidence is needed to understand this mechanism in HF.

Allogeneic clinical ADSCs transplant is safe in HF, and may the therapeutic effects be mediated by paracrine mechanisms, such as immunomodulation, pro-angiogenic signaling, antiapoptotic effects, and antifibrotic remodeling. These molecular mechanisms align with clinical observations and represent possible pathways for improving heart function. The upregulation of VEGF pathways and reduction of fibrosis markers could be related to reported improvements in LVEF [65]. Similarly, the immunomodulatory effects, including macrophage polarization and NF- κ B inhibition, may contribute to improved functional status, as reflected in improvement of NYHA class [67]. Therefore, while current clinical trials support the therapeutic potential of ADSCs in HF, particularly through their molecular actions, further studies are needed to standardize protocols and better define patient subgroups most likely to benefit from this regenerative strategy.

Taken together, microRNAs such as miR-21, miR-146a, and miR-205 represent promising mediators of ADSC-induced cardioprotection. However, their roles appear context-dependent and variably validated across different HF etiologies. Ischemic HF is marked by a robust acute inflammatory response, making miR-21 especially relevant due to its regulation of ERK/MAPK signaling and targets like Sprouty Homolog 1 (Spry-1) and Programmed Cell Death 4 (PDCD4), which contribute to remodeling and fibrosis [76,77]. Although preclinical studies support its therapeutic potential, clinical validation remains limited [78]. In non-cardiac models, miR-146a exhibits anti-inflammatory effects via NF- κ B pathway suppression, though evidence in HF-specific contexts is scarce [79]. Conversely, recent studies demonstrated that miR-205-enriched ADSC-derived exosomes promote angiogenesis and reduce apoptosis in acute MI models, improving cardiac function and attenuating fibrosis [50]. Moreover, a sub-analysis of the SCIENCE trial showed that ADSC therapy modestly reduced miR-126 expression in ischemic HF patients. However, these effects were not assessed in chronic HF, underscoring translational challenges [64]. Thus, while miR-21 appears most relevant in ischemic remodeling, miR-146a and miR-205 show context-dependent promise. Further studies comparing their roles in ischemic vs. non-ischemic HF are needed to optimize ADSC-based therapies.

4 Conclusions and Perspectives

This review explores the therapeutic potential of ADSCs and their derivatives in the treatment of heart failure (HF). Through the secretion of angiogenic factors, modulation of apoptosis, reduction of fibrosis, and immunomodulatory effects, ADSCs contribute to favorable cardiac remodeling. Emerging evidence suggests improvements in cardiac function, reduced end-systolic volume, enhanced exercise tolerance, and alleviation of HF symptoms.

Although clinical trials have demonstrated the feasibility and safety of ADSC-based therapies in patients with HF, several challenges remain. Not all clinical trial outcomes have achieved statistical significance, underscoring the need for further investigation. Critical issues, including optimal methods for stem cell isolation and expansion, as well as determining appropriate dosage and administration routes, must be addressed in future experimental and clinical investigations. Developing strategies to enhance the survival, engraftment, and therapeutic efficacy of ADSCs could represent a groundbreaking advancement, offering new hope for individuals living with HF.

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Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest to report regarding the present study.

Abbreviations

ADSC	Adipose-derived stem cell
ANP	Atrial natriuretic peptide
Akt	Protein kinase B
bFGF	Basic fibroblast growth factor
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass graft
CXCR4	C-X-C chemokine receptor type 4
ECM	Extracellular matrix
ERK	Extracellular signal-regulated kinase
Esm1	Endothelial cell-specific molecule-1
FAK	Focal adhesion kinase
Gαq	G-protein alpha q subunit
HF	Heart failure
HFrEF	Heart failure with reduced left ventricular ejection fraction
HGF	Hepatocyte growth factor
HLA	Human leukocyte antigen
IGF-1	Insulin-like growth factor-1
IL-10	Interleukin-10
IL-6	Interleukin-6
LGE-MRI	Late gadolinium enhancement magnetic resonance imaging
MAPK	Mitogen-activated protein kinase
MI	Myocardial infarction
M1	Macrophage type 1 phenotype
M2	Macrophage type 2 phenotype
MMP	Matrix metalloproteinases
MSC	Mesenchymal stem cells
Ncad	N-cadherin
NF-κB	Nuclear factor kappa B
NO	Nitric oxide
NT-proBNP	N-terminal pro-b-type natriuretic peptide
NYHA	New York Heart Association
PDCD4	Programmed Cell Death 4
PI3K	Phosphoinositide 3-kinase
PTEN	Phosphatase and tensin homolog
S1P	Sphingosine-1-phosphate
S1PR1	Sphingosine-1-phosphate receptor
SK1	Sphingosine kinase-1
Spry-1	Sprouty Homolog 1
Src	Steroid receptor coactivator
Stc1	Stanniocalcin-1
t-Bid	Truncated BH3 interacting-domain death agonist
Tcad	T-cadherin
TGF-β	Transforming growth factor-β
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2
α5β1	Integrin alpha-5 beta-1

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