https://doi.org/10.31925/farmacia.2025.2.2 **REVIEW**

MESENCHYMAL STEM CELLS IN CARDIOVASCULAR PHARMACOTHERAPY: MECHANISMS, CLINICAL APPLICATIONS, AND FUTURE PERSPECTIVES

ALIN CONSTANTIN PINZARIU [1], MINELA AIDA MARANDUCA [1], CRISTINA ARSENE [1]*, ANDREEA CLIM [1], IRENE PAULA POPA [1], NINA FILIP [1], ROXANA MOSCALU [2], RADU PETRU SOROCEANU [1], DANIEL VASILE TIMOFTE [1], MIHAELA MOSCALU [1], BOGDAN HUZUM [1], DRAGOMIR NICOLAE SERBAN [1], IONELA LACRAMIOARA SERBAN [1]

[1]*Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, 16 University Street, 700115, Iaşi, România*
[2]*Division of Cell Matrix Biology & Regenerative Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PL, UK*

**corresponding author: cris_arsene@yahoo.com*

Manuscript received: December 2024

Abstract

Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic strategy in cardiovascular pharmacotherapy due to their immunomodulatory, regenerative, and angiogenic properties. Unlike conventional pharmacological treatments that primarily target symptoms, MSCs offer a disease-modifying approach by addressing the underlying pathophysiological mechanisms of cardiovascular diseases. This review explores the pharmacological mechanisms of MSC therapy, emphasising their role in paracrine signalling, cytokine modulation, angiogenesis, and myocardial regeneration. MSCs exert their effects predominantly through the secretion of growth factors, extracellular vesicles (EVs), and exosomes, influencing cardiomyocyte survival, vascular repair, and immune regulation. Clinical and preclinical studies suggest that MSC therapy can improve left ventricular function, reduce infarct size, and enhance myocardial perfusion, particularly in ischemic heart disease (IHD) and congestive heart failure (CHF). However, challenges remain regarding optimal cell delivery methods, patient selection, and long-term safety. As research advances, further large-scale clinical trials and genetic or pharmacological enhancements of MSCs will be critical for refining their clinical applications and integration into standard cardiovascular therapy.

Rezumat

Celulele stem mezenchimale (MSC) reprezintă o strategie terapeutică promițătoare în farmacoterapia cardiovasculară, datorită proprietăților imunomodulatoare, regenerative și angiogenice. Spre deosebire de tratamentele farmacologice convenționale, care au ca scop principal ameliorarea simptomelor, MSC-urile acționează asupra mecanismelor fiziopatologice care stau la baza afecțiunilor cardiovasculare. Această articol examinează mecanismele farmacologice ale terapiei cu MSC-uri, cu accent pe rolul acestora în semnalizarea paracrină, modularea citokinelor, angiogeneză și regenerarea miocardică. Efectele terapeutice ale MSC-urilor se exercită în principal prin secreția de factori de creștere, vezicule extracelulare (EV) și exozomi, influențând astfel supraviețuirea cardiomiocitelor, repararea vasculară și reglarea răspunsului imun. Studiile clinice și preclinice sugerează că terapia cu MSC-uri poate îmbunătăți funcția ventriculară stângă, reduce riscul de infarct și crește perfuzia miocardică, în special în boala cardiacă ischemică (IHD) și insuficiența cardiacă congestivă (CHF). Totuși, există anumite provocări legate de metodele optime de administrare, selecția pacienților și siguranța pe termen lung.

Keywords: mesenchymal stem cells, therapeutics, cardiovascular disease, cardiac regeneration

Introduction

Since their discovery, mesenchymal stem cells (MSCs) have emerged as a remarkable therapeutic option in regenerative medicine. Their versatility, stemming from a range of tissue sources like bone marrow, brain, kidneys, liver, adipose tissue and beyond, positions them as a practical choice for tackling various diseases, among them cardiovascular diseases shown in Figure 1. With their impressive ability to differentiate into diverse cell types and straight-forward multiplication *in vitro*, MSCs are drawing increasing attention for their potential to repair damaged tissues or address other medical conditions [1]. These cells can be isolated from adult human tissues and possess the unique ability to self-renew and differentiate into different mesenchymal lineages. After undergoing proliferation and manipulation in a laboratory setting, the cells are re-cultured [2]. Upon transplantation, they acquire immunosuppressive properties, adapt to the structure of the transplanted tissue, and subsequently advance into progenitor cells within the microenvironment, functioning both as stem cells and their progeny [3].

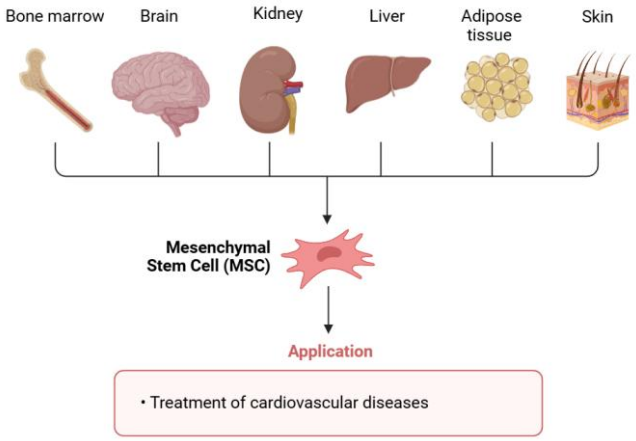

Figure 1.
Sources and Potential Application of Mesenchymal Stem Cells

The multiple potentials, immunomodulatory capacity, and secretion of anti-inflammatory molecules are properties that explain the effectiveness of using MSCs in managing chronic diseases [4-6]. Still, for all this progress, there is a question on how the pharmacological mechanisms of MSCs-tied to where they come from, their paracrine effects, and their interactions with the host environment-lead to reliable results in patients. The gap between the exciting preclinical data and clinical outcomes makes it clear that a thorough roundup of what is known so far is needed to strengthen MSC therapy for heart conditions. This review aims to strengthen stem cells' therapeutic impact by refining their preparation, so they endure longer and merge effectively with damaged heart tissue. Among the options considered, IGF-1, the pairing of HGF with IGF-1 and Cardiotrophin-1 are especially valuable for enhancing what stem cells can achieve.

Pharmacological Mechanisms of MSC Therapy in Cardiovascular Diseases

MSCs have demonstrated significant therapeutic potential in cardiovascular diseases by modulating inflammation, promoting angiogenesis, reducing fibrosis, and enhancing myocardial regeneration. Bone marrow-derived MSCs (BM-MSCs), which have been studied more thoroughly than most, show impressive resilience in hypoxic settings-ideal for sticking around in ischemic zones over the long haul-though their ability to multiply tends to wane as donors get older [7]. Adipose tissue-derived MSCs distinguish themselves through enhanced proliferative capacity and notably higher extracellular vesicles (EVs) production. The EVs from AD-MSCs enhance paracrine signalling, and given the increased secretion of vascular endothelial growth factor (VEGF) observed in preclinical myocardial infarction models, they clearly give these cells a distinct advantage in driving angiogenesis-a vital step in repairing cardiac tissue [8]. Umbilical cord-derived MSCs, by contrast, excel in their immunomodulatory role. They secrete substantial quantities of anti-inflammatory mediators, such as transforming growth factor-beta (TGF-β), and maintain reduced expression of MHC class I, which equips them to effectively temper immune responses in experimental models of cardiovascular damage [9]. MSCs tackle the underlying disease issues in a way that is quite different from standard drug treatments, which mainly focus on easing symptoms. What sets MSCs apart is their use of paracrine signalling-they release various bioactive molecules that interact with nearby cells. Beyond that, they can calm inflammation, encourage new blood vessel growth through angiogenesis, and even transform into heart muscle cells [10]. This makes them especially promising for conditions like congestive heart failure and ischemic heart disease. The problem is, while MSCs show real potential for repairing heart damage and improving blood vessel function, two major factors in these diseases-we still do not have a clear picture of how they work at a pharmacological level. Getting a handle on these details is crucial if we are going to make the most of them in clinical practice [10, 11].

Paracrine Signalling and Growth Factor Secretion

The way MSCs help in cardiovascular diseases comes down to paracrine signalling. Mesenchymal stem cells churn out various bioactive players-chemokines, cytokines, extracellular vesicles, and growth factors-that work together to patch up and regrow tissue. In the literature, we call this mix the secretome, and it is fascinating how it pulls the strings on key processes like sparking angiogenesis, blocking apoptosis, reshaping the extracellular matrix, and keeping the immune system balanced [12]. Some aspects of this secretome truly stand out in myocardial repair-they trigger angiogenesis, cut back on fibrotic buildup, and bolster cardiomyocyte survival. A great example is VEGF, which spurs endothelial cells to

proliferate and migrate, laying the groundwork for neovascularisation in oxygen-starved heart regions [13].
In addition to their angiogenic effects, MSCs can secrete hepatocyte growth factor (HGF), which has been shown to have anti-fibrotic properties by preventing fibroblast activation and collagen deposition. This action helps prevent premature myocardial scarring and maintain tissue elasticity, which is essential for maintaining normal cardiac function [14].
IGF-1 improves MSC survival, reducing apoptosis and stimulating cardiac regeneration. Studies show that co-administration of MSCs and IGF-1 in acute myocardial infarction, their effects will improve post-infarction cellular recovery and integration, having a protective effect on this myocardial tissue [15, 16]. Furthermore, this growth factor stabilises cardiac function following an infarction by preventing further cardiomyocyte loss and enhancing cell viability within the ischemic myocardium [17].
MSCs generate exosomes, extracellular vesicles (EVs), and soluble components. These two substances are essential for intercellular communication. These nanovesicles carry proteins, lipids, and microRNAs, which control cellular processes related to angiogenesis, immunological control, and cell survival [18]. MSCs are a promising technique in cardiovascular treatment because they deliver bioactive molecules to target cells, enhancing their capacity for regeneration. The ability of MSC-derived EVs to introduce bioactive substances into a range of cell types makes them appealing. Studies have demonstrated that MSC-derived EVs can enhance cardiac regeneration as effectively as, or even more so than, MSCs themselves. Consequently, researchers are increasingly exploring cell-free therapies utilizing MSC exosomes as promising treatment options for cardiac disorders.

Immune-Modulating Effects

Inflammation plays a pivotal role in both acute and chronic cardiovascular conditions, especially after a myocardial infarction. When the heart sustains damage, it sets off an inflammatory cascade-think immune cell activation, cytokine release, and fibrotic remodelling-all of which can drive the gradual decline of cardiac function. This is precisely where mesenchymal stem cells (MSCs) step in, making a mark by interacting with the immune system. They connect with all sorts of immune cells-macrophages, T lymphocytes, and dendritic cells-and manage to tone down the pro-inflammatory response while helping the tissue heal [19].
One of MSCs' key strengths is their knack for managing cytokine production. This helps tamp down the excessive inflammation that often ramps up before a myocardial infarction, which plays an important role in cardiovascular therapy [20]. The inflammatory response post-infarction can either pave the way for heart repair or tip the scales toward harmful remodelling-it all depends on how it's managed. MSCs step in by curbing pro-inflammatory cytokines and boosting anti-inflammatory mediators, effectively fostering a microenvironment that leans more toward regeneration [19, 20].
MSCs have many properties that are particularly important for treating inflammatory and degenerative diseases [21]. They possess natural abilities to detect changes in their environment, such as the appearance of inflammation. Under such conditions, they can induce the release of bioactive agents and form progenitor cells in response to these changes [22]. Additionally, it has been demonstrated that MSCS migrate to sites of inflammation far from their injection site [23, 24].
MSCs can be easily obtained through well-established procedures such as bone marrow aspiration. Moreover, transplanted MSC cells do not pose a risk of rejection by the patient's body as they are derived from the patient's own tissue [5]. From the mesoderm germ layer, mesenchymal stem cells are multipotent progenitor cells that can develop into multiple cell types. This multilineage potential permits them to develop into adipocytes (fat cells), osteocytes (bone cells), and chondrocytes (cartilage cells), among others [25-27]. A significant advantage of MSCs in regenerative medicine and treatments lies in their potential to differentiate into different cell types. The ability of MSCs to proliferate widely in culture and to be isolated from a range of adult tissues adds to their potential as a treatment approach for several clinical illnesses. MSCs are becoming more widely acknowledged for their unique and beneficial therapeutic qualities as cellular treatments and regenerative medicine research advances [23].
Currently, research is underway to examine the therapeutic benefits of MSCs in patients with various conditions. These conditions include orthopaedic injuries, acute graft rejection following bone marrow transplantation, cardiovascular diseases, autoimmune disorders, and liver diseases. Moreover, the genetic engineering of MSCs to enhance the expression of antitumor genes has opened up promising perspectives for their potential clinical application as an antineoplastic therapy [5].
In 1995, the first clinical research of MSCs grown in culture media was carried out, in which autologous cells were given to 15 patients. Since this first study, several clinical investigations have been carried out to assess the viability and effectiveness of MSC therapy for various illnesses. These studies often fall into one of three categories: Phase I, which assesses safety; Phase II, which focuses on proving effectiveness and concept in human subjects; or Phase I/II, which combines the two [5].
As demonstrated by many studies showing the absence of substantial medium-term adverse events,

MSCs generally have a favourable safety profile. However, a few studies have shown the incidence of moderate and temporary peri-injection effects, which are often ephemeral and not very concerning [22]. Acute myocardial ischemia, stroke, liver cirrhosis, amyotrophic lateral sclerosis, and osteoarticular disorders are among the other conditions for which several comprehensive clinical investigations have shown the efficacy of MSCS infusion [5].

Therapeutic Use of MSCs in Cardiovascular Diseases

Despite advances in treatment options, ischemic heart disease (IHD) and congestive heart failure (CHF) were indeed significant global health concerns, and they likely continue to be major causes of morbidity and mortality in recent years. Both disorders are intimately connected to the heart and circulatory system functioning, yet they have unique features [28].

Ischemic Heart Disease (IHD)

Impairment of cardiac function due to an imbalance between myocardial oxygen supply and demand is known as IHD, a syndrome with multiple causes. Several pathological entities are included in the concept of ischemic heart disease, including stable or unstable angina pectoris (AP), acute or chronic myocardial infarction, rhythm and conduction disorders, silent myocardial ischemia, heart failure, and sudden coronary death. The primary cause of IHD is atherosclerosis (90%), a process in which fatty deposits (plaque) are localised primarily on the subepicardial conductance vessels, restricting blood flow. When an atheromatous plaque becomes complicated, sudden thrombotic obstruction of the involved coronary artery occurs, which can lead to angina pectoris or cause a myocardial infarction (MI), which can be life-threatening [28-30].

The available treatments for IHD have improved over time. These include medication administration (such as beta-blockers, statins, and antiplatelet medications), interventional techniques (*e.g.*, angioplasty and stent placement), and coronary artery bypass surgery. In addition, lifestyle changes, such as stress management, smoking cessation, regular exercise, and a heart-healthy diet, are essential for the prevention and management of high blood pressure (IHD) [31, 32].

Congestive Heart Failure (CHF)

CHD, also known as heart failure, is an abnormality or dysfunction of the heart structure that results in the inability of the heart to deliver oxygen at a rate commensurate with the needs of the metabolising tissues despite normal filling pressure (or only at the cost of elevated pressure). Left ventricular systolic or diastolic dysfunction is the substrate of heart failure [33]. While the left ventricle's residual and end-diastolic blood volumes increase, left ventricular systolic dysfunction results from a decrease in the emptying capacity of the left ventricle, whose ejection fraction (EF) falls below 35%. An incomplete filling of the ventricles, while their emptying capacity is preserved, is a sign of diastolic dysfunction of the ventricles. Pericardial thickening, cardiac wall hypertrophy, and myocardial infiltration reduce the distensibility of the ventricles [34-36].

The treatment goals of patients with proven CHF involve a combination of lifestyle changes (exercise restriction adapted to the NYHA functional class. Patients in class I do not need restrictions; patients in class II should refrain from sports and strenuous exercise; patients in class III should reduce the amount of time spent working and intersperse periods of rest; and patients in class IV should relax in bed or on an armchair; sodium, in any form ingested, worsens heart failure. Therefore, it is restricted [37] and medications (such as diuretics, the only ones that can combat salt and water retention, ACE inhibitors, which can reduce vasoconstriction caused by neuroendocrine activation and protect the myocardium from neurohormonal aggression, thus delaying the progression of heart failure) or an aldosterone antagonist, which is indicated in patients with NYHA class IV HF or class III with EF below 35% and who are receiving standard therapy, ACE inhibitor, beta-blocker and diuretic [38-40].

Public health efforts are particularly important in educating patients and their families about the causes and treatment of the disease and lifestyle changes. A variety of lifestyle interventions are recommended, such as regular health check-ups and interventions, treatment adherence, symptom recognition, weight monitoring, sodium and fluid restriction, alcohol and smoking cessation, weight loss, regular physical activity, and treatment of depression [38].

Investigations into the application of cell therapy, with a particular focus on MSCs, in the context of cardiovascular disease offer considerable scientific intrigue. These studies have demonstrated substantial potential for ameliorating circulatory function in pathologies such as dilated cardiomyopathy and myocardial infarction [41].

The therapeutic allure of MSCs rests on a set of notable properties that distinguish them in clinical research. Regenerative potential- MSCs demonstrate a remarkable capacity to regenerate and differentiate into various cell lineages, such as smooth muscle cells, endothelial cells, and cardiomyocytes. When introduced into cardiac tissue compromised or modified by injury, they play an active role in repairing and renewing the affected regions [41, 42]. Moreover, MSCs influence immune system dynamics through mechanisms that become particularly significant following cardiac damage. This ability allows them to dampen inflammation and cultivate

conditions that favour tissue healing [43]. Additionally, the paracrine communication, by releasing bioactive agents like growth factors and cytokines, MSCs support tissue regeneration and promote angiogenesis, thereby amplifying the repair process [44]. Furthermore, the low immunogenic potential, marked by their subdued immunogenicity, MSCs elicit only a faint immune response when transplanted, making them strong contenders for allogeneic applications with minimal rejection risk [44].

Some studies [13, 45, 46] highlight the early research in this field and provide evidence supporting the potential benefits of MSCS therapy in cardiovascular diseases:

Katritsis DG *et al*. evaluated the use of intracoronary infusion of autologous bone marrow-derived MSCs in patients with acute myocardial infarction. The study found that MSCS therapy was safe and resulted in significant improvements in left ventricular function [45]. Moreover, Nagaya *et al*. researched intramyocardial transplantation of autologous bone marrow-derived MSCs in patients with dilated cardiomyopathy. The study reported improved cardiac function and exercise capacity in patients who received MSC therapy [13]. Xu *et al*. conducted a study on delivering autologous MSCs harvested from patients *via* intracoronary infusion in individuals with acute myocardial infarction. Their data pointed to some encouraging outcomes: MSC therapy appeared to enhance cardiac function and reduce the extent of infarcted tissue [46]. That being said, it is worth stressing that while these findings are hopeful, the use of cell therapy in cardiovascular diseases is still a work in progress. Further studies are going to need more robust research-more extensive clinical trials with extended follow-up periods-to pin down the safety, effectiveness, and ideal administration techniques for MSC therapy in these conditions.

Over the past few years, several active studies and clinical trials have been probing the potential of stem cells, MSCs included, in tackling cardiovascular diseases. These efforts are all about deepening our insight and, with any luck, paving the way for new treatment options for patients with heart conditions.

In preclinical studies of animal models of cardiovascular disease, it has been observed that MSCs have a real knack for settling into cardiac injury sites-whether they're given systemically or directly-and they do a solid job of helping repair myocardial infarcts [47-49]. Other studies took this further by transplanting MSCs into rats with lab-induced dilated cardiomyopathy, and the outcomes appeared encouraging, with positive outcomes in this procedure. The procedure significantly augmented capillary density and reduced the collagen volume fraction within the myocardium. Additionally, it led to a decrease in left ventricle end-diastolic pressure, indicating improved cardiac function [5].

Clinical studies based on the use of stem cells to improve cardiac function have highlighted that intracoronary administration of autologous MSCs after AMI (acute myocardial infarction) has contributed to a significant improvement in left ventricular function, with a noticeable increase in the ejection fraction, statistically significant compared to the pre-implantation stage [46].

Moreover, recent investigations have elucidated that mesenchymal stem cells facilitate cardiac restoration through the secretion of SEVs *via* a paracrine modality. These SEVs have been identified as notably efficacious in conferring cardioprotection within myocardial ischemia-reperfusion injury, surpassing the therapeutic efficacy of MSCs themselves in a rodent model of MI. The core of this research centres on unravelling the mechanisms by which SEVs MSCs protect myocardial tissue. It's fascinating how they manage this-carrying critical biomolecules, tamping down inflammation, encouraging angiogenesis, and fine-tuning the immune response [18].

To enhance stem cell therapy for myocardial infarction, several preconditioning strategies have been explored and documented. In this sense, we present in Table I some data from the literature regarding preconditioning with drugs/chemical substances and growth factors.

The evolution of stem cell therapy as a promising avenue for MI treatment has significantly benefited from preconditioning stem cells with specific chemicals and growth factors.

One study by Guo *et al*. demonstrated that IGF-1 exerts a significant influence following myocardial infarction by mitigating inflammation and ameliorating cardiac dysfunction. It enhances the survival of transplanted MSCs and reduces myocardial cell apoptosis, constituting a pivotal mechanism in cardiac repair. Then there is Zhang *et al*. who searched into HGF and IGF-1 together and found they ramp up the protective effects of bone marrow stem cells-a combination that hints at some real synergy for heart recovery [14, 17].

Additionally, Ling *et al*. discovered that bFGF activates Sca-1+ cardiac stem cells *via* the PI3K/Akt pathway, which is directly related to the importance of angiogenesis and cell migration in the healing process. Likewise, Bortolotti *et al*. observed that cardiotrophin-1 facilitates the engraftment of mesenchymal stromal cells, enhancing outcomes in the treatment of infarcted myocardium [50, 51].

Furthermore, additional substances such as dimethyloxaloylglycine, angiotensin II, and statins, including atorvastatin and simvastatin, have been evaluated for preconditioning. Zhang *et al*. observed that it enhances angiogenesis *via* the PI3K/Akt pathway, illustrating the complexity of stem cell modifications and tissue healing. Statins-atorvastatin and simvastatin in particular-improve heart function,

keep cells alive, and nudge them toward cardiovascular differentiation, which underlines how varied these preconditioning tricks can be. These strategies focus on stem cell survival and enhancing their functional capabilities once engrafted into damaged tissues [52, 55-57].

Table I

Research on preconditioning of stem cells with chemicals and growth factors

Study	Substance	Main findings
Guo *et al*. [10]	IGF-1	attenuate cardiac dysfunction, increase the survival of engrafted cells in the ischemic heart, decrease myocardium cell apoptosis
Zhang GW *et al*. [9]	HGF combined with IGF-1	promoted the protective potential of transplanted BMSCs to repair infarcted myocardium
Ling L *et al*. [41]	bFGF	increased cell migration to the infarct area, improved angiogenesis
Bortolotti F *et al*. [42]	Cardiotrophin-1	improving cell therapy of the infarcted myocardium
Zhang J *et al*. [43]	Dimethyloxaloylglycine	promotes the angiogenesis
Mias C *et al*. [44]	Melatonin	increase in the antifibrotic activity
Shinmura D *et al*. [45]	Pioglitazone	improved cardiac function
Chao L *et al*. [46]	Angiotensin IIAng II)	improved angiogenesis and gap junction formation
Li *et al*. [47]	Atorvastatin	improves cardiac performance
Yue-Jin Y *et al*. [48]	Simvastatin	promoting cell survival and cardiovascular differentiation
Hoke *et al*. [49]	Sildenafil (Viagra)	improves survival under conditions of ischemia
Wisel *et al*. [50]	Trimetazidine	increase in the recovery of myocardial function

Emerging substances such as sildenafil (Viagra®) and trimetazidine also present interesting avenues for further research, suggesting the potential for repurposing well-known pharmaceuticals to support stem cell-based therapies [58, 59].

Evidence gathered from these studies underscores the role that preconditioning plays in elevating the effectiveness of stem cell therapy for myocardial infarction (MI). By leveraging the distinctive properties and functional mechanisms of these compounds, researchers are developing pathways to more precise, potent, and personalised therapeutic solutions, which are likely to enhance recovery results and the well-being of myocardial infarction patients.

To assess the utility of MSC therapy in cardiovascular diseases, a systematic differentiation between preclinical observations and clinical outcomes is indispensable. Preclinical investigations, such as those conducted in rodent models, have demonstrated the capacity of MSCs to reduce infarct dimensions and stimulate angiogenesis, thereby providing foundational mechanistic insights that underpin potential therapeutic strategies [60]. In contrast, clinical investigations-specifically Phase I/II trials involving human subjects-have documented enhancements in left ventricular ejection fraction (LVEF) following MSC administration, with the magnitude of these effects varying according to the underlying pathology, such as acute myocardial infarction versus chronic heart failure [61].

Conclusions

Therapies grounded in MSCs have surfaced as a significant prospect for tackling cardio-vascular disorders, delivering a multifaceted therapeutic approach that transcends the boundaries of traditional pharmacotherapy. Through their proficiency in moderating immune responses, promoting the development of new blood vessels, and secreting factors that aid regeneration, MSCs have demonstrated notable effectiveness in facilitating myocardial repair after ischemic injury. However, despite this potential, significant hurdles remain in bringing these therapies into routine clinical application. Future efforts must concentrate on perfecting administration methods, bolstering cell survival, and establishing sustained safety profiles. A thorough understanding of how MSCs interact with existing cardiovascular drugs is necessary to ensure their effective integration into standard care protocols. The capacity of MSCs to simultaneously influence multiple pathological processes emphasises their substantial pharmacological relevance in cardiovascular medicine. Continued developments in genetic engineering, biomaterial frameworks, and preconditioning techniques offer opportunities to further elevate their therapeutic value, potentially marking the dawn of a new era in regenerative cardiovascular treatment.

Conflict of interest

The authors declare no conflict of interest.

References

1. Prado-Yupanqui JW, Ramírez-Orrego L, Cortez D, Vera-Ponce VJ, Chenet SM, Tejedo JR, Tapia-Limonchi R, The hidden power of the secretome: Therapeutic potential on wound healing and cell-free regenerative medicine-a systematic review. *Int J Mol Sci.*, 2025; 26(5): 1926-1926.
2. Niu X, Zhang L, Xing S, Liu J, Li D, Wang Y, Wang Y, Su M, Targeting lung damage: Amniotic mesenchymal stem cells mitigate lipopolysaccharide-induced acute lung injury *via* multiple signaling pathways. *Int J Mol Sci.*, 2025; 26(5): 2314-2314.

3. Javan MR, Khosrojerdi A, Moazzeni SM, New insights into the implementation of mesenchymal stem cells in cancer therapy: Prospects for anti-angiogenesis treatment. *Front Oncol.*, 2019; 9(8): 840-840.
4. Ullah I, Subbarao RB, Rho GJ, Human mesenchymal stem cells-current trends and future prospective, *Biosci Rep.*, 2015; 35(2): e00191-e00191.
5. Wang S, Qu X, Zhao RC, Clinical applications of mesenchymal stem cells. *J Hematol Oncol.*, 2012; 5(4): 19-19.
6. Siennicka K, Zołocińska A, Dębski T, Pojda Z, Comparison of the donor age-dependent and *in vitro* culture-dependent mesenchymal stem cell aging in rat model. *Stem Cells Int.*, 2021; 2021(6): 6665358.
7. Bagno L, Hatzistergos KE, Balkan W, Hare JM, Mesenchymal stem cell-based therapy for cardiovascular disease: Progress and challenges. *Mol Ther.*, 2018; 26(7): 1610-1623.
8. van der Bogt KEA, Schrepfer S, Yu J, Sheikh AY, Hoyt G, Govaert JA, Velotta JB, Contag CH, Robbins RC, Wu JC, Comparison of transplantation of adipose tissue- and bone marrow-derived mesenchymal stem cells in the infarcted heart. *Transplantation*, 2009; 87(5): 642-652.
9. Song N, Scholtemeijer M, Shah K, Mesenchymal stem cell immunomodulation: Mechanisms and therapeutic potential. *Trends Pharmacol Sci.*, 2020; 41(9): 653-664.
10. Zhang J, Zhang B, Zhang L, Xu X, Cheng Q, Wang Y, Li Y, Jiang R, Duan S, Zhang L, Engineered nanovesicles mediated cardiomyocyte survival and neovascularization for the therapy of myocardial infarction. *Colloids Surf B Biointerfaces*, 2024; 243(11): 114135-114135.
11. Sepehri M, Rabbani S, Ai J, Bahrami N, Ghanbari H, Namini MS, Sharifi M, Kouchakzadeh F, Esfahlani MA, Ebrahimi-Barough S, Therapeutic potential of exosomes derived from human endometrial mesenchymal stem cells for heart tissue regeneration after myocardial infarction. *Regen Ther.*, 2025; 28(12): 451-461.
12. Ehlen QT, Costello JP, Mirsky NA, Slavin BV, Parra M, Ptashnik A, Nayak VV, Coelho PG, Witek L, Treatment of bone defects and nonunion *via* novel delivery mechanisms, growth factors, and stem cells: A review. *ACS Biomater Sci Eng.*, 2024; 10(11): 7314-7336.
13. Nagaya N, Kangawa K, Itoh T, Iwase T, Murakami S, Miyahara Y, Fujii T, Uematsu M, Ohgushi H, Yamagishi M, Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. *Circulation*, 2005; 112(8): 1128-1135.
14. Zhang GW, Gu TX, Guan XY, Sun XJ, Qi X, Li XY, Wang XB, Lv F, Yu L, Jiang DQ, HGF and IGF-1 promote protective effects of allogeneic BMSC transplantation in rabbit model of acute myocardial infarction. *Cell Prolif.*, 2015; 48(6): 661-670.
15. Rabbani S, Soleimani M, Sahebjam M, Imani M, Haeri A, Ghiaseddin A, Nassiri SM, Majd Ardakani J, Tajik Rostami M, Jalali A, Simultaneous delivery of Wharton's jelly mesenchymal stem cells and insulin-like growth factor-1 in acute myocardial infarction. *Iran J Pharm Res.*, 2018; 17(2): 426-441.
16. Gómez-Mauricio G, Moscoso I, Martín-Cancho MF, Crisóstomo V, Prat-Vidal C, Báez-Díaz C, Sánchez-Margallo FM, Bernad A, Combined administration of mesenchymal stem cells overexpressing IGF-1 and HGF enhances neovascularization but moderately improves cardiac regeneration in a porcine model. *Stem Cell Res Ther.*, 2016; 7(7): 94-94.
17. Guo J, Zheng D, Li W, Li H, Zhang A, Li Z, Insulin-like growth factor 1 treatment of MSCs attenuates inflammation and cardiac dysfunction following MI. *Inflammation*, 2014; 37(6): 2156-2163.
18. Wu H, Qian X, Liang G, The role of small extracellular vesicles derived from mesenchymal stromal cells on myocardial protection: A review of current advances and future perspectives. *Cardiovasc Drugs Ther.*, 2023; 37(1): 1-12.
19. Marigo I, Dazzi F, The immunomodulatory properties of mesenchymal stem cells. *Semin Immunopathol.*, 2011; 33(6): 593-602.
20. Hou H, Zheng M, Pan K, Wang G, Li Z, Li Q, Therapeutic potential of CD73+ mesenchymal stem cells for myocardial infarction and beyond. *Histol Histopathol.*, 2024; 18859(10): 18859-18859.
21. Turovsky EA, Golovicheva VV, Varlamova EG, Danilina TI, Goryunov KV, Shevtsova YA, Pevzner IB, Zorova LD, Babenko VA, Evtushenko EA, Mesenchymal stromal cell-derived extracellular vesicles afford neuroprotection by modulating PI3K/AKT pathway and calcium oscillations. *Int J Biol Sci.*, 2022; 18(13): 5345-5368.
22. Otto WR, Wright NA, Mesenchymal stem cells: From experiment to clinic. *Fibrogenesis Tissue Repair*, 2011; 4(9): 20-20.
23. Uder C, Brückner S, Winkler S, Tautenhahn HM, Christ B, Mammalian MSC from selected species: Features and applications, *Cytometry A*, 2018; 93(1): 32-49.
24. Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, Bonifazi F, Ciceri F, Cornelissen J, Malladi R, Duarte RF, Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: Updated consensus recommendations of the European Society for Blood and Marrow Transplantation. *Lancet Haematol.*, 2020; 7(2): e157-e167.
25. Haliga R, Zugun-Eloae F, Oboroceanu T, Pînzariu A, Mocanu V, Vitamin D and tissular expression of vitamin D receptor in obesity. *Rev Med Chir Soc Med Nat Iasi*, 2016; 120(2): 404-408.
26. Hristov I, Mocanu V, Zugun-Eloae F, Labusca L, Cretu-Silivestru I, Oboroceanu T, Tiron C, Tiron A, Burlacu A, Pinzariu AC, Association of intracellular lipid accumulation in subcutaneous adipocyte precursors and plasma adipokines in bariatric surgery candidates. *Lipids Health Dis.*, 2019; 18(6): 141.
27. Pinzariu AC, Oboroceanu T, Eloae FZ, Hristov I, Costan VV, Labusca L, Cianga P, Verestiuc L, Hanganu B, Crauciuc DV, Vitamin D as a regulator of adipocyte differentiation effects *in vivo* and *in vitro*. *Rev Chim.*, 2018; 69(3): 731-734.
28. Pagliaro BR, Cannata F, Stefanini GG, Bolognese L, Myocardial ischemia and coronary disease in heart failure. *Heart Fail Rev.*, 2020; 25(1): 53-65.

29. Marin LM, Sîrbu I, Ozon EA, Skotnicki M, Lulek J, Chivu RD, Drăgănescu D, Ticagrelor - mechanism of action and its impact on drug efficacy. *Farmacia*, 2024; 72(2): 273-279.
30. Antman EM, Braunwald E, Managing stable ischemic heart disease. *N Engl J Med.*, 2020; 382(15): 1468-1470.
31. Jia S, Liu Y, Yuan J, Evidence in guidelines for treatment of coronary artery disease. *Adv Exp Med Biol.*, 2020; 1177(2): 37-73.
32. Perera D, Crake T, Lee V, Angiography-guided multivessel percutaneous coronary intervention versus ischemia-guided percutaneous coronary intervention versus medical therapy in the management of significant disease in non-infarct-related arteries in ST-elevation myocardial infarction patients with multivessel coronary disease. *Crit Pathw Cardiol.*, 2018; 17(2): 77-82.
33. Borlaug BA, Paulus WJ, Heart failure with preserved ejection fraction: Pathophysiology, diagnosis, and treatment. *Eur Heart J.*, 2011; 32(6): 670-679.
34. Chen J, Aronowitz P, Congestive heart failure. *Med Clin North Am.*, 2022; 106(3): 447-458.
35. Thibodeau JT, Drazner MH, The role of the clinical examination in patients with heart failure. *JACC Heart Fail.*, 2018; 6(7): 543-551.
36. Petris OR, Cojocaru E, Fildan AP, Cojocaru C, COPD and anticoagulation therapy: Time for a new approach? *COPD*, 2021; 16(12): 3429-3436.
37. Shah AM, Mann DL, In search of new therapeutic targets and strategies for heart failure: Recent advances in basic science. *Lancet*, 2011; 378(9792): 704-712.
38. Alkhuraisi F, Alqarni F, Daghriri O, Algarni T, Alqahtani A, Syed W, Al-Rawi MBA, Angiotensin receptor–neprilysin inhibitors (ARNI) and tolerability in heart failure patients – a retrospective observational study from Prince Sultan Cardiac Centre. *Farmacia*, 2023; 71(1): 44-49.
39. Maranduca MA, Tanase DM, Cozma CT, Dima N, Clim A, Pinzariu AC, Serban DN, Serban IL, The impact of angiotensin-converting enzyme-2/ angiotensin 1-7 axis in establishing severe COVID-19 consequences. *Pharmaceutics*, 2022; 14(9): 1906-1906.
40. Cojocaru E, Cojocaru C, Vlad CE, Eva L, Role of the renin-angiotensin system in long COVID's cardiovascular injuries. *Biomedicines*, 2023; 11(7): 2004-2004.
41. Yamanaka S, Pluripotent stem cell-based cell therapy-promise and challenges. *Cell Stem Cell*, 2020; 27(4): 523-531.
42. Li D, Sun J, Zhong TP, Wnt signaling in heart development and regeneration. *Curr Cardiol Rep.*, 2022; 24(10): 1425-1438.
43. Grinnemo KH, Löfling M, Nathanson L, Baumgartner R, Ketelhuth DFJ, Beljanski V, Davies LC, Österholm C, Immunomodulatory effects of interferon-γ on human fetal cardiac mesenchymal stromal cells. *Stem Cell Res Ther.*, 2019; 10(12): 371-371.
44. Elshaer SL, Bahram SH, Rajashekar P, Gangaraju R, El-Remessy AB, Modulation of mesenchymal stem cells for enhanced therapeutic utility in ischemic vascular diseases. *Int J Mol Sci.*, 2021; 23(1): 249-249.
45. Katritsis DG, Sotiropoulou P, Giazitzoglou E, Karvouni E, Papamichail M, Electrophysiological effects of intracoronary transplantation of autologous mesenchymal and endothelial progenitor cells. *Europace*, 2007; 9(3): 167-171.
46. Chen SL, Krishnan L, Srinivasan S, Benziger J, Bocarsly AB, Ion exchange resin/polystyrene sulfonate composite membranes for PEM fuel cells. *J Membr Sci.*, 2004; 243(1-2): 327-333.
47. Yang Z, Zhang F, Ma W, Chen B, Zhou F, Xu Z, Zhang Y, Zhang D, Zhu T, Wang L, A novel approach to transplanting bone marrow stem cells to repair human myocardial infarction: Delivery *via* a noninfarct-relative artery. *Cardiovasc Ther.*, 2010; 28(6): 380-385.
48. White SJ, Chong JJH, Mesenchymal stem cells in cardiac repair: Effects on myocytes, vasculature, and fibroblasts. *Clin Ther.*, 2020; 42(10): 1880-1891.
49. Tang J, Wang J, Huang K, Ye Y, Su T, Qiao L, Hensley MT, Caranasos TG, Zhang J, Gu Z, Cardiac cell-integrated microneedle patch for treating myocardial infarction. *Sci Adv.*, 2018; 4(11): eaat9365-eaat9365.
50. Ling L, Gu S, Cheng Y, Ding L, bFGF promotes Sca-1+ cardiac stem cell migration through activation of the PI3K/Akt pathway. *Mol Med Rep.*, 2018; 17(2): 2349-2356.
51. Bortolotti F, Ruozi G, Falcione A, Doimo S, Dal Ferro M, Lesizza P, Zentilin L, Banks L, Zacchigna S, Giacca M, *In vivo* functional selection identifies cardiotrophin-1 as a cardiac engraftment factor for mesenchymal stromal cells. *Circulation*, 2017; 136(15): 1509-1524.
52. Zhang J, Guan J, Qi X, Ding H, Yuan H, Xie Z, Chen C, Li X, Zhang C, Huang Y, Dimethyloxaloylglycine promotes the angiogenic activity of mesenchymal stem cells derived from iPSCs *via* activation of the PI3K/Akt pathway for bone regeneration. *Int J Biol Sci.*, 2016; 12(6): 639-652.
53. Mias C, Lairez O, Trouche E, Roncalli J, Calise D, Seguelas MH, Ordener C, Piercecchi-Marti MD, Auge N, Salvayre AN, Mesenchymal stem cells promote matrix metalloproteinase secretion by cardiac fibroblasts and reduce cardiac ventricular fibrosis after myocardial infarction. *Stem Cells*, 2009; 27(11): 2734-2743.
54. Shinmura D, Togashi I, Miyoshi S, Nishiyama N, Hida N, Tsuji H, Tsuruta H, Segawa K, Tsukada Y, Ogawa S, Pretreatment of human mesenchymal stem cells with pioglitazone improved efficiency of cardiomyogenic transdifferentiation and cardiac function. *Stem Cells*, 2011; 29(2): 357-366.
55. Liu C, Fan Y, Zhou L, Zhu HY, Song YC, Hu L, Wang Y, Li QP, Pretreatment of mesenchymal stem cells with angiotensin II enhances paracrine effects, angiogenesis, gap junction formation and therapeutic efficacy for myocardial infarction. *Int J Cardiol.*, 2015; 188(6): 22-32.
56. Li N, Yang YJ, Qian HY, Li Q, Zhang Q, Li XD, Dong QT, Xu H, Song L, Zhang H, Intravenous administration of atorvastatin-pretreated mesenchymal stem cells improves cardiac performance after acute myocardial infarction: Role of CXCR4. *Am J Transl Res.*, 2015; 7(6): 1058-1070.
57. Yang YJ, Qian HY, Huang J, Li JJ, Gao RL, Dou KF, Yang GS, Willerson JT, Geng YJ, Combined therapy with simvastatin and bone marrow-derived

mesenchymal stem cells increases benefits in infarcted swine hearts. *Arterioscler Thromb Vasc Biol.*, 2009; 29(12): 2076-2082.

58. Hoke NN, Salloum FN, Kass DA, Das A, Kukreja RC, Preconditioning by phosphodiesterase-5 inhibition improves therapeutic efficacy of adipose-derived stem cells following myocardial infarction in mice. *Stem Cells*, 2012; 30(2): 326-335.
59. Wisel S, Khan M, Kuppusamy ML, Mohan IK, Chacko SM, Rivera BK, Sun BC, Hideg K, Kuppusamy P, Pharmacological preconditioning of mesenchymal stem cells with trimetazidine (1-[2,3,4-trimethoxybenzyl]piperazine) protects hypoxic cells against oxidative stress and enhances recovery of myocardial function in infarcted heart through Bcl-2 expression. *J Pharmacol Exp Ther.*, 2009; 329(2): 543-550.
60. Shen T, Xia L, Dong W, Wang J, Su F, Niu S, Wang Q, Fang Y, A systematic review and meta-analysis: Safety and efficacy of mesenchymal stem cells therapy for heart failure. *Curr Stem Cell Res Ther.*, 2021; 16(4): 354-365.
61. Karantalis V, Hare JM, Use of mesenchymal stem cells for therapy of cardiac disease. *Circ Res.*, 2015; 116(8): 1413-1430.