REVIEW ARTICLE

# Mesenchymal Stem Cell-Derived Exosomes and Treatment in Atherosclerosis: A Scoping Review

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**ABSTRACT**

Atherosclerosis is an inflammatory disease that involves the formation of plaque in large arteries. It is a leading cause of vascular death worldwide, and current therapy is not effective for all patients. Recently, mesenchymal stem cell-derived exosome particles have shown potential as treatment for this disease. Therefore, this scoping review is to provide an overview and determines the extent of research on its potential for use as treatment in atherosclerosis. For article search, five online databases were used, namely Scopus, Science Direct, Cambridge Journal, PubMed, and Cochrane Library. Keywords (atherosclerosis OR atherogenesis) AND ('mesenchymal cell' OR 'stem cell') AND (exosome OR exosomes) were used. After the screening steps, irrelevant articles were removed and the final retrieval steps provided 10 full-text articles to be reviewed. The summary of the core concepts that were used in all relevant articles showed that inflammation is the most targeted process in this disease development followed by inhibition of apoptosis and facilitation of movement of cells that contributes to the atherogenesis. In most papers, exosomes from mesenchymal stem cells were used as vehicles to transport biological components to the targeted site, in vitro or in vivo. Only one paper reported on the antiatherogenic effect of exosomes in vivo. Several issues remain to be elucidated, such as the best method to extract the exosomes, their specific component that promotes antiatherogenic effects, their interaction with the inflammatory and immune cells, the optimum level needed for intervention and their stability once injected in vivo. In conclusion, there are a lot of research gaps that should be addressed in order to use exosomes from mesenchymal cells in atherosclerosis treatment.

**Keywords:**
scoping review; mesenchymal stem cell; exosome

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## INTRODUCTION

Atherosclerosis is the main cause of cardiovascular disease. This disease is the leading cause of death in Malaysia in 2021, where it contributed to 17% of the total deaths of the population (Department of Statistic, 2022). Atherosclerosis involves chronic inflammation that leads to the formation of plaque in the major artery wall (Lu et al., 2019). The atherosclerotic plaque could rupture and cause an atherosclerotic stroke. Atherogenesis involves interaction between inflammatory cytokines, smooth muscle cells and macrophages. The presence of ox-LDL is also one of the important key triggers for atherogenesis (Lu et al., 2019). Ox-LDL is formed when its lipid components, such as polyunsaturated fatty acids are oxidized by reactive oxygen species (Munno et al. 2024).

Despite the advancements in medicine, the effectiveness of treatment for atherosclerosis remains completely effective (Wang et al., 2018). Current medical treatment for this condition is statin which is a cholesterol-lowering drug. Patient management also involves changes in lifestyle and supplementation with natural remedies. In many cases, all these can only to prevent complications of atherosclerosis but cannot treat the condition completely. Statin treatment alone showed only a small reduction of coronary disease, and this raises a concern about the balance of the majority of the patients who did not respond to the statin therapy (Wang et al., 2018).

The exosome is an extracellular vesicle of the size 30-150 nm (Chen et al., 2020). It is generated by the inward budding of a mesenchymal cell's membrane that forms an endosome intracellularly where biological substances can be infused into it (Ailawadi et al., 2015). Then, the endosome will form a multivesicular body that will be secreted by the cell as an exosome and can exert its paracrine effect via cell-to-cell communication (Lu et al., 2019). The exosomes can be isolated from various sources, including adipose tissue, bone marrow, human umbilical cord, gingival tissue, dermis, and lung. The cells can also secrete growth factors and immunomodulatory agents (Gomez-Salazar et al., 2020).

The exosomes derived from the mesenchymal stem cells (MSC) can be used to transport various biological substances, including mRNA and miRNA (Wei et al., 2021). Scientists and researchers, particularly in tissue

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engineering and tissue regeneration, are interested in using mesenchymal cells due to their ability to differentiate into different cell types and the simplicity of the exosome's extraction process (Yu et al., 2021). Mesenchymal cell-derived exosomes have demonstrated promising potential as an atherosclerotic treatment (Lin et al., 2020), owing to their capacity to transport biological substances such as microRNA and facilitate cell-to-cell communication (Sun et al., 2021).

Thus, this scoping review was conducted to review the extent of research using exosomes derived from mesenchymal cells in atherosclerosis. Hopefully, this review will provide insight on the fundamental concepts and potential of the exosomes to be used in atherosclerosis treatment.

## METHODOLOGY

Research articles were searched using 5 databases subscribed by IIUM library namely Scopus, Cambridge Journal, ScienceDirect, Cochrane library and PubMed. The search was done by using keywords (atherosclerosis OR atherogenesis) AND ('mesenchymal cell' OR 'stem cell') AND (exosome OR exosomes). The Boolean operator "AND" is used to restrict the search, whereas the search was extended by the word "OR". The articles retrieved from the databases were selected and filtered based on inclusion and exclusion criteria. All duplicates were removed, and the remaining articles were screened for eligibility based on the criteria described below.

### Selection of Publication for Review

*Inclusion Criteria*

Publications included for this review were English-language research papers, books, and journals that were published between 2015 and 2022.

*Exclusion Criteria*

Publications retrieved but excluded were review papers and gray literature such as unpublished papers, patents, posters and infographics. Studies that used other extracellular vesicles instead of exosomes were also excluded as the focus was only for exosome-related experiments. Additionally, research papers that use exosomes as biomarkers were also rejected as our focus was on the mechanism and treatment of atherosclerosis involving MSC exosomes.

*Selection Method*

The initial selection of publications was based on their titles. Publications included in the review were studies using exosomes generated from mesenchymal cells and studies involving exosomes secreted by other than mesenchymal stem cells were eliminated. Publications involving diseases other than atherosclerosis were also discarded. Selection of publications was done by the first reviewer and verified by the second reviewer.

## RESULTS

A summary of the article searched was presented in Figure 1. Article search retrieved a total of 46,059 articles from the chosen databases but only 2,831 were screened because the rest were duplicates and not accessible. Further screening filtered 256 articles. The others were excluded for not complying with the inclusion criteria for this review. One relevant article was removed because we were unable to retrieve the full text of the article from our library. The effort to retrieve the full article from another local academic library was also not successful.

Further screening of the 255 articles based on the abstract removed more irrelevant articles. 102 of them were excluded because they were review articles; 66 articles involved other extracellular vesicles, and the other 78 articles focused on diseases other than atherosclerosis. Only 9 articles were eligible for the full-text review. Therefore, to gain more articles, citation searching methods were used and 3 articles were found eligible to be included for this review. However, the full-text of the two articles was unable to be retrieved. The final number of articles used for this review was 10. Each of the 10 selected full-text articles was read thoroughly, several times by the authors, to capture all relevant information and ensure that nothing important was missed. The dataset for the paper was constructed by extracting findings that were relevant to the aim of this review.

The articles showed that exosomes were extracted from various tissues of humans or mice. Tibia and femurs of mice were the most popular sources of MSC (Table 1). Researchers conducted both in vitro and in vivo studies. In vitro studies showed that the human monocytic line was the most used study model. Whereas in vivo studies mainly used atherosclerosis-prone apolipoprotein E-deficient (ApoE−/−) mice.

Four out of 10 papers investigated apoptosis inhibition in cells that contributed to atherogenesis, while two papers observed cell apoptosis that could reduce atherosclerosis progression. Most of the papers explored the anti-inflammatory property of MSC-exosomes, including their effect on macrophages and inflammatory cell movements.

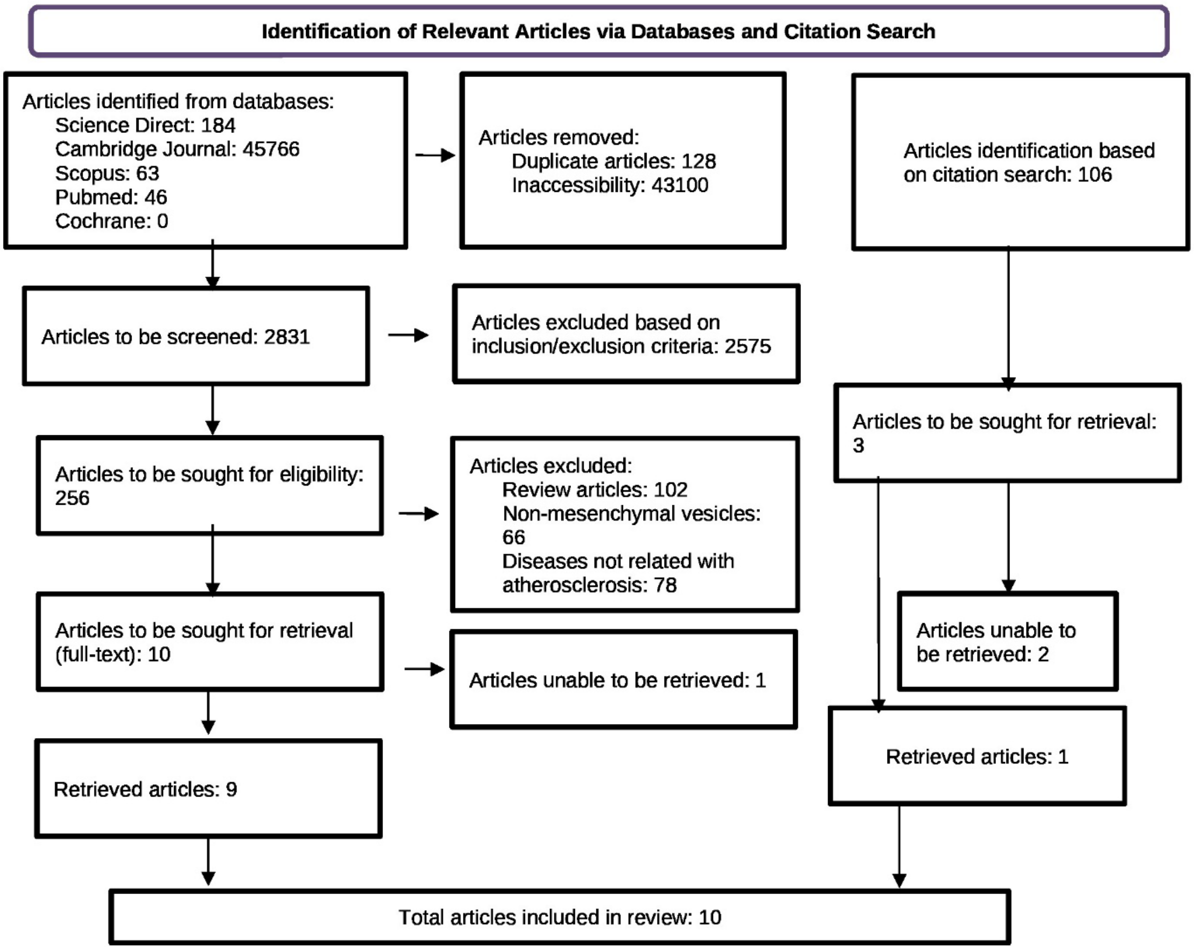


**Figure 1:** Summary of articles screening for review

## DISCUSSION

In vitro models are essential for gathering fundamental data in order to screen for therapeutic effects and understand the mechanism of a particular target. The human monocytic-cell line is the most commonly used in vitro atherosclerotic model by researchers because these cells can develop into macrophage-like cells that are similar to the native monocyte-derived macrophages (Bosshart et al., 2016). Other than that, authors from selected studies used human umbilical vein endothelial cells (HUVEC), aorta endothelial cells from mice, eosinophils from mice's bone marrow, and human smooth muscle cells as in vitro atherosclerotic study models. These cells were either exposed to oxidative stress, such as H2O2, cultivated with ox-LDL, or co-cultured with multiple compounds, such as phorbol myristate acetate to create a suitable atherosclerosis lesion (Xiaohui et al., 2021; Chen et al., 2021; Wenzhi et al., 2021; Feng et al., 2021).

Gathering data from animal models is important because it provides estimations of how a particular target affects an intact organism in a normal or diseased state which could be applicable to humans. Several of the selected studies reviewed used ApoE−/− mice as in vivo models. This mouse model displays poor lipoprotein clearance with subsequent accumulation of cholesterol ester-enriched particles in the blood, which promotes the development of atherosclerotic plaques (Lo Sasso et al., 2016).

As of the date of this review, no research has used exosomes to treat atherosclerosis in human subjects. The data from all of the reviewed papers could be considered preliminary but provided fundamental data before a clinical trial could be considered. Additionally, the papers reviewed showed that the MSC-exosomes were used mainly as carriers for different types of miRNA, proteins and lipids that can interact with different targets at different stages of atherosclerosis progression. It was hypothesized that the delivery of exosomes to the target site could modulate immune cells and reduce inflammation (Brandon et al., 2018).

According to the reviewed articles, only one study used extracted MSCs directly as compounds for atherosclerosis intervention (Xing et al. 2020). The MSC-exosomes were extracted from adipose-derived mesenchymal stem cells (ADSCs) and treated on atherosclerotic endothelial cells.

The treatment reduced the atherosclerotic lesion by inhibiting miR-342-5p expression (Xing et al. 2020). Caspase-3, a protein that promotes apoptotic cell death, was increased in atherosclerosis, and delivery of miR-512-3p using MSC-exosomes could inhibit this protein (Chen et al. 2021).

The remaining reviewed papers revealed that MSC-exosomes primarily function as carriers of microRNA to polarize macrophages. In atherosclerotic plaque, the M1 macrophage phenotype takes up ox-LDL in the tunica intima and forms foam cells. M1 also releases pro-inflammatory cytokines that enhance inflammation. Macrophage has plasticity, allowing it to polarize towards M2 macrophages that promote inflammation termination and eventually reduce atherosclerosis (Bobryshev et al., 2016). M1 macrophages can be reduced by transfection with the miR-let7 family using MSC-exosomes as carriers (Jiangbing et at., 2019). Transfected M1 polarized into M2 and suppressed their infiltration into the atherosclerotic plague.

**Table 1:** Summary of articles used for the review

| Authors | Location of MSC taken | Type of Study Model Used | Summary of findings |
|---|---|---|---|
| Xing et al., (2020) | Human facial adipose tissue | *In vitro* | ADCSs-derived exosome restrained the expression of miR-324-5p in lesion model. |
| Chen et al., (2020) | Bilateral leg bone of mice | *In vitro* | miR-512-3p shuttled by MSC-derived exosomes protects EC against ox-LDL by targeting Keap1. |
| Jiangbing et al., (2019) | Tibia and femur of mice | *In vitro, in vivo* | MSC-exosome could improve atherosclerosis by promoting M2 macrophage polarization and suppressed infiltration in the plaque. |
| Sun et al., (2021) | Human bone marrow | *In vitro, in vivo* | Exosomal-mediated delivery of si-LOC100129516 promoted cholesterol efflux and suppressed intracellular lipid accumulation. |
| Wenzhi et al., (2021) | Human umbilical cord | *In vitro, in vivo* | Treatment of miR-145-rich exosomes could downregulate JAM-A and reducing atherosclerotic plaque. |
| Gao et al., (2021) | Human umbilical cord | | HuCMSC-Ex-miR-100-5p inhibits cell proliferation and inflammatory response in eosinophil. |
| Feng et al., (2021) | Thigh bone and shin bone | *In vitro, in vivo* | BMSC-EXO decreases inflammatory reaction, blood lipid, plaque area, MMP-expression, increases α-SMA expression, and inhibits apoptosis. |
| Jian et al., (2021) | Femur and tibia of mice | *In vivo* | MSC-derived exosomes containing miR-21-a5p promoted macrophage polarization and reduce macrophage infiltration. |
| Yalong et al., (2021) | Human gingival tissue | *In vitro* | GMSC-Exos reduced the level and expression of inflammatory factors, inhibit lipid accumulation, and promote polarization of pro-inflammatory macrophage. |
| Yu et al., (2021) | Human adipose tissue | *In vitro, in vivo* | miR-125b-1-3p expressed in hMSCs-Ad exosomes can promote T lymphocyte apoptosis. |

Additionally, Jian et al. (2021) demonstrated that increased M2 macrophage polarization occurs through inhibition of transcription factor KLF6. MSC exosomes were employed to deliver miR-21a-5p into M1 macrophages. Furthermore, Gao et al. (2021) demonstrated that miR-100-5p, a microRNA that targets the FZD5 gene to lower the expression of inflammatory cytokines, can be carried by MSC exosomes. Additionally, the reviewed article suggested that miRNA that might boost antioxidant activities in atherogenesis could be delivered via MSC-exosomes. Chen et al.'s study from 2021 demonstrated this, using the delivery of miR-512-3p into atherogenic model-induced ox-LDL-induced endothelial cells to interact with Keap1, resulting in protection against ox-LDL (Tu et al., 2019).

In the early stage of atherosclerosis development, endothelial cell migration results in the loosening of tight junctions (Wenzhi et al., 2021). Transfection of endothelial cells with that microRNA-145 and si-LOC100129516 using MSC-exosome reduced its migration ability [Wenzhi et al., (2021 and Gao et al., (2021)]. Moreover, proliferation of vascular smooth muscle cells (VSMCs) also contributes to the formation of atherosclerotic plaque (Bennett et al., 2016). Feng et al., (2021) found that miR-125b-5p could significantly reverse the proliferation process via inhibition of Map4k4 gene expression that participates in cell proliferation and cell mortality.

Cell apoptosis in atherosclerosis treatment can be disadvantageous or beneficial depending on the type of cell involved, localizations, and the stage of atherogenesis. For instance, eosinophils in atherosclerotic plaque released a number of cytotoxic and prothrombotic mediators, such as eosinophil peroxidase, which can produce reactive oxygen species (ROS) and promote atherosclerosis (Gao et al., 2021. MSC-exosomes that carry miR-100-5p were shown to reduce atherosclerotic plaque formation by promoting apoptosis (Gao et al., 2021).

MSC-exosome experimentation in animal models is also important because the animal models can provide reliable preclinical data on a particular intervention in atherosclerosis. The reviewed papers indicate that ApoE-/- mice were the subjects of all in vivo studies. Even when fed a normal diet, ApoE-/- mice severely impair their ability to clear plasma lipoproteins, leading to elevated blood cholesterol levels (Zhang et al., 2021). According to the reviewed papers, researchers also used exosomes derived from mesenchymal cells as a carrier for microRNA in an animal model, leading to a reduction in the animal's lipid profile [Yu et al. (2020), Sun et al. (2021)].

MSC-exosomes can promote angiogenesis, gene alteration, and have a vital role in cell-to-cell communication (Lu et al., 2019; Wei et al., 2021; Yang et al., 2021). Moreover, Thomas et al., (2021) stated that exosomes derived from MSCs have a role in promoting the apoptosis rate of cells, attenuating blood lipid levels, and reducing atherosclerosis in an in vivo model. The MSC-exosome may bring a light in the future treatment because it is found to have less tumorigenicity which is one of the problems faced in MSC transplantation treatment (Lu et al., 2019; Neri, 2019). Neri, (2019) added that gene alteration and modification of the expression often become a topic of discussion in MSC transplantation treatment. However, Harrell et al., (2019) stated that exosomes derived from mesenchymal cells can avoid the potential of unwanted immunogenicity response and possible tumorigenicity because the structure of it has a similar biological composition with the human cell.

In conclusion, the reviewed papers showed that MSC exosomes were mainly used as carriers for microRNA. Thus, treatment of atherosclerosis using exosome technology derived from mesenchymal cells has yet to reach clinical trial. Nevertheless, the ability of the exosome as a nanocarrier may open many gates for future research in finding new technologies for treatment of various diseases. MicroRNA carried by exosomes was shown to inhibit atherosclerosis formation and progression. However, current knowledge of this technology is still lacking in many parts for instance, the best method to extract higher quality exosomes, the uncertainty of how the injected exosome will crosstalk with the local immune cell in endothelial cells, and the survival rate of the exosome after implantation (Lin et al., 2020). Moreover, as the progression of atherosclerosis involves numerous processes, the research area can be wide-ranging and open to a lot of options.

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