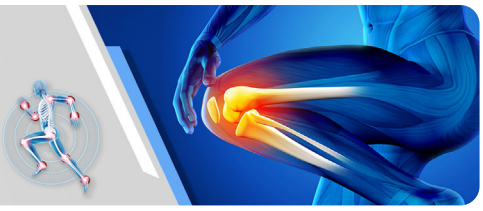
fortune Journals

Review Article

JOURNAL OF ORTHOPAEDICS AND SPORTS MEDICINE

ISSN: 2688-5115



Exosome Based Therapy for Osteoarthritis: A Systematic Review

Torbjörn Ogéus DC, PgD, MSc, ScA*

Abstract

Introduction: Osteoarthritis (OA) is a chronic degenerative joint disease characterized by the progressive breakdown of articular cartilage, subchondral bone changes, and synovial inflammation. Recent advances in regenerative medicine have focused on exosome-based therapies as a promising approach to address this challenge. Exosomes, small extracellular vesicles derived from various cell types, play crucial roles in intercellular communication and tissue homeostasis. These exosomes demonstrate the capacity to modulate inflammatory responses, promote chondrocyte proliferation, and enhance extracellular matrix synthesis. Understanding the mechanisms underlying exosome-mediated tissue repair and their interactions within the joint microenvironment is crucial for the development of effective exosome-based therapies for OA.

Methods: A systematic search was undertaken across Pubmed, Google Scholar and Scopus for relevant studies published from 2014 to 2024. Keywords included “"exosomes", "stem cells", "osteoarthritis", "chondrocytes", "amniotic fluid", and "regenerative medicine".

Results: This systematic review yielded a total of 390 articles. After the removal of duplicates and an initial abstract and title screening 201 full-text articles were assessed for eligibility. Of these, 27 studies met the inclusion criteria and were included in this review.

Conclusion: In conclusion, exosome-based therapies hold tremendous promise for the treatment of osteoarthritis by harnessing their regenerative and anti-inflammatory properties.

While further research is needed to address technical and clinical challenges, the growing body of preclinical evidence supports the potential of exosomes as a novel therapeutic strategy in OA management, however more clinical trials and human studies are warranted.

Keywords: Stem cell; Exosome; Amniotic; Mesenchymal; Muse; Regenerative medicine; Osteoarthritis

Abbreviations: OA: Osteoarthritis; miRNAs: microRNAs; MSCs: Mesenchymal stem cells; hUC-MSCs: Human umbilical cord mesenchymal stem cells; BM-MSC: Bone marrow-derived MSC; Muse: Multilineage-differentiating stress enduring cells; ECM: extracellular matrix; PRP: Platelet Rich Plasma; PRF: Platelet Rich Fibrin

Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by the progressive breakdown of articular cartilage, subchondral bone changes, and synovial inflammation [1]. It is one of the leading causes of disability

Affiliation:

Stockholms led- & smärtklinik, 11424, Stockholm, Sweden

***Corresponding Author:**

Torbjörn Ogéus, Stockholms led- & smärtklinik, 11424, Stockholm, Sweden.

Citation: Torbjörn Ogéus. Exosome Based Therapy for Osteoarthritis: A Systematic Review. Journal of Orthopedics and Sports Medicine. 6 (2024): 156-162.

Received: July 15, 2024
Accepted: July 23, 2024
Published: July 30, 2024

Torbjörn Ogéus DC., J Ortho Sports Med 2024
DOI:10.26502/josm.511500155

worldwide, particularly affecting the elderly population [2]. Current treatments aim at alleviating symptoms and improving joint function, ranging from non-pharmacological interventions to surgical options like joint replacement [3]. Despite these treatment modalities, there is an unmet need for disease-modifying therapies that can halt or reverse the progression of OA [4]. Recent advances in regenerative medicine have focused on exosome-based therapies as a promising approach to address this challenge [5]. Exosomes, small extracellular vesicles derived from various cell types, play crucial roles in intercellular communication and tissue homeostasis [6]. The therapeutic potential of exosomes lies in their ability to transfer bioactive molecules such as proteins, lipids, and nucleic acids, including microRNAs (miRNAs), to recipient cells [7]. In the context of OA, exosomes derived from mesenchymal stem cells (MSCs), chondrocytes, and more recently, amniotic fluid have shown promising results in preclinical studies [8,9]. These exosomes demonstrate the capacity to modulate inflammatory responses, promote chondrocyte proliferation, and enhance extracellular matrix synthesis [10]. Understanding the mechanisms underlying exosome-mediated tissue repair and their interactions within the joint microenvironment is crucial for the development of effective exosome-based therapies for OA [11]. This literature review aims to consolidate current knowledge and research findings on exosome treatments for osteoarthritis, highlighting their potential as a novel therapeutic strategy.

Method

This literature review aimed to consolidate current knowledge and research findings on exosome treatments for osteoarthritis (OA). The review was conducted through systematic searches of electronic databases including PubMed, Google Scholar, and Scopus. The search strategy involved using combinations of keywords such as "exosomes", "stem cells", "osteoarthritis", "chondrocytes", "amniotic fluid", and "regenerative medicine".

Inclusion Criteria

1. Relevance: Studies and reviews published in peer-reviewed journals that discussed exosome-based therapies for osteoarthritis.
2. Publication Date: Articles published in the last 10 years (2014-2024), with preference given to recent studies to capture the latest advancements.
3. Study Type: Preclinical studies, clinical trials, case reports, and systematic reviews focusing on the therapeutic potential of exosomes in OA treatment.

Exclusion Criteria

1. Articles not available in English.
2. Studies focusing solely on exosomes in conditions other than osteoarthritis.
3. Studies lacking original data or with insufficient detail on exosome characterization or outcomes.

Data Extraction

Data extraction included information on study design, exosome source (e.g., mesenchymal stem cells, amniotic fluid), outcomes (e.g., cartilage regeneration, inflammation modulation), and conclusions regarding the efficacy and safety of exosome therapy in osteoarthritis. The extracted data were synthesized to provide an overview of the current state of research and identify key findings supporting the potential of exosome-based therapies for OA.

Analysis

The data were analyzed descriptively to summarize findings related to exosome biology, mechanisms of action in osteoarthritis, preclinical and clinical studies, as well as challenges and future directions in exosome research for OA treatment. The synthesis aimed to provide a comprehensive overview of the therapeutic potential of exosomes and highlight areas for future research.

Literature Review Flow Diagram

1. Database Selection

- PubMed, Google Scholar, Scopus

2. Search Strategy

- Keywords: exosomes, mesenchymal stem cells, osteoarthritis, chondrocytes, amniotic fluid, regenerative medicine
- Boolean operators: AND, OR

3. Total Articles Identified

- Total initial search results: [390]

4. Screening

- Relevance screening based on title and abstract
- Exclusion based on criteria:
  - Non-English articles
  - Studies not focused on exosome therapies for osteoarthritis
  - Lack of original data or detailed exosome characterization/outcomes
- Number of Excluded Articles: [363]
- Number of Included Articles: [27]

Torbjörn Ogéus DC., J Ortho Sports Med 2024
DOI:10.26502/josm.511500155

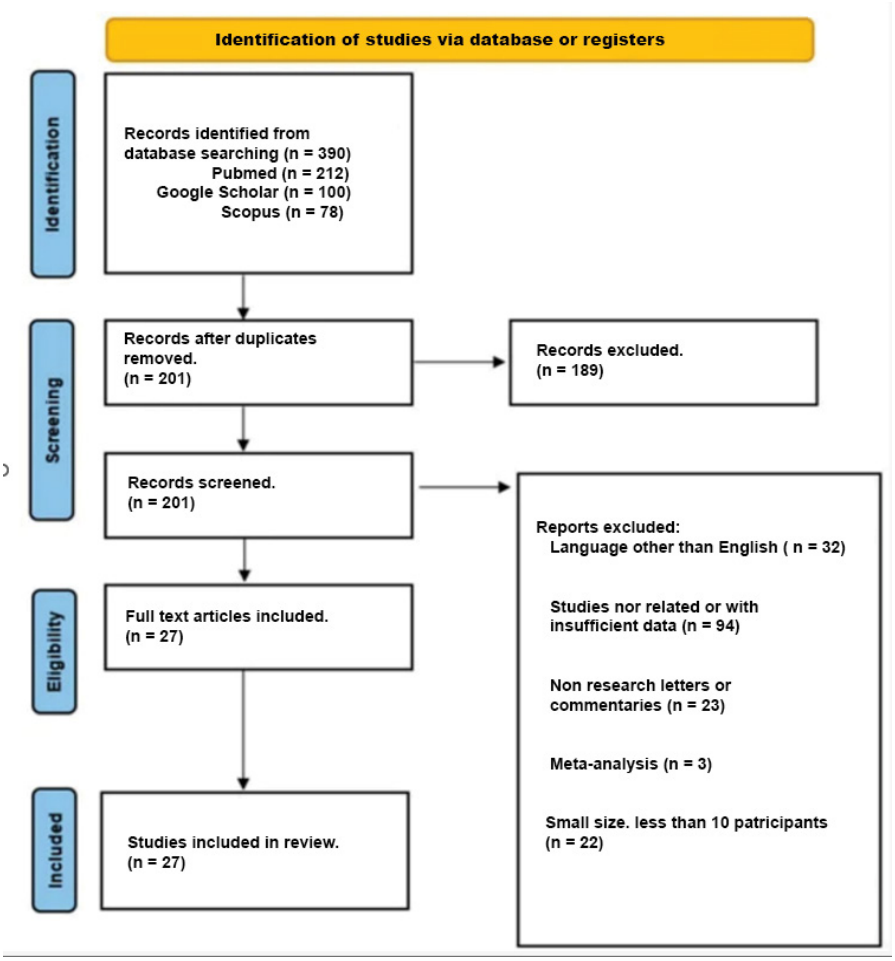


Figure 1: Flow diagram of the literature review process.

Results

Literature Review: Exosome Treatments for Osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease characterized by the breakdown of cartilage and underlying bone changes, leading to pain and functional impairment. Traditional treatments focus on symptomatic relief and joint replacement surgery in severe cases. Recently, exosome-based therapies have emerged as a promising approach for OA treatment due to their ability to modulate cellular processes and promote tissue regeneration.

1. Exosome biology and therapeutic potential

Exosomes are small extracellular vesicles (30-150 nm) released by various cell types, containing proteins, lipids, and nucleic acids such as miRNAs. These vesicles facilitate intercellular communication and have been implicated in tissue repair mechanisms [6]. Their natural role in cell signaling makes them attractive candidates for therapeutic delivery.

2. Mechanisms of exosome action in OA

Exosomes derived from MSCs or chondrocytes have been shown to suppress inflammation, reduce apoptosis, and stimulate chondrogenesis in OA models [7]. These effects are mediated through the transfer of bioactive molecules to recipient cells within the joint microenvironment.

3. Preclinical studies supporting exosome therapy

Preclinical studies have demonstrated the efficacy of exosome therapy in OA animal models. For instance, MSC-derived exosomes attenuated cartilage degradation and promoted matrix synthesis in a rat OA model [8]. Similarly, exosomes derived from synovial fluid MSCs improved joint function and reduced inflammation in rabbits with OA [9].

4. Clinical trials and human studies

Early-phase clinical trials have explored the safety and efficacy of exosome therapy in human subjects with OA. A study reported significant pain relief and improved joint function in OA patients treated with autologous adipose-derived exosomes [10]. These findings highlight the

Torbjörn Ogéus DC., J Ortho Sports Med 2024
DOI:10.26502/josm.511500155

translational potential of exosome-based therapies for clinical applications.

5. Amniotic-Derived exosomes in OA Therapy

Amniotic fluid-derived exosomes have also shown promise in OA therapy. These exosomes are rich in growth factors and anti-inflammatory molecules, promoting tissue repair and modulating immune responses [11,12]. Studies have demonstrated their ability to enhance cartilage regeneration and reduce joint inflammation in preclinical models of OA [13]. A recent case series investigated the use of amniotic-derived exosomes in the treatment of degenerative bone and cartilage diseases, reporting improvements in cartilage regeneration and increased joint space following exosome treatment [14]. This underscores the potential of amniotic-derived exosomes as a non-invasive therapeutic option for OA.

6. Mesenchymal-derived exosomes in OA therapy

Exosomes derived from MSCs have garnered significant interest due to their ability to mediate intercellular communication and deliver bioactive molecules, thereby influencing the disease microenvironment and promoting tissue repair. One of the significant breakthroughs in OA therapy involves the use of exosomes derived from human umbilical cord mesenchymal stem cells (hUC-MSCs). In a study from 2021 it was demonstrated that these exosomes play a crucial role in attenuating OA by rejuvenating cartilage stem/progenitor cells. The study found that hUC-MSC-derived exosomes enhance the proliferation and migration of these progenitor cells, which are essential for maintaining cartilage homeostasis and promoting repair processes in the damaged joint [15].

The therapeutic potential of MSC-derived exosomes has also been shown to significantly inhibit the formation and activity of osteoclasts, thereby protecting against bone degradation often associated with OA and osteoporosis. This inhibition is particularly beneficial in preserving subchondral bone integrity, which is critical for overall joint function [16]. The study highlights the dual role of MSC-derived exosomes in not only promoting cartilage repair but also preventing bone loss, making them a comprehensive therapeutic option for OA.

In a study from 2020, Kim et al. [17] focused on the anti-inflammatory effects of bone marrow-derived MSC (BM-MSC) exosomes in OA. The study showed that BM-MSC-derived exosomes possess potent anti-inflammatory properties, effectively reducing the expression of pro-inflammatory cytokines and mediators in the joint environment. These exosomes achieve this by modulating immune cell activity and altering inflammatory signaling pathways, thereby alleviating the inflammatory response and promoting a more conducive environment for tissue repair [17].

Further elucidating the protective mechanisms of MSC-derived exosomes, a study from 2021 identified a specific microRNA, miR-136-5p, within hUC-MSC exosomes that plays a pivotal role in preventing cartilage degeneration. The study demonstrated that miR-136-5p targets the TLR4/NF-κB signaling axis, a critical pathway in inflammatory and catabolic processes within OA joints. By inhibiting this pathway, hUC-MSC-derived exosomes reduce cartilage breakdown and inflammation, underscoring their potential as a targeted therapeutic strategy [18] These findings were confirmed and discussed in recent reviews [19,20]. Similar protective mechanisms were demonstrated in a study from 2020 demonstrating that bone marrow mesenchymal stem cell-derived exosomes may relieve osteoarthritis by promoting the phenotypic transformation of synovial macrophages from M1 to M2 [21].

A study from 2019 demonstrated that MSC exosomes reduce pain, promote temporomandibular joint repair and regeneration in OA in an animal model [22].

7. Multilineage-differentiating stress enduring (Muse) cells-derived exosomes in OA therapy

Recently, a new group of pluripotent cells with broad differentiation capacity has been discovered within the mesenchymal stem cell population. This subpopulation of cells are stress-tolerant stem cells named multilineage-differentiating stress enduring cells, or Muse cells first described in 2010 [23]. Unlike normal MSCs, this particular cell subpopulation has been proven to have the potential capacity to differentiate into every cell type of the human body but without the risk of tumorigenicity [24,25].

One of the included studies explored exosome therapy based on Muse exosomes in the treatment of osteochondral lesions in the trochlear groove cartilage, with promising effects in a study on rats [26].

8. Platelet-derived exosomes in OA therapy

In one of the included studies Platelet derived exosomes were studied in an animal model. The authors found that Platelet-Rich-Plasma-derived exosomes had positive therapeutic effects on OA. The exosomes contained in growth factors activated the Wnt/β-catenin signaling pathway and thereby initiated the positive effects according to the authors [27].

9. Challenges and considerations

Despite promising results, several challenges remain in the development of exosome therapies for OA. Issues such as standardization of isolation methods, scalability of production, and long-term safety need to be addressed. Additionally,

Torbjörn Ogéus DC., J Ortho Sports Med 2024
DOI:10.26502/josm.511500155

optimizing exosome cargo to enhance therapeutic efficacy represents a critical area of ongoing research [28].

10. Future directions

Future research directions include exploring combinatorial approaches with other OA therapies, such as biomaterial scaffolds or gene editing technologies [29]. Furthermore, understanding the mechanisms underlying exosome-mediated tissue repair will facilitate the development of targeted and personalized treatments for OA [30]. Additionally, large-scale clinical trials are warranted to validate the safety, efficacy, and long-term benefits of exosome therapy in diverse patient populations with OA [31].

Discussion

Exosome-based therapies represent a promising frontier in the treatment of osteoarthritis (OA), leveraging their role in intercellular communication and tissue regeneration. This discussion synthesizes the findings from the literature review and methodological approach to evaluate the current state, challenges, and future directions of exosome therapies for OA.

The therapeutic potential of exosomes in OA lies in their ability to modulate cellular processes critical to joint homeostasis. Exosomes derived from various sources, including mesenchymal stem cells (MSCs), amniotic fluid Muse-cells and platelets, have demonstrated anti-inflammatory properties, capacity to enhance chondrogenesis, and promote extracellular matrix (ECM) synthesis. These effects are attributed to their cargo of bioactive molecules such as proteins, lipids, and microRNAs (miRNAs), which can regulate gene expression and cellular responses within the joint microenvironment.

Preclinical studies have consistently shown the efficacy of exosome therapy in OA animal models. For instance, MSC-derived exosomes have been shown to attenuate cartilage degradation, promote cartilage matrix synthesis, and improve joint function in rodent and rabbit models. At the same time studies utilizing exosomes derived from amniotic fluid have reported enhanced cartilage regeneration and reduced inflammation in OA animal models and clinical case series.

Early-phase clinical trials have provided preliminary evidence supporting the safety and efficacy of exosome therapy in human subjects with OA.

Despite promising results, several challenges hinder the widespread clinical implementation of exosome therapies for OA. Standardization of exosome isolation methods, scalability of production, and optimization of exosome cargo remain key hurdles. The variability in exosome composition depending on the cell source and culture conditions further complicates the development of consistent therapeutic formulations. Moreover, long-term safety assessments and regulatory approvals are essential to ensure the clinical viability and patient safety of exosome therapies.

Most studies included in the review were animal or laboratory studies, they all show very promising results. Most of the studies found were on mesenchymal derived exosomes, secondarily amniotic derived exosomes with promising results but few studies. A handful of the studies included were on the topic of Muse-cell derived exosomes, presenting a unique potential of phagocytosis and cell renewal with a slightly different approach, one main advantage presented in the material was the fact that Mesenchymal stem cell populations already contain Muse cells, therefore the safety and tolerability has already been studied in prior studies on mesenchymal stem cells and exosomes.

Only one study mentioned platelet derived exosomes, it was rather old, and no recent studies have continued that path of research.

Future Directions

Future research directions should focus on addressing the aforementioned challenges to advance exosome-based therapies for OA. Enhancing our understanding of exosome biogenesis, cargo loading mechanisms, and interactions within the joint microenvironment will facilitate the development of targeted and personalized treatments.

Some studies in other fields of regenerative medicine have combined stem cells and exosomes with promising results in brain injuries [32] and skin repair [33]. One other area of combination researched is biomaterial scaffolds that might enhance the effects of stem cells or exosomes [34-36]. Other popular combined treatments with exosomes are autologous platelets, such as platelet rich Plasma (PRP) or platelet rich fibrin (PRF), which has seen a rising number of publications in other areas of medicine recently [37,38].

Exploring such combinatorial approaches with biomaterial scaffolds, gene editing technologies, or other OA therapies may further enhance therapeutic outcomes. Additionally, large-scale clinical trials are warranted to validate the safety, efficacy, and long-term benefits of exosome therapy in diverse patient populations with OA. The central issue of clinical dosing remains unstudied and poses another question for future clinical studies to address.

Conclusion

In conclusion, exosome-based therapies hold tremendous promise for the treatment of osteoarthritis by harnessing their regenerative and anti-inflammatory properties.

While further research is needed to address technical and clinical challenges, the growing body of preclinical evidence

supports the potential of exosomes as a novel therapeutic strategy in OA management, however more clinical trials and human studies are warranted.

Declarations

Ethics Approval: Not applicable.

Consent to participate: Not applicable.

Consent for Publication

This manuscript does not contain any individual person's data.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Acknowledgement

The author was the main and only contributor to the manuscript.

Competing Interests

The author declares that he has no competing interests. However, one of the included studies in the review was published by the author of this review, which might be worth mentioning.

Authors' contributions

All texts, design, literature review and drafting of this study was done by TO, responsible for the submitted manuscript.

Availability of Data and Materials

All data generated or analyzed during this study can be provided by the corresponding author upon reasonable request and is available for review by the Editor-in-Chief of this journal.

References

1. Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. Lancet 377 (2011): 2115-2126.
2. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 73 (2014): 1323-1330.
3. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 393 (2019): 1745-1759.
4. Goldring MB, Goldring SR. Osteoarthritis. J Cell Physiol 213 (2007): 626-634.
5. Zhang W, Ouyang H, Dass CR, et al. Current research on pharmacologic and regenerative therapies for osteoarthritis. Bone Res 4 (2016): 15040.
6. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science 367 (2020): 1427-1432.
7. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu Rev Cell Dev Biol 30 (2014): 255-289.
8. Zhang S, Chu WC, Lai RC, et al. Exosomes derived from human embryonic mesenchymal stem cells promote osteochondral regeneration. Osteoarthritis Cartilage 24 (2016): 2135-2140.
9. Cosenza S, Ruiz M, Toupet K, et al. Mesenchymal stem cells-derived exosomes are more immunosuppressive than microparticles in inflammatory arthritis. Theranostics 7 (2017): 1476-1493.
10. Vial IN, da Silva ML, Lima KW, et al. Autologous mesenchymal stem cells derived from adipose tissue and exosomes with platelet-rich plasma accelerate the healing of rotator cuff tears in a rabbit model. Am J Sports Med 48 (2020): 34-44.
11. Ragni E, Perucca Orfei C, De Luca P, et al. Amniotic membrane-mesenchymal stromal cells secretome in joint regeneration: a potential therapeutic application. J Clin Med 9 (2020): 734.
12. Li J, Ding Z, Li Y, et al. Human umbilical cord mesenchymal stem cell-derived exosomes ameliorate osteoarthritis by inhibiting the TLR4/NF-κB signaling pathway in chondrocytes. J Immunol Res 2021 (2021): 5474710.
13. Zhang S, Teo KYW, Chuah SJ, et al. Human umbilical cord mesenchymal stem cell-derived exosomes attenuate osteoarthritis by rejuvenating cartilage stem/progenitor cells. Aging (Albany NY) 13 (2021): 1654-1668.
14. Ogéus T. Amniotic derived exosomes in the treatment of degenerative bone- and cartilage disease: A case series. Open J Orthop Rheumatol 9 (2024): 001-006.
15. Guo L, Lai P, Wang Y, et al. Extracellular vesicles derived from adipose mesenchymal stem cells alleviate osteoarthritis by regulating inflammatory and immune responses. Int Immunopharmacol 95 (2021): 107568.
16. Shen H, Yoneda S, Abu-Amer Y, et al. Exosomes from IL-1β-primed mesenchymal stem cells inhibited osteoclastogenesis and protected mice from osteoporosis. Sci Transl Med 11 (2019).
17. Kim J, Lee HJ, Lee H, et al. Anti-inflammatory effect of exosomes derived from bone marrow-derived

Torbjörn Ogéus DC., J Ortho Sports Med 2024
DOI:10.26502/josm.511500155

mesenchymal stem cells in osteoarthritis. Sci Rep 10 (2020): 21107.

18. Tao S, Yuan T, Zhang Y, et al. Exosomes derived from human umbilical cord mesenchymal stem cells prevent cartilage degeneration via miR-136-5p/TLR4/NF-κB axis. Front Cell Dev Biol 9 (2021): 631109.

19. Yu H, Huang Y, Yang L. Research progress in the use of mesenchymal stem cells and their derived exosomes in the treatment of osteoarthritis. Ageing Res Rev 80 (2022): 101684.

20. Wu Y, Li J, Zeng Y, et al. Exosomes rewire the cartilage microenvironment in osteoarthritis: from intercellular communication to therapeutic strategies. Int J Oral Sci 14 (2022): 40.

21. Zhang J, Rong Y, Luo C, et al. Bone marrow mesenchymal stem cell-derived exosomes prevent osteoarthritis by regulating synovial macrophage polarization. Aging (Albany NY) 12 (2020): 25138-25152.

22. Zhang S, Teo KYW, Chuah SJ, et al. MSC exosomes alleviate temporomandibular joint osteoarthritis by attenuating inflammation and restoring matrix homeostasis. Biomaterials 200 (2019): 35-47.

23. Wakao S, Akashi H, Kushida Y, et al. Muse Cells, Newly Found Non-Tumorigenic Pluripotent Stem Cells, Reside in Human Mesenchymal Tissues. Pathol Int 64 (2014): 1-9.

24. Heneidi S, Simerman AA, Keller E, et al. Awakened by Cellular Stress: Isolation and Characterization of a Novel Population of Pluripotent Stem Cells Derived from Human Adipose Tissue. PLoS ONE 8 (2013): e64752.

25. Ossanna R, Veronese S, Quintero Sierra LA, et al. Multilineage-Differentiating Stress-Enduring Cells (Muse Cells): An Easily Accessible, Pluripotent Stem Cell Niche with Unique and Powerful Properties for Multiple Regenerative Medicine Applications. Biomedicines 11 (2023): 1587.

26. Mahmoud EE, Kamei N, Shimizu R, et al. Therapeutic Potential of Multilineage-Differentiating Stress-Enduring Cells for Osteochondral Repair in a Rat Model. Stem Cells Int 2017 (2017): 8154569.

27. Liu DH, Jheng YC, Chen PY, et al. Frontier review of the roles of exosomes in osteoarthritis. J Chin Med Assoc 84 (2021): 754-756.

28. Zhang S, Teo KYW, Chuah SJ, et al. MSC exosomes alleviate temporomandibular joint osteoarthritis by attenuating inflammation and restoring matrix homeostasis. Biomaterials 281 (2022): 121334.

29. Zhao H, Shang Q, Pan Z, et al. Exosomes from adipose-derived stem cells attenuate adipose inflammation and obesity through polarizing M2 macrophages and beiging in white adipose tissue. Diabetes 67 (2018): 235-247.

30. Liu X, Li Q, Niu X, et al. Exosomes secreted from human-induced pluripotent stem cell-derived mesenchymal stem cells prevent osteoarthritis by promoting chondrocyte proliferation via inhibition of miR-146a-5p. Aging (Albany NY) 11 (2019): 7492-7511.

31. Wu J, Kuang L, Chen C, et al. miR-100-5p-abundant exosomes derived from infrapatellar fat pad MSCs protect articular cartilage and ameliorate gait abnormalities via inhibition of mTOR in osteoarthritis. Biomaterials 206 (2019): 87-100.

32. Yuan J, Botchway BOA, Zhang Y, et al. Combined bioscaffold with stem cells and exosomes can improve traumatic brain injury. Stem Cell Rev and Rep 16 (2020): 323-334.

33. Park G-H, Kwon HH, Seok J, et al. Efficacy of combined treatment with human adipose tissue stem cell-derived exosome-containing solution and microneedling for facial skin aging: A 12-week prospective, randomized, split-face study. J Cosmet Dermatol 22 (2023): 3418-3426.

34. Evans N, Gentleman E, Polak J. Scaffolds for stem cells, Materials Today 9 (2006): 26-3

35. Zhao X, Li Q, Guo Z. et al. Constructing a cell microenvironment with biomaterial scaffolds for stem cell therapy. Stem Cell Res Ther 12 (2021): 583.

36. Lopes TF, Levandowski A, da Fonseca SC, et al. Stem cells scaffolds as a carrier for tissue engineering. RSBO 13 (2016): 98-103.

37. Shimizu Y, Ntege EH, Sunami H, et al. Regenerative medicine strategies for hair growth and regeneration: A narrative review of literature. Regen Ther 21 (2022): 527-539.

38. Hilmy F, Dilogo IH, Reksodiputro MH, et al. Evaluation of adipose-derived stem cells (ASCS) exosome implantation and platelet-rich fibrin (PRF) on critical long bone defects in Sprague-Dawley rats. Eur J Orthop Surg Traumatol (2024).