

## **Future Potential of Stem Cells Conditioned Medium (Secretome) in Osteoarthritis**

**Anas Khoerulumam**

Universitas Malahayati, Indonesia

Email: anaskhoerulumam@yahoo.co.id

---

### **Abstract**

Osteoarthritis (OA) is a leading cause of disability worldwide, particularly among the elderly, and is characterized by progressive cartilage degeneration. Despite various therapeutic options, no treatment currently exists to reverse cartilage damage. This systematic review aims to evaluate the potential of mesenchymal stem cell (MSC) secretomes as a novel therapeutic approach for OA. MSCs are known for their regenerative and immune-modulating properties, and their secretomes, which include bioactive molecules like growth factors and cytokines, have shown promise in promoting cartilage repair and reducing inflammation. The review synthesizes findings from clinical trials and studies that explore the efficacy of MSC secretomes in OA treatment. The studies' results indicate that MSC secretomes can improve clinical outcomes, enhance cartilage regeneration, and provide long-term pain relief with minimal side effects. However, the studies also highlight the need for further research, particularly large-scale, multi-center trials, to standardize protocols and assess long-term outcomes. This review underscores the potential of MSC secretomes as a safe and effective alternative or adjunct to conventional OA therapies, offering new insights into regenerative medicine for OA management.

**Keywords:** Osteoarthritis; Secretome; MSCs; cartilage damage; cartilage healing

---

### **INTRODUCTION**

Osteoarthritis (OA) is one of the leading causes of disability worldwide, especially in the elderly population (Hall, 2019). The disease is characterized by progressive degeneration of the cartilage joints, causing pain and loss of joint function. Although there are various therapies available, there is no treatment that can reverse irreversible cartilage damage in OA (Liu et al., 2022). Conventional therapies for OA usually focus on symptomatic therapies, such as the use of analgesics and anti-inflammatories, as well as surgical intervention in severe cases. However, these therapies cannot fundamentally address cartilage damage, as they only aim to address the symptoms that occur. Therefore, a more innovative and regenerative therapeutic approach is needed to address OA (l'Escalopier P.AU3 - Biau D., 2016; Natz K. R.AU3 - Loeser R. F., 2021).

Mesenchymal stem cells (MSCs) have emerged as promising candidates for OA therapy due to their strong differentiation and immune regulatory capabilities (Brito et al., 2019). MSCs are obtained from various tissue sources, such as bone marrow, fatty tissue, placenta, and umbilical

cord. In addition, MSCs can facilitate cartilage anabolism and extracellular matrix regulation through paracrine factors such as TGF- $\beta$ , HGF, PGE2, PDGF, and IL-10 (Palumbo G.AU3 - Carreca A. P.AU4 - Iannolo G., 2024).

Secretomes are a collection of bioactive molecules secreted by cells, including MSCs, which include exosomes and other paracrine factors (Daneshmandi S.AU3 - Jafari T.AU4 - Bhattacharjee M., n.d.). Secretome shows great potential in regenerative therapy (Bar A. L.AU3 - Grelewski P. G., 2021). These components can repair cartilage damage by improving chondrogenic ability and reducing inflammation. Studies have shown that secretome MSCs can accelerate cartilage regeneration in animal models and in vitro (Damajanti, 2015).

Several studies have explored the relationship between leadership strategies, employee satisfaction, and work stress, influencing employee performance. For instance, Cahyani, Adisti, and Naufal (2023) found that talent management significantly impacts organizational and individual performance, which aligns with this study's findings regarding the influence of talent management on employee performance. Similarly, Syam and Rauf (2022) explored the relationship between strategic leadership and job satisfaction, confirming the positive impact of leadership on employee performance, which supports the hypotheses in this study. Furthermore, the research conducted by Manihuruk and Tirtayasa (2020) highlighted the negative impact of work stress on employee enthusiasm and performance, which echoes the findings in the current study regarding the detrimental effects of work stress on performance.

The novelty of this research lies in its unique approach to integrating four key factors—leadership strategy, talent management, employee satisfaction, and work stress—into a comprehensive model for analyzing employee performance. Previous studies have generally examined these factors separately or in different organizational contexts, often overlooking the interplay between these variables in the public sector, particularly at the local government level. This study provides a fresh perspective by combining all these factors into a unified framework, offering new insights into the specific dynamics at play within government organizations.

The urgency of this study stems from the increasing demand for improved public service efficiency and effectiveness in the era of government transformation. As the South Magelang District and other local governments strive to enhance service delivery, understanding the factors that influence employee performance is critical. By examining how leadership strategies, talent management, job satisfaction, and work stress affect employee performance, this study provides timely insights for policymakers and government leaders to enhance human resource management practices and improve public service outcomes.

This systematic review aims to comprehensively and transparently evaluate the available evidence regarding the potential of secretome MSCs in OA therapy. This review will identify, select, and critically assess relevant studies to summarize the current state of knowledge and identify gaps in the existing literature.

This study offers both academic and practical benefits. Academically, it contributes to the literature on human resource management in the public sector by exploring the combined effect of

leadership, talent management, job satisfaction, and work stress on employee performance. The findings enrich the understanding of how these factors interact and influence performance at the local government level. Practically, the results can serve as a valuable resource for government officials and managers in the South Magelang District and beyond, offering evidence-based recommendations for improving employee performance through effective leadership, talent management strategies, and better management of work stress.

### **METHOD**

The search was carried out using databases from EMBASE, Medline, and PLOS One using the keyword “((mesenchymal stem cells) OR (MSCs) OR (stem cell-conditioned medium) OR (secretome)) AND ((osteoarthritis) OR (OA)).” After the search was completed, the screening and synthesis process was carried out according to the PRISMA Guideline in making a Systematic Review.

#### **Criterion**

##### **A. Inclusion**

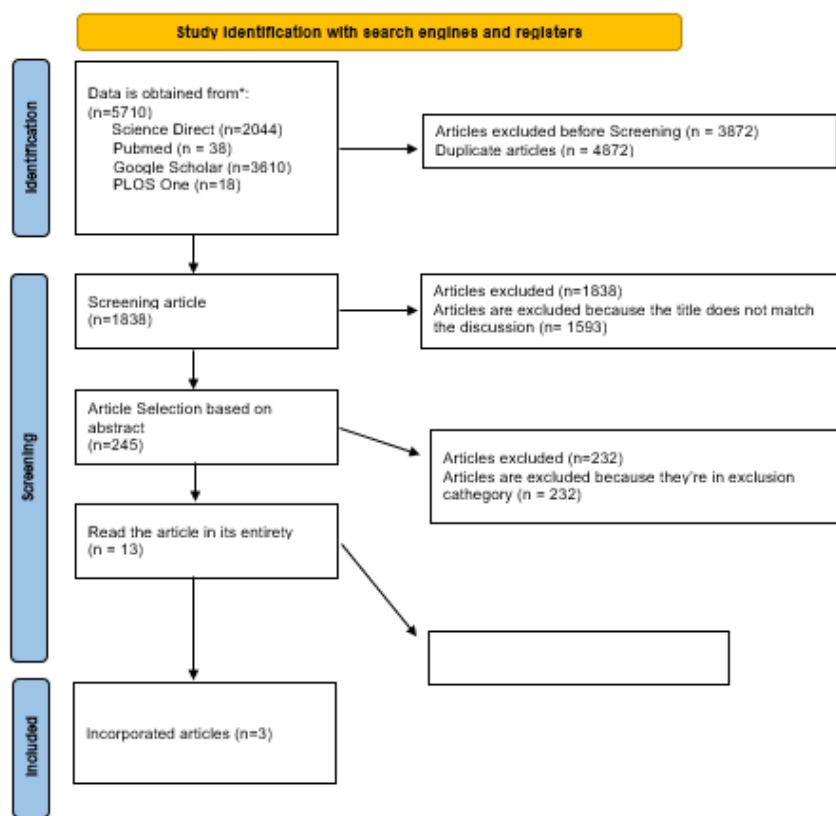
1. Articles published in 2019-2024
2. English-language articles
3. Articles published online

##### **B. Exclusion**

1. Literature Review, Systematic Review, Meta-Analysis, and non-experimental articles
2. Articles that are not accessible for free

#### **Review Procedure**

1. Literature search
2. Conducting a duplicate article screening process
3. Screening process based on the article abstract
4. Article screening process by reading the article in its entirety
5. Synthesis of articles included in the study



**Figure 1. Selection Process for Articles to be Synthesized**

**Table 1. Synthesis Article**

No.	Author/Year	Title	Study Design	Journal	Results
1	Damjanov N., et al	Intra-articular autologous conditioned serum and triamcinolone injections in patients with knee osteoarthritis: a controlled, randomized, double-blinded study	Randomized Controlled Trial	J Int Med Res	Autologous conditioned serum adds long-term pain relief and functional improvement to the short-term pain relief provided by glucocorticoids

<b>2</b>	(Dilogo A. F.AU3 - Hanitya A. I.AU4 - Pawitan J. A., 2020)	Umbilical cord-derived mesenchymal stem cells for treating osteoarthritis of the knee: a single-arm, open-label study	Open Label Clinical Trial	European Journal of Orthopaedic Surgery & Traumatology	human umbilical cord-derived The mesenchymal stem cells' secretome could be a potentially new regenerative treatment for knee osteoarthritis. The maximum effect of the secretome was achieved after 6 months of injection
<b>3</b>	Partan RU., et al	Umbilical Cord Mesenchymal Stem Cell Secretome Improves Clinical Outcomes and Changes Biomarkers in Knee Osteoarthritis	Open Label Clinical Trial	J Clin Med	Secretome derived from umbilical cord mesenchymal stem cells injection via intra-articular showed superior clinical improvement, biomarker changes, and no side effects compared to hyaluronic acid over a 5-week interval

### Article Description

Damjanov N., et al. (Intra-articular autologous conditioned serum and triamcinolone injections in patients with knee osteoarthritis: a controlled, randomized, double-blind study)

This study, conducted by Damjanov and colleagues, aimed to evaluate the effectiveness of autologous conditioned serum (ACS) in combination with triamcinolone injections for patients suffering from knee osteoarthritis (OA). The research was designed as a randomized controlled trial, ensuring a rigorous comparison between the treatment groups. The findings revealed that the use of ACS provided long-term pain relief and significantly improved functional outcomes for patients, extending the short-term benefits typically associated with glucocorticoid treatments. This suggests that ACS may play a crucial role in enhancing the management of knee OA, offering patients sustained relief and improved quality of life.<sup>10</sup>

Dilogo IH., et al. (Umbilical cord-derived mesenchymal stem cells for treating osteoarthritis of the knee: a single arm, open-label study)

In this open-label clinical trial, Dilogo and colleagues explored the potential of umbilical cord-derived mesenchymal stem cells (UC-MSCs) as a novel regenerative treatment for knee osteoarthritis. The study focused on assessing the efficacy and safety of the UC-MSC secretome, rich in bioactive molecules that could promote cartilage repair and regeneration. The results

indicated that the secretome demonstrated promising outcomes, with the maximum therapeutic effect observed six months post-injection. This study highlights the potential of UC-MSC secretome as a transformative approach in managing knee OA, paving the way for further research into its regenerative capabilities.<sup>11</sup>

Partan RU., et al. (Umbilical Cord Mesenchymal Stem Cell Secretome Improves Clinical Outcomes and Changes Biomarkers in Knee Osteoarthritis)

Partan and colleagues conducted an open-label clinical trial to investigate the effects of umbilical cord mesenchymal stem cell (UC-MSC) secretome on clinical outcomes and biomarker changes in patients with knee osteoarthritis. The study involved intra-articular injections of UC-MSC secretome, which were compared against hyaluronic acid, a commonly used treatment for OA. The findings revealed that patients receiving the UC-MSC secretome experienced superior clinical improvements, as evidenced by enhanced functional metrics and favorable changes in biomarkers associated with inflammation and cartilage health. Importantly, the treatment was well-tolerated, with no reported side effects, underscoring the secretome's potential as a safe and effective therapeutic option for knee OA management <sup>12</sup>

These articles collectively underscore the growing interest and promising results surrounding the use of stem cell-derived secretomes in the treatment of osteoarthritis, indicating a shift towards more regenerative and effective therapeutic strategies.

## **RESULT AND DISCUSSION**

### **Discussion**

The systematic review presented herein highlights the emerging potential of mesenchymal stem cell (MSC) secretome as a promising therapeutic strategy for osteoarthritis (OA). The findings from the selected studies indicate that MSC-derived secretomes can significantly improve clinical outcomes in OA patients, suggesting a paradigm shift in how we approach the management of this debilitating condition. Unlike conventional therapies that primarily focus on symptom relief, the regenerative properties of MSC secretomes offer a more holistic approach that targets the underlying pathology of OA—cartilage degeneration

(Tenti O.<sup>AU3</sup> - Cheleschi S.<sup>AU4</sup> - Reginster J. Y., 2023)

One of the most compelling aspects of the studies reviewed is the consistent demonstration of the MSC secretome's ability to enhance cartilage repair and regeneration<sup>15</sup>. For instance, the findings from Dilogio et al<sup>11</sup> and Partan et al<sup>12</sup> emphasize the secretome's role in promoting chondrogenic activity and improving biomarkers associated with cartilage health. This regenerative capability is attributed to the rich composition of bioactive molecules present in the secretome, such as growth factors and cytokines, which play critical roles in inflammation modulation and tissue repair promotion. This highlights the need for further exploration into the specific components of the secretome that contribute to these beneficial effects, as understanding these mechanisms could lead to optimized therapeutic applications.

Additionally, the study by Damjanov et al. provided valuable insights into the effectiveness of autologous conditioned serum (ACS) combined with triamcinolone injections for patients suffering from knee OA. This randomized controlled trial revealed that the use of ACS provided long-term pain relief and significantly improved functional outcomes for patients, extending the short-term benefits typically associated with glucocorticoid treatments. This suggests that ACS may play a crucial role in enhancing the management of knee OA, offering patients sustained relief and improved quality of life (Huang S.AU3 - Cao M.AU4 - Lin Z., 2023).

Moreover, the long-term efficacy of MSC secretome, as observed in the studies, raises essential considerations regarding dose, frequency, and route of administration. The study by Dilogio et al. noted that the maximum therapeutic effect was achieved six months post-injection, indicating that the timing of treatment may be crucial for maximizing benefits. This finding suggests that future research should focus on establishing standardized protocols for the administration of MSC secretome, which could enhance its clinical applicability and effectiveness in diverse patient populations (Palk S. T.AU3 - Keam S. J., 2019).

The safety profile of MSC secretome treatments is another significant advantage that emerged from the reviewed studies. Both the open-label trials reported no adverse effects associated with the use of umbilical cord-derived secretome, which contrasts with some conventional OA treatments that carry risks of side effects

(Bina A. M.AU3 - Calìogna L.AU4 - Berni M., 2024; Giannasi D.AU3 - Cadelano F.AU4 - Valenza A., 2024; Partan K. M.

AU3 - Kusuma N. F.

AU4 - Darma S., 2023)

. This finding is particularly relevant for elderly populations, who are often at higher risk of complications from pharmacological interventions. The favorable safety profile of MSC secretome positions it as a viable alternative or adjunct to existing OA therapies, providing a new avenue for clinicians to consider in their treatment regimens

(Cadet M.AU3 - French Arghum Group, 2021)

. Despite the promising results, several knowledge gaps and limitations warrant attention. Most of the studies included in this review were open-label trials with limited sample sizes, which raises questions about the generalizability of the findings. Additionally, the lack of long-term follow-up data in some studies limits our understanding of the durability of the therapeutic effects. Future research should prioritize large-scale, multi-center randomized controlled trials to validate the efficacy and safety of MSC secretome in OA treatment and to establish long-term outcomes

(Angadi H.AU3 - Atwal N., 2020; Cubero M. L. G.AU3 - Blanco M. E.AU4 - Castrillo S. P., 2024; Nabavizadeh T. T.AU3 - Zarej M.AU4 - Zare S., 2022)

. Furthermore, the variability in the methodologies used across studies, such as differences in the source of MSCs and the specific techniques used for secretome extraction, presents challenges in drawing definitive conclusions. Standardization of these processes is essential to ensure

reproducibility and comparability of results. Collaborative efforts among researchers and institutions could facilitate the development of unified protocols, thereby enhancing the robustness of future studies

(Ding X.AU3 - Li T. S.AU4 - Li Y. F., 2024)

## CONCLUSION

This systematic review has emphasized the promising potential of mesenchymal stem cell (MSC) secretome as a therapeutic strategy for osteoarthritis (OA). The reviewed studies consistently show that MSC-derived secretomes can improve clinical outcomes, promote cartilage regeneration, and reduce inflammation in OA patients. Unlike conventional therapies that focus on symptom management, MSC secretomes offer a regenerative approach that targets the underlying cause of OA, particularly cartilage degeneration. The studies reviewed also suggest that MSC secretomes have a favorable safety profile, with no significant side effects reported, which makes them a viable alternative to existing OA treatments. However, despite these promising results, there are still gaps in knowledge, including variations in study methodologies and the need for long-term follow-up data. Future research should focus on larger, more standardized trials to validate the therapeutic potential of MSC secretomes and optimize treatment protocols for clinical use. Future research should focus on larger-scale, multi-center randomized controlled trials to better understand MSC secretomes' long-term efficacy and safety for OA treatment. Standardization of the MSC extraction methods and secretome administration protocols ensures consistency and comparability across studies. Additionally, researchers should explore the underlying molecular mechanisms driving the regenerative effects of MSC secretomes, which could further enhance their clinical applications. Lastly, long-term follow-up studies are essential to evaluate the durability of the therapeutic effects of MSC secretomes in managing osteoarthritis.

## REFERENCES

- Angadi H. AU3 - Atwal N., D. S. A.-M. (2020). Autologous cell-free serum preparations in the management of knee osteoarthritis: what is the current clinical evidence? *Knee Surgery & Related Research*, 32(16), 1–10.
- Bar A. L. AU3 - Grelewski P. G., J. K. A.-N. (2021). Dental Pulp Stem Cell-Derived Secretome and Its Regenerative Potential. *International Journal of Molecular Sciences*, 22(12018), 1–39.
- Bina A. M. AU3 - Caliozna L. AU4 - Berni M., V. A.-B. (2024). Mesenchymal Stem Cells and Secretome as a New Possible Approach to Treat Cartilage Damage: An In Vitro Study. *Biomolecules*, 14(1068), 1–15.
- Brito, F. F., Fialho, M., Virgolino, A., Neves, I., Miranda, A. C., Sousa-Santos, N., Caneiras, C., Carriço, L., Verdelho, A., & Santos, O. (2019). Game-based interventions for neuropsychological assessment, training and rehabilitation: which game-elements to use? A systematic review. *Journal of Biomedical Informatics*, 103287.
- Cadet M. AU3 - French Arghum Group, C. A.-M. (2021). Non-steroidal anti-inflammatory drugs in the pharmacological management of osteoarthritis in the very old: prescribe or proscribe? *Therapeutic Advances in Musculoskeletal Disease*, 13.



- Cubero M. L. G. AU3 - Blanco M. E. AU4 - Castrillo S. P., E. G. A.-F. (2024). The Therapeutic Potential of Adipose-Derived Mesenchymal Stem Cell Secretome in Osteoarthritis: A Comprehensive Study. *International Journal of Molecular Sciences*, 25(20), 1–37.
- Damajanti, A. (2015). Pengaruh Pengetahuan Terhadap Kepatuhan Wajib Pajak Perorangan Di Kota Semarang. *Jurnal Dinamika Sosial Budaya*, 17(1), 12–28.
- Daneshmandi S. AU3 - Jafari T. AU4 - Bhattacharjee M., L. A.-S. (n.d.). *Emergence of the Stem Cell Secretome in Regenerative Engineering*.
- Dilogo A. F. AU3 - Hanitya A. I. AU4 - Pawitan J. A., I. H. A.-C. (2020). Umbilical cord-derived mesenchymal stem cells for treating osteoarthritis of the knee: a single-arm, open-label study. *European Journal of Orthopaedic Surgery & Traumatology*.
- Ding X. AU3 - Li T. S. AU4 - Li Y. F., Q. X. A.-W. (2024). Comparative analysis of short-term and long-term clinical efficacy of mesenchymal stem cells from different sources in knee osteoarthritis: a network meta-analysis. *Wiley*, 1–23.
- Giannasi D. AU3 - Cadelano F. AU4 - Valenza A., C. A.-M. (2024). Boosting the therapeutic potential of cell secretome against osteoarthritis: Comparison of cytokine-based priming strategies. *Biomedicine & Pharmacotherapy*, 170, 1–11.
- Hall, J. E. (2019). *Guyton dan Hall buku ajar fisiologi kedokteran*. Elsevier Health Sciences.
- Huang S. AU3 - Cao M. AU4 - Lin Z., Z. A.-Z. (2023). What is the optimal dose of adipose-derived mesenchymal stem cells treatment for knee osteoarthritis? A conventional and network meta-analysis of randomized controlled trials. *Stem Cell Research & Therapy*, 14(245), 1–53.
- l’Escalopier P. AU3 - Biau D., N. D. A.-A. (2016). Surgical treatments for osteoarthritis. *Annals of Physical and Rehabilitation Medicine*, 59, 227–233.
- Liu, M., Ogunmoroti, A., & Liu, W. (2022). Assessment and projection of environmental impacts of food waste treatment in China from life cycle perspectives. *Science of the Total Environment*, 807, 150751.
- Nabavizadeh T. T. AU3 - Zarej M. AU4 - Zare S., S. S. A.-K. (2022). Attenuation of osteoarthritis progression through intra-articular injection of a combination of synovial membrane-derived MSCs (SMMSCs), platelet-rich plasma (PRP) and conditioned medium (secretome). *Journal of Orthopaedic Surgery and Research*, 17(102), 1–12.
- Natz K. R. AU3 - Loeser R. F., J. N. A.-A. (2021). Diagnosis and treatment of hip and knee osteoarthritis: A review. *JAMA*, 325(6), 568–578.
- Palk S. T. AU3 - Keam S. J., J. A.-D. (2019). Triamcinolone Acetonide Extended-Release: A Review in Osteoarthritis Pain of the Knee. *Drugs*, 79, 455–462.
- Palumbo G. AU3 - Carreca A. P. AU4 - Iannolo G., F. S. A.-F. (2024). Modulating the release of bioactive molecules of human mesenchymal stromal cell secretome: Heparinization of hyaluronic acid-based hydrogels. *International Journal of Pharmaceutics*, 653, 1–9.
- Partan K. M. AU3 - Kusuma N. F. AU4 - Darma S., R. U. A.-P. (2023). Umbilical Cord Mesenchymal Stem Cell Secretome Improves Clinical Outcomes and Changes Biomarkers in Knee Osteoarthritis. *Journal of Clinical Medicine*, 12(7138), 1–11.
- Tenti O. AU3 - Cheleschi S. AU4 - Reginster J. Y., S. A.-B. (2023). An update on the use of conventional and biological disease-modifying anti-rheumatic drugs in hand osteoarthritis. *Therapeutic Advances in Musculoskeletal Disease*, 15, 1–24.