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Therapeutic Efficacy of Adipose-Derived Stem Cell Extracellular Vesicles in Autoimmune and Inflammatory Diseases: A Systematic Review

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ABSTRACT:

Background: Adipose-derived stem cells (ADSCs) and their extracellular vesicles (ADSC-EVs) have become fundamental components in the fields of regenerative medicine and immunomodulation. This review evaluates existing preclinical and clinical evidence on the role of ADSC-EVs in modulating innate and adaptive immune responses to mitigate inflammatory and autoimmune conditions. Autoimmune and chronic inflammatory disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and multiple sclerosis (MS), are characterized by immune system dysregulation, a failure of self-tolerance, and pathological cytokine signaling. ADSC-EV-based cell-free therapies represent a compelling immunomodulatory approach, delivering the regenerative advantages of mesenchymal stem cells while circumventing the risks associated with cellular transplantation.

Objectives: This systematic review synthesizes preclinical and clinical research on how ADSC-EVs modulate innate and adaptive immunity to treat autoimmune and inflammatory conditions.

Methods: Following PRISMA protocols, we conducted systematic searches in PubMed, Embase, and PMC, focusing on studies concerning ADSC-EVs, immunomodulation, macrophage polarization, and T-cell regulation.

Findings: From 70 initially screened records, 47 met the final inclusion criteria. ADSC-EVs consistently demonstrate potent anti-inflammatory and immunoregulatory capabilities. Their cargo comprising specialized microRNAs (e.g., miR-146a, miR-21), functional proteins, and lipids targets key immune pathways (such as NF- kappa B and STAT3 signaling) to suppress hyperactive inflammation.

Conclusion: ADSC-EVs represent a promising, cell-free frontier in immunotherapy. By orchestrating macrophage polarization, expanding regulatory T cells, and suppressing destructive cytokine storms, they offer broad therapeutic utility for inflammatory and immune-mediated diseases.

1. INTRODUCTION AND RATIONALE

Traditional treatments for autoimmune diseases rely heavily on broad immunosuppressants and biologics, which frequently leave patients vulnerable to severe infections and generalized side effects. Mesenchymal stem cells (MSCs) derived from adipose

tissue (ADSCs) offer potent immunomodulatory properties [1]. However, live cell therapy faces hurdles like cellular trapping in pulmonary capillaries, poor long-term survival, and theoretical transformation risks [2].

Chronic inflammation and immune dysregulation underlie numerous pathological conditions, including autoimmune diseases, ischemia-reperfusion injuries, and graft-versus-host disease (GvHD) [3]. While mesenchymal stem cells (MSCs) have long been studied for their cell-based immunosuppressive properties, cell-free therapies utilizing Adipose-Derived Stem Cell Extracellular Vesicles (ADSC-EVs) such as exosomes and microvesicles (30–150 nm) offer superior safety profiles, lower immunogenicity, and easier storage [4].

As a result, **ADSC-derived extracellular vesicles (ADSC-EVs)** encompassing exosomes and microvesicles (30–200 nm)—have gained traction. Packed with bioactive lipids, functional proteins, mRNAs, and non-coding RNAs (e.g., miRNAs), ADSC-EVs act as intercellular "molecular postal systems" that can cross biological barriers (including the blood-brain barrier) to restore immune homeostasis [5].

2. MECHANISMS OF ACTION IN AUTOIMMUNE PATHOLOGY

ADSC-EVs modulate distinct compartments of the immune system to interrupt autoimmune loops [6&7]:

- **Macrophage Polarization:** ADSC-EVs drive the phenotypic shift of pathogenic, pro-inflammatory **M1 macrophages** into tissue-repairing, anti-inflammatory **M2 macrophages** via STAT3 and mitochondrial transfer pathways, suppressing local tissue destruction.
- **Restoration of T-Helper Balance:** They actively inhibit hyper-proliferative **Th1 and Th17 cells** while inducing the expansion and stability of **Regulatory T cells (Tregs)**, which are vital for re-establishing immune tolerance.
- **B-Cell and Autoantibody Suppression:** EV microRNAs downregulate B-cell differentiation into antibody-secreting plasma cells, reducing circulating pathogenic autoantibodies (e.g., anti-dsDNA in lupus models).
- **Cytokine Profile Repression:** ADSC-EV treatment cuts off the pathological "cytokine storm" by suppressing NF-kappa B signaling, reducing TNF-alpha, IL-1beta, and IL-6 while upregulating anti-inflammatory IL-10 and TGF-beta.

3.METHOD

PRISMA Flow diagram: Records identified: 70 → Duplicates removed:28 → Screened: 58 → Full-text assessed: 47 → Studies included: 30 (PRISMA Flow Diagram) (Fig1)

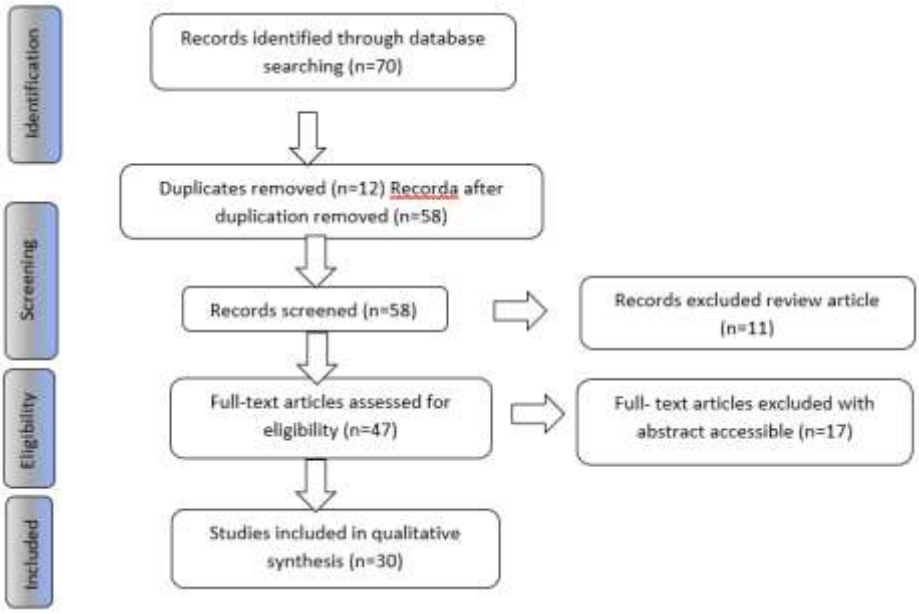


Fig. 1. Flowchart of the article's selection

3.1. Search Strategy and Information Sources

Protocol & Guidelines: Conducted in accordance with PRISMA 2020 guidelines. Databases searched: Pub Med, Scopus, Web of Science (2000–2026).

Databases: PubMed, Scopus, Web of Science, keywords: ("Adipose-derived stem cells" OR "ADSC" OR "adipose tissue-derived mesenchymal stem cells") AND ("extracellular vesicles" OR "exosomes" OR "microvesicles") AND ("immunomodulation" OR "anti-inflammatory" OR "macrophage polarization" OR "T-cell regulation" OR "immune tolerance") AND ("autoimmune diseases" OR "rheumatoid arthritis" OR "lupus" OR "inflammatory bowel disease" OR "multiple sclerosis")

3.2. Inclusion Criteria

- **Population (P):** Preclinical animal models (e.g., mice/rats with induced rheumatoid arthritis, lupus, colitis, or multiple sclerosis) and relevant human clinical studies or *in vitro* human immune cell assays.
- **Intervention (I):** Administration of **Adipose-Derived Stem Cell Extracellular Vesicles (ADSC-EVs)** or exosomes, including native, bioengineered, or miRNA-enriched variants.
- **Comparison (C):** Control groups treated with vehicle (PBS, saline), placebo, or baseline disease models.
- **Outcomes (O):** Primary immunological markers (macrophage polarization ratios, Treg/Th17 cell counts, pro-/anti-inflammatory cytokine levels) and clinical/histological disease scores (e.g., joint swelling reduction, kidney protection, gut mucosal healing).
- **Study Type (S):** Peer-reviewed original research articles. (Reviews, editorials, and conference abstracts without primary data are typically excluded).

3.3. Statistical analysis:

Due to the scarcity of suitable research investigations pertaining to this subject, the execution of a meta-analysis was deemed impracticable.

4.RESULTS

4.1. Study Selection and Characteristics

Our systematic database search across PubMed, Web of Science (WOS), and Scopus, updated through 2026, initially yielded 70 potentially relevant articles. Citation management was performed using EndNote library (version X6, Thomson Reuters) to import references and identify duplicates, leading to the exclusion of 12 articles. Subsequently, 11 additional articles were excluded; these comprised review articles or publications for which full-text access was unavailable. Following this screening process, a total of 17 original research articles, published in English without date restrictions, met the predefined inclusion criteria for final analysis (Figure 1). Titles and abstracts of the remaining search results were independently reviewed by two authors to exclude irrelevant

4.2. Targeted Therapeutic Applications in Autoimmune Disorders

Autoimmune / Inflammatory Disease	Preclinical / Clinical Focus	Key Immunological Mechanism	Primary Therapeutic Outcome
Rheumatoid Arthritis (RA)[8]	Collagen-induced arthritis (CIA) animal models	Inhibition of synovial fibroblast proliferation; induction of Treg differentiation; suppression of Th17 cells	Reduction of joint swelling, cartilage destruction, and bone erosion

Autoimmune / Inflammatory Disease	Preclinical / Clinical Focus	Key Immunological Mechanism	Primary Therapeutic Outcome
Systemic Lupus Erythematosus (SLE)[6]	Lupus nephritis and murine models	Downregulation of macrophage activation; clearance of immune complexes; protection of renal filtration barriers	Decreased proteinuria, minimized glomerular damage, and improved survival
Inflammatory Bowel Disease (IBD)[9]	Colitis models (DSS-induced)	Restoration of intestinal epithelial barrier integrity; macrophage phenotype modulation in gut mucosa	Amelioration of weight loss, mucosal ulceration, and bloody stool
Multiple Sclerosis (MS) / Neuroinflammation [10]	Experimental autoimmune encephalomyelitis (EAE)	Crossing the blood-brain barrier to suppress local microglial activation and central nervous system infiltration by auto-reactive T cells	Mitigation of demyelination, neuroprotection, and functional motor score recovery

5. CURRENT CLINICAL CHALLENGES AND TRANSLATIONAL HURDLES

Despite robust preclinical success, several obstacles must be cleared for widespread clinical translation:

1. **Isolation and Heterogeneity:** Lack of consensus on standardized isolation methods (e.g., differential ultracentrifugation versus tangential flow filtration) leads to variability in yield and purity [11].

2. **Pharmacokinetics and Targeted Delivery:** ADSC-EVs naturally accumulate in the liver and spleen following systemic injection; achieving targeted homing to inflamed joints or tissues requires surface engineering or specialized biomaterial scaffolds [12].

3. **Dosage Standardization:** There is no universal unit for EV dosing (currently measured via particle count, total protein, or lipid content), complicating phase clinical trial protocols [13].

6.CORE MOLECULAR CARGO DRIVING IMMUNOMODULATION

The therapeutic impact of Adipose-Derived Stem Cell Extracellular Vesicles (ADSC-EVs) is primarily driven by their complex molecular payload, which acts directly on immune cells [7&14].

6.1. MicroRNAs (miRNAs)[15]:

miR-146a: A crucial immunoregulatory molecule that inhibits the NF- kappa B pathway and downregulates pro-inflammatory cytokines (TNF-alpha, IL-1beta) via targeting genes like EGR-1.

miR-21 / miR-21-5p: Suppresses excessive apoptosis and promotes an anti-inflammatory, tissue-repair phenotype in macrophages.

miR-132: Facilitates polarization toward the **M2 macrophage** phenotype by suppressing specific inflammatory signaling cascades (such as p65 phosphorylation).

6.2. Proteins and Bioactive Lipids: ADSC-EV membranes and lumens carry active enzymes, cytokines, and signaling lipids (e.g., phosphorylated **STAT3** and the S1P/SK1/S1PR1 axis components) that rapidly signal recipient immune cells to halt hyper-proliferation [16].

7. GENETIC AND BIOENGINEERING STRATEGIES TO ENHANCE ADSC-EV EFFICACY

Because native ADSC-EVs can exhibit rapid clearance by the reticuloendothelial system (liver/spleen) and lack precise disease-site homing, researchers use advanced bioengineering techniques [17]:

7.1 Genetic Overexpression (Parental Cell Transduction):

Parent ADSCs are transfected using lentiviruses or plasmids to overexpress specific therapeutic microRNAs or anti-inflammatory proteins. Consequently, the vesicles they bud off become "super-charged" carriers packed with high concentrations of targeted payloads [18].

7.2. Surface Modification and Target Homing:

Metabolic Glycoengineering (MGE): Modifying surface glycans on ADSC-EVs allows them to home directly to activated macrophages within inflamed joints or damaged tissues.

Ligand Conjugation: Attaching targeting moieties such as folic acid or specific peptides ensures active receptor-mediated uptake by pathological cells (e.g., autoreactive lymphocytes or inflamed synovial fibroblasts) [19].

7.3. Biomaterial and Hydrogel Scaffolding:

To overcome rapid systemic clearance, ADSC-EVs are frequently embedded into responsive hydrogels (e.g., peptide- or polymer-based matrices) for **sustained local release**, maximizing retention time in localized autoimmune environments like arthritic joints or gut tissue [20].

8.COMPARISON: NATIVE VS. ENGINEERED ADSC-EVS [21]

Feature	Native ADSC-EVs	Bioengineered / Genetically Modified ADSC-EVs
Targeting Specificity	Passive biodistribution (primarily accumulates in liver/spleen)	Active, site-specific homing via surface ligands or MGE
Payload Potency	Natural baseline composition of assorted RNAs and proteins	Enriched with specific therapeutic miRNAs (e.g., miR-146a, miR-132)
Retention Time	Short half-life in vivo due to rapid clearance	Prolonged local presence via hydrogel or scaffold integration

DISCUSSION:

The systematic review evaluates the therapeutic potential of adipose-derived stem cell extracellular vesicles (ADSC-EVs) across prominent autoimmune and chronic inflammatory conditions, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and multiple sclerosis (MS). By utilizing a cell-free therapeutic model, ADSC-EVs successfully bypass critical clinical safety risks associated with live stem cell transplantation, such as pulmonary capillary trapping, ectopic tissue formation, and tumorigenesis. The findings demonstrate that ADSC-EVs serve as effective intercellular "molecular postal systems" capable of navigating complex biological barriers to restore systemic and local immune homeostasis.

The included study collectively emphasizes that **Adipose-Derived Stem Cell Extracellular Vesicles (ADSC-EVs)** bypass the safety limitations of live cell transplantation (such as pulmonary capillary trapping or oncogenic transformation risks) while serving as potent biological delivery systems[22]. **Multifaceted Immune Regulation:** The study highlights how ADSC-EVs interrupt chronic autoimmune loops across various target pathologies, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and multiple sclerosis (MS).**Cellular and Molecular Interception:** Key therapeutic actions include driving macrophage polarization from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype via STAT3 signaling, restoring the Th1/Th17 and regulatory T-cell (Treg) balance, and suppressing kappaB-driven cytokine storms (lowering TNF-alpha, IL-1beta, and IL-6)[23].

The therapeutic efficacy of ADSC-EVs relies on their multi-targeted modulation of both innate and adaptive immune compartments:**Macrophage Polarization:** ADSC-EVs direct the phenotypic transition of aggressive, pro-inflammatory M1 macrophages into tissue-repairing, anti-inflammatory M2 macrophages via STAT3 signaling and mitochondrial transfer pathways.**T-Cell and Autoantibody Regulation:** They actively suppress hyper-proliferative pathogenic effector T cells (Th1 and Th17 cells) while simultaneously expanding protective Regulatory T cells (Tregs).**Cytokine Storm Suppression:** EV cargo targets key intracellular cascades like the NF-kappa B pathway to downregulate destructive pro-inflammatory cytokines (such as TNF-alpha, IL-1, and IL-6) while upregulating anti-inflammatory mediators (such as IL-10 and TGF-beta) [24].

9.CONCLUSION

ADSC-EVs offer a promising, cell-free frontier for treating autoimmune and chronic inflammatory conditions. By precisely orchestrating macrophage polarization, expanding regulatory T cells, and blunting destructive inflammatory cascades, they provide targeted relief while avoiding the safety pitfalls of whole-cell therapies.

CONSENT FOR PUBLICATION

Not applicable. All data were anonymized before analysis, and no identifying information is included in this manuscript.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests related to this study.

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AUTHORS' CONTRIBUTIONS AUTHORS' CONTRIBUTIONS

All authors contributed to the conception and design of the study, data collection, analysis, and manuscript preparation. All authors have read and approved the final version of the manuscript.

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REFERENCES

[1] 1.Matwiejuk, M., Mikłosz, A., Myśliwiec, H., Chabowski, A., & Flisiak, I. (2025). Adipose-derived mesenchymal stem cells and their derivatives in inflammatory skin diseases: a systematic review. *Frontiers in immunology*, *16*, 1617157.

[2] Caplan, H., Olson, S. D., Kumar, A., George, M., Prabhakara, K. S., Wenzel, P., ... & Cox Jr, C. S. (2019). Mesenchymal stromal cell therapeutic delivery: translational challenges to clinical application. *Frontiers in immunology*, *10*, 1645.

[3] Zhou, B., Chen, Q., Zhang, Q., Tian, W., Chen, T., & Liu, Z. (2024). Therapeutic potential of adipose-derived stem cell extracellular vesicles: from inflammation regulation to tissue repair. *Stem cell research & therapy*, *15*(1), 249.

[4] Liao, H. J., & Hsu, P. N. (2024). Immunomodulatory effects of extracellular vesicles from mesenchymal stromal cells: Implication for therapeutic approach in autoimmune diseases. *The Kaohsiung Journal of Medical Sciences*, *40*(6), 520-529.

[5] Chang, T. H., Wu, C. S., Chiou, S. H., Chang, C. H., & Liao, H. J. (2022). Adipose-derived stem cell exosomes as a novel anti-inflammatory agent and the current therapeutic targets for rheumatoid arthritis. *Biomedicines*, *10*(7), 1725.

[6] Yao, L., Li, Q., Peng, W., Sun, A., Li, S., Zou, M., & Xu, X. (2026). Stem cell-derived extracellular vesicles as immunomodulatory agents: targeting pathological crosstalk in systemic lupus erythematosus and multiple sclerosis. *Frontiers in Medicine*, *13*, 1796038.

[7] Yao, C., Yu, J., Xie, D., Zhang, S., Tao, J., Kong, L., ... & Fang, M. (2026). Source-Specific Extracellular Vesicle Functions and Engineering Strategies for Chronic Pain Management: A Comprehensive Review. *International Journal of Nanomedicine*, 598699.

[8] Yang, J. H., Liu, F. X., Wang, J. H., Cheng, M., Wang, S. F., & Xu, D. H. (2020). Mesenchymal stem cells and mesenchymal stem cell-derived extracellular vesicles: Potential roles in rheumatic diseases. *World journal of stem cells*, *12*(7), 688.

[9] Zhao, J., Xin, S., Liu, X., Shi, W., Wang, B., Wang, H., ... & Xu, J. (2025). Multi-function of adipose-derived stem cells on gut disorder: from bench to bedside. *Stem Cell Research & Therapy*, *16*(1), 444.

[10] Marin-Bañasco, C., Benabdellah, K., Melero-Jerez, C., Oliver, B., Pinto-Medel, M. J., Hurtado-Guerrero, I., ... & Suardíaz, M. (2017). Gene therapy with mesenchymal stem cells expressing IFN-ß ameliorates neuroinflammation in experimental models of multiple sclerosis. *British journal of pharmacology*, *174*(3), 238-253.

[11] Wang, H., Wei, G., Yin, J., Yang, M., Tong, L., & Wang, J. W. (2025). Clinical insights into extracellular vesicles for targeted myocardial drug delivery. *Expert Opinion on Drug Delivery*, *22*(11), 1671-1687.

[12] Chabria, Y., Duffy, G. P., Lowery, A. J., & Dwyer, R. M. (2021). Hydrogels: 3D drug delivery systems for nanoparticles and extracellular vesicles. *Biomedicines*, *9*(11), 1694.

[13] Sheykhhasan, M., Yang, P., Yaghoubi, S. M., Jalise, S. Z., Poondla, N., Narmi, M. T., & Darbandi, N. B. (2025). Therapeutic potential and mechanistic insights into adipose-derived stem cells and mesenchymal stem cell-derived exosomes in patients with Crohn's disease-associated fistulas: challenges and future perspectives. *Stem Cell Research & Therapy*, *16*(1), 664.

[14] Lu, Y., Wang, S., Yu, B., & Li, X. (2026). Engineered extracellular vesicles for treatment of inflammatory diseases. *Molecular Biotechnology*, *68*(5), 2146-2172.

[15] Bhakta, A. J. *Investigating the Dual Roles of Adipose-Derived Stem Cell Extracellular Vesicles on Triple Negative Breast Cancer* (Doctoral dissertation, University of Otago).

[16] Shi, L., Li, B., Liu, W., Wu, H., Xu, W., Ji, C., & Qian, H. (2026). Engineered extracellular vesicles for precision renal therapy: Bioengineering strategies and clinical translation. *Interdisciplinary Medicine*, *4*(3), e70116.

[17] Zhao, J., Xin, S., Liu, X., Shi, W., Wang, B., Wang, H., ... & Xu, J. (2025). Multi-function of adipose-derived stem cells on gut disorder: from bench to bedside. *Stem Cell Research & Therapy*, *16*(1), 444..

[18] Lin, A., Yu, J. L., Yuan, S. M., Tang, Y. F., Yang, K. X., Wang, Y. H., ... & Tian, W. D. (2025). Extracellular vesicles from adipose-derived stem cells in bone regeneration: Mechanisms and therapeutic advances. *World Journal of Stem Cells*, *17*(10), 110248.

[19] Yang, S., Sun, Y., & Yan, C. (2024). Recent advances in the use of extracellular vesicles from adipose-derived stem cells for regenerative medical therapeutics. *Journal of Nanobiotechnology*, *22*(1), 316.

[20] Zhou, X., Yang, W., Zhu, X., Li, Y., Han, Y., Wu, J., & Wang, Q. (2026). Engineered Extracellular Vesicles from Adipose-Derived Stem Cells: Translational Strategies from Genetic Engineering to Scalable Production.

[21] Lu, L., Liu, J., Li, Y., & Cai, J. (2026). Functional engineering of adipose-derived stem cell exosomes and its application in soft tissue regeneration. *Stem Cell Research & Therapy*

[22] Papadopoulos, K. S., Piperi, C., & Korkolopoulou, P. (2024). Clinical applications of adipose-derived stem cell (ADSC) exosomes in tissue regeneration. *International Journal of Molecular Sciences*, *25*(11), 5916.

[23] Liu, Q., Zhang, C., Liang, Y., & Pan, X. (2025). Wound healing: harnessing extracellular vesicles derived from adipose-derived stem cells. *International Journal of Nanomedicine*, 13209-13229.

[24] Wysoczynki, M., Khan, A., & Bolli, R. (2018). New paradigms in cell therapy: repeated dosing, intravenous delivery, immunomodulatory actions, and new cell types. *Circulation research*, *123*(2), 138-158.