

REVIEW

Adipose-derived mesenchymal stem cell secretome promotes testicular regeneration following chemically induced injury: A review of preclinical studies

Nadya Nathalia Evangelista¹, Indah Dian Shafira¹, Nova Sylviana^{1,2}, Andri Rezano^{1,2}

¹ Graduate School of Master Program in Anti-Aging and Aesthetic Medicine, Faculty of Medicine, Universitas Padjadjaran, Jl. Prof Eyckman No. 38, Bandung, West Java, Indonesia;

² Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Sumedang, Indonesia.

Summary *Introduction: Male infertility is a rising problem globally with male factors contributing up to 50% of all couple infertility cases. The sperm quality decline raises serious concerns regarding future population sustainability and male reproductive health. Adipose-derived mesenchymal stem cell (AdMSC) secretome, defined as a cell-free product comprising paracrine factors secreted by these cells, has emerged as a promising cell-free regenerative therapy for testicular injury, offering advantages of accessibility and therapeutic potential. This systematic review aimed to evaluate the effectiveness of AdMSC secretome in chemically induced testicular injury models.*

Methods: A systematic literature search was conducted across four electronic databases (PubMed, Google Scholar, OVID and Cochrane) covering publications from 2015 to 2025. Preclinical studies investigating the therapeutic effects of AdMSC secretome in murine models of chemically induced testicular injury were included.

Results: Three preclinical studies utilizing male murine models were analysed. Testicular injury was induced using busulfan, doxorubicin or acrylamide. AdMSC secretome was administered via intra-testicular injection (n = 2) and intravenous injection (n = 1). All studies demonstrated partial regeneration of seminiferous tubule in secretome-treated groups compared with controls. Two studies reported reduced cellular apoptosis using TUNEL assay and acridine orange staining. An increase in Leydig cell numbers was observed following secretome treatment, while Sertoli cells remained unchanged. One study identified vascular endothelial growth factor (VEGF) as a key paracrine mediator, with anti-VEGF intervention abolishing the therapeutic effect. Testosterone levels were consistently higher in secretome-treated groups compared to those receiving AdMSC transplantation.

Conclusions: AdMSC secretome demonstrates therapeutic potential in chemically-induced testicular injury by promoting seminiferous tubule regeneration, reducing apoptosis, and enhancing Leydig cell recovery, with VEGF playing a critical mechanistic role. These findings support the potential AdMSC secretome as a cell-free regenerative approach for male infertility.

KEY WORDS: Secretome; Adipose-derived mesenchymal stem cell; Regenerative medicine; Testicular injury; Male infertility

Submitted 15 December 2025; Accepted 30 December 2025

INTRODUCTION

Infertility is a globally rising problem affecting 13-15% of all couples. Infertility can be caused by female or male factors, but approximately, 50% of the cases comes from the male factors. Other than systemic diseases, use of medications (chemotherapy, etc) and surgical procedures, undeniable changes in environment (pollution, occupational hazard, etc.), genetic and lifestyle played a role in the rise of male infertility. Seventy percent of all male infertility cases are uncorrectable or sub-fertile. The most basic test a man can undergo is a semen analysis to check his semen quality (1, 2). The more urgent issue amidst the ongoing infertility crisis that is reported in numerous studies from all around the world is the decline in sperm quality and other parameters that marks the decrease of male reproductive health (3, 4). Currently, researchers are working on finding ways to resolve this problem. *Mesenchymal stem cells* (MSC) and its derivatives have currently emerged as a promising therapy for regenerative medicine. One of the sources of MSC and their derivatives that is gaining popularity over the past years is adipose tissue. It is easily accessible compared to other source of MSC and has the potential in treating male infertility (5). Recent animal studies have explored the therapeutic effects of secretome-derived from *adipose-derived mesenchymal stem cell* (AdMSC) in the treatment of male infertility. Secretome refers to biologically active products secreted by the stem cells into the extracellular space (6). Generally, secretome is categorized into soluble factors comprising growth factors, cytokines, chemokines and enzymes, and also extracellular vesicles including microvesicles and exosomes. AdMSC secretome exhibits a wide range of effects such as anti-inflammatory, anti-apoptotic, anti-oxidant, anti-fibrotic, pro-angiogenic, neurotrophic effect and also facilitates tissue re-epithelization (7-9). Several studies have demonstrated improvements in testicular regeneration and sperm parameters following AdMSC secretome administration. However, reported outcomes vary considerably due to differences in experimental design, including routes of administration, dosing regimens, and treatment protocols. To date, no comprehensive synthesis of preclinical evidence has specifically evaluated the effects of AdMSC secretome in male infertility. Therefore, this sys-

tematic review aims to assess the therapeutic efficacy of AdMSC secretome in preclinical models of chemically induced testicular injury.

METHODS

This study is a systematic review of animal studies conducted by other researchers. The study population consisted of murine models of chemically induced testicular injury. The intervention of interest was the administration of AdMSC secretome for the treatment of infertility in these animal models, compared with placebo or other therapeutic interventions. The primary outcome was improvement in testicular histology following chemically induced damage. Secondary outcomes included restoration of spermatogenesis and changes in hormonal profiles in animal models with chemically induced testicular injury.

Search strategy

A systematic literature search was conducted across four electronic databases; PubMed, Cochrane Library, OVID, and Google Scholar, using Medical Subject Headings (MeSH) and relevant keywords. Search terms included combinations of: “Mesenchymal Stem Cell”, “Adipose-Derived Mesenchymal Stem Cells”, “Adipose Tissue-Derived”, “Mesenchymal Stromal Cells”, “Conditioned Medium”,

“Secretome”, “Culture Media”, “Testes”, “Testicles”, “Testicular”, “Testicular Injury”, “Male Infertility”, and “Spermatogenesis”. The search was independently performed by two reviewers (NNE and IDS) between 05 June 2025 and 16 June 2025.

Eligibility criteria

The inclusion criteria of this study were: (1) studies published in English language; (2) study subject was limited to male murine models (rats and mice) aged > 8 weeks to reduce variability; (3) testicular injury was induced by any kind of chemical agent; (4) animals of the studies were treated using AdMSC secretome. Comparison of other treatment is not limited; (5) studies published in the past 10 years. The exclusion criteria of this study were: (1) Studies published in other language; (2) young or neonatal murine models; (3) female rats of any age group and other type of animals; (4) testicular injury induced by surgery; (5) treated using Adipose Mesenchymal Stem Cell, not the secretome; (6) treated using secretome of other MSC.

Study selection

All authors were trained in the use of Mendeley for reference management and Rayyan AI for systematic review screening to ensure methodological consistency. Title and abstract screening as well as duplicate removal, were inde-

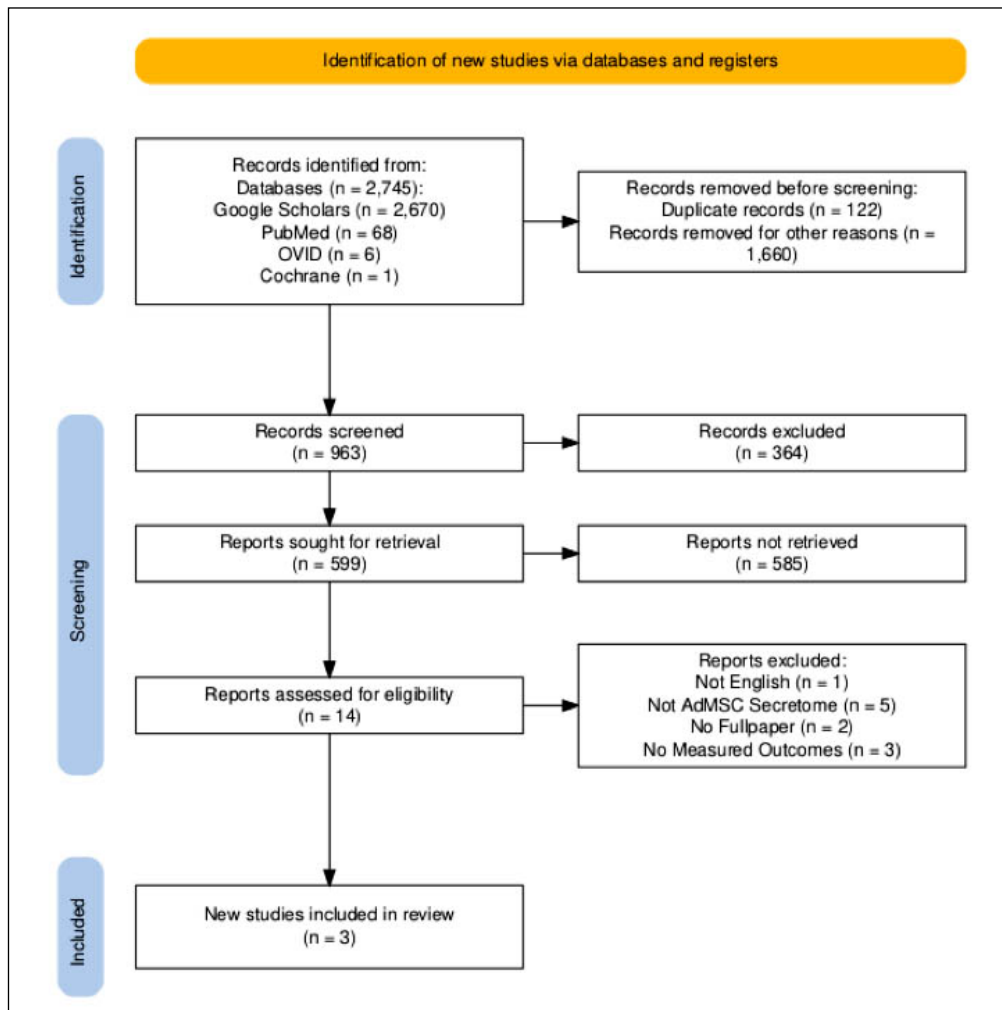


Figure 1. PRISMA Flow Chart.

pently conducted by two reviewers (NNE, IDS) using Rayyan AI. Studies that did not meet the predefined inclusion criteria were excluded at this stage. Full-text articles of potentially eligible studies were independently retrieved and assessed by the same two reviewers. Any disagreements, discrepancies or uncertainties during the screening and selection process were resolved through discussion, with final agreement by the supervising authors (NS, AR). The study selection process is presented in the PRISMA flow diagram (Figure 1).

Data extraction

Data extraction was performed using a standardized data extraction sheet (Microsoft Excel). Extracted variables included author names, year of publication, study design, country of origin, animal species, age of animals, sample size and grouping, testicular damaging agent, source of AdMSCs, secretome dose and route of administration, secretome composition analysis, and study outcomes (Table 1A-B).

Table 1A.
Study characteristics of AdMSC secretome in testicular injury.

Reference	Year	Study design	Country	Type of animal used and number of groups	Number of animal used and number groups	Testicular damaging chemical agent	Source of adipose mesenchymal stem cell	Secretome dose and application	Secretome composition analysis
Abdollahifar et al. (10)	2022	Experimental	Iran	NMRI Male Mice; 8 weeks	Forty male mice; Divided into 5 groups, each with 8 mice (control; DMEM (10 µl); 2% DMSO (10 µl); BSU+ AdMSC-CM; BSU)	Busulfan 40 mg/kg intratesticular injection	Human Ad-MSC from Royan Institute	10 µl Ad-MSC CM injection into each testes (once)	Epithelial growth factor (EGF) 42.33 pg/ml; Platelet Derived Growth Factor (PDGF) 85 pg/ml & Vascular Endothelial Growth Factor (VEGF) 74 pg/ml
Monakova et al. (11)	2022	Experimental	Russia	C57bl/6 Male Mice (in vivo); NA Wistar Rats (Leydig Cell Assay); 8 months	36 male mice; divided into 5 groups: 1. intact (n = 5) 2. DOX (n = 10) 3. DOX+CM (n = 16); 4. DOX+CM-VEGF (n = 2); 5. DOX+CM+isoVEGF (n = 3)	Doxorubicin 1 mg/kg intraperitoneal injection once in two days for 20 days to reach cumulative dose of 10 mg/kg	Human AdMSC from 8 healthy donors aged 18-53 years (MSU biobank)	50 µL of AdMSC-CM + 2% porcine collagen; subcutaneous testicular injection (once)	VEGF; no report of other composition
Atia et al. (12)	2024	Experimental	Egypt	Adult Male Rats; NA	70 male rats; divided into 5 groups: 1. Untreated (n = 10) 2. Acrylamide (AC) (n = 15) 3. AC+AdMSC (n = 15) 4. AC+AdMSC-CM (n = 15) 5. Recovery group (n = 15)	Acrylamide, 3 mg/kg orally for 30 days	Rat visceral adipose tissue (P3 passage MSCs)	0.5 mL CM or 0.65 × 10 ⁶ MSCs in 0.5 mL PBS, via caudal vein (once); applied after 4 weeks of AC, monitored for 15 days	NA

Table 1B.
Experimental outcomes of AdMSC secretome treatment in testicular injury models.

Reference	Results
Abdollahifar et al. (10)	<ul style="list-style-type: none"> · No significant difference in volume of testis and testis interstitium between AdMSC-CM+BSU group compared to BSU group · Significant increase in volume of seminiferous tubule in Ad-MSC-CM compared to BSU group (p < 0.05) · Total number of spermatogonia, primary spermatocytes, spermatids and sertoli decreased in AdMSC-CM+BSU group compared to control, DMEM and DMSO group, but when compared to BSU only group, AdMSC+BSU group showed significant increase in sperm number and sperm motility. · AdMSC+BSU group showed significant increase in number of Leydig Cells compared to BSU only group, but there is no significant difference in number of Sertoli Cells · TUNEL assay showed reduced apoptosis in testicular cells of AdMSC+BSU group compared to BSU alone group.
Monakova et al. (11)	<ul style="list-style-type: none"> · Slight increase of regenerating tubules in DOX+CM mice group 5 months after CM injection · Restoration of sperm motility and total count in DOX+CM group compared to the DOX-only group · DOX+CM-VEGF group showed no histological improvement of the testes indicating VEGF as one of the paracrine mediators in restoration of testicular microenvironment · VEGF concentration in the AdMSC secretome stimulates testosterone production secretion of the primary Leydig Cells in a dose dependent manner.
Atia et al. (12)	<ul style="list-style-type: none"> · Histologically: AC+AdMSC group had nearly normal seminiferous tubules and Leydig cells; AC+AdMSC-CM group showed moderate recovery with reduction of collagen fibers around blood vessels and seminiferous tubules compared to AC group. The number of Leydig Cells in AD+AdMSC-CM group was also increased significantly compared to control, but not as high as the AC+AdMSC group. Some germinal epithelium appeared disorganized with edema found in the interstitial spaces. · Significant increase in normal cells and reduced apoptotic cells in AC+AdMSC and AC+AdMSC-CM group compared to acrylamide group (404.78% and 79.68%) · Decreased expression of p53 in AC+AdMSC and AC+AdMSC-CM group compared to acrylamide group (48.76% and 65.11%) · Respectively, in AC+AdMSC and AC+AdMSC-CM group, there are significant increase of free testosterone (34.31% and 114.89%) and total testosterone (47.42% and 75.27%) compared to control group · Significant decrease of Lipid Peroxidation (apoptosis) in AC+AdMSC and AdMSC+CM group compared to acrylamide group.

Quality assessment

Methodological quality and risk of bias of the included studies were independently assessed by two reviewers (NNE and IDS) using the *Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias (RoB)* tool.

RESULTS

Study selection and characteristics

A total of 2.745 articles were found at the initial search using the specified MESH keywords: 2.670 articles discovered from Google Scholar, 68 from PubMed, 6 from OVID and one from the Cochrane Library. Following title and abstract screening and application of the predefined inclusion and exclusion criteria, three preclinical studies were included in this systematic review (10-12).

All included studies employed adult male murine models. One study used NMRI male mice aged 8 weeks, one study utilized two murine models, C57BL/6 male mice of unspecified age and Wistar rats aged 8 months, and the remaining study reported the use of adult male rats without specifying age. Most studies did not report animal body weight. Sample sizes ranged from 36 to 70 animals per study, which were allocated into five to six experimental groups.

Experimental model and intervention

Chemical induction of testicular injury varied across studies and included busulfan (40 mg/kg, intratesticular), doxorubicin (10 mg/kg, intratesticular), and acrylamide (3 mg/kg, oral administration for 30 days). All studies confirmed testicular damage through histopathological assessment before or after intervention. Secretome was derived from either human AdMSCs in two studies and rat AdMSCs in one study. In all studies, secretome was administered as a single-dose treatment. Two studies delivered the secretome via intratesticular injection, while one study used intravenous administration through the tail vein. Injection volumes ranged from 10 µL to 0.5 mL, and no repeated administrations were reported. Only two studies described the composition of the secretome, identifying *vascular endothelial growth factor (VEGF)*, *epidermal growth factor (EGF)* and *platelet-derived growth factor (PDGF)*, although only one study performed quantification analyses of secretome's component.

Histological and cellular outcomes

Overall, all included studies demonstrated beneficial effects of AdMSC secretome administration in murine models of chemically induced testicular injury. Consistently, partial regeneration of seminiferous tubules was observed in secretome-treated groups compared with chemically injured control groups. One study reported a reduction in collagen fiber deposition surrounding blood vessels and seminiferous tubules in the acrylamide-induced injury model following secretome treatment. Partial restoration of the germinal epithelium accompanied by interstitial edema was reported in one study. Additionally, *Monakova et al.* referenced their previous work in a cryptorchidism rat model, demonstrating that secretome administration enhanced the

production of germ cells and promoted recovery of spermatogenesis (13).

Apoptosis of Leydig Cell

Assessment of cellular apoptosis was performed in two of the three included studies. One study employed the terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay, while the other used acridine orange staining. Despite methodological differences, the available evidence consistently demonstrated both studies reported a significant reduction in apoptotic activity in secretome-treated groups compared with chemically injured controls. An increase in Leydig cell numbers was consistently observed in groups receiving AdMSC secretome relative to untreated chemically injured groups, whereas Sertoli cell numbers remained unchanged following treatment. When compared directly with AdMSC transplantation, secretome treatment resulted in a greater recovery of Leydig cells.

Monakova et al. further demonstrated that administration of AdMSC secretome combined with anti-VEGF antibody abolished histological improvement, indicating a critical role of VEGF as a paracrine mediator in restoring the testicular microenvironment. The authors also highlighted the importance of VEGF concentration within the secretome in influencing testosterone production. These findings are consistent with the study by *Atia et al.*, which reported significantly higher free and total testosterone levels in animals treated with AdMSC-conditioned medium compared with those receiving AdMSC transplantation. A summary of the characteristics and outcomes of the included studies is presented in Table 1B.

Risk of Bias assessment

All included studies were assessed for risk of bias using the *SYRCLE Risk of Bias (RoB)* tool. The assessment was independently performed by two reviewers (NNE and IDS) and verified by a third reviewer (AR). The results of the risk of bias assessment are summarized in Table 2 (14).

As summarized, in Table 2, all the included study were

Table 2.
SYRCLE Risk of Bias assessment.

Domain	Abdollahifar et al. (2022)	Monakova et al. (2022)	Atia et al. (2024)
Sequence generation	Low risk	Low risk	Unclear risk
Baseline characteristics	Low risk	Low risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk
Random housing	Unclear risk	Unclear risk	Unclear risk
Blinding of caregivers	High risk	High risk	High risk
Random outcome assessment	Unclear risk	Unclear risk	Unclear risk
Blinding of outcome assessor	High risk	High risk	High risk
Incomplete outcome data	Low risk	Low risk	Low risk
Selective outcome reporting	Low risk	Low risk	Low risk
Other sources of bias	Low risk	Low risk	Low risk
Overall Risk of Bias (ROB)	Moderate	Moderate	Moderate

conducted within the year of 2022-2024 and were assessed as having an overall a moderate risk of bias. The studies by *Abdollahifar et al.* and *Monakova et al.* demonstrated low risk of bias in the domain of sequence generation as both reported random allocation of animals into experimental groups in contrast, the study by *Atia et al.* did not clearly describe the randomization process used for group allocations, resulting in higher concern for selection bias in this domain compared to the other studies. None of the included studies reported procedures for allocation concealment, random housing, or randomization of outcome assessment; therefore, the risk of bias in these domains was judged as unclear. Furthermore, outcome assessors were not blinded in any of the studies, leading to a high risk of performance and detection bias across all included studies. All studies reported complete outcome data with no evidence of attrition bias. Outcomes were consistently reported as prespecified, and no additional sources of bias were identified.

DISCUSSION

The present systematic review synthesized evidence from three preclinical studies investigating the therapeutic potential of AdMSC secretome in chemically induced testicular injury murine models (10-12). Our findings demonstrate that AdMSC secretome shows promising therapeutic effects for testicular regeneration, with consistent improvements in histological parameters and partial restoration of spermatogenesis across different chemical injury models.

Secretome refers to the collection of biological factors and molecules produced by the cells and released into the extracellular space, thereby mediating paracrine and autocrine functions (8, 15). Secretome is considered as a cell-free therapeutic approach because it exerts biological effect without direct transplantation of viable cells (16).

The biological activity of AdMSC secretome is mediated through a complex array of bioactive molecules, including cytokines, growth factors, chemokines, morphogens, and extracellular vesicles, which collectively regulate cellular signaling, survival, and regeneration (9).

All included studies reported improvements in seminiferous tubule regeneration following AdMSC secretome administration, suggesting that the paracrine factors within the secretome create a favorable microenvironment for testicular tissue repair (10-12).

This finding is consistent with the previous report demonstrating the regenerative potential of AdMSC in repairing tissues of other organ, such as excised skin of murine models. *Silveira et al.* found that accelerated wound healing process in their study was due to neovascularization driven by interaction of angiogenic paracrine factors including VEGF, and angiogenin with a crucial chemokine such as C-C Motif Chemokine Ligand 2 (CCL2) and *Interleukin-8* (IL-8), as well as *Insulin-like Growth Factor-Binding Protein 3* (IGFBP-3) that promotes cell growth, proliferation and tissue survival (17).

The cytoprotective effects of AdMSC secretome can be seen within two studies that found a significant reduction in cellular apoptosis following AdMSC secretome treatment despite different detection methods (TUNEL assay

and Acridine Orange Staining). This anti-apoptotic effect of AdMSC secretome can further be seen through the study of *Atia et al.*, which reported reduction of p53 expression in AdMSC secretome group (10, 12). This findings were consistent with previous studies demonstrating the anti-apoptotic activity of MSC secretome in other tissues, including hepatocytes and salivary glands (18, 19). One proposed mechanism underlying this protective effect is the inhibition of caspase-mediated apoptotic pathway, which has been widely reported in MSC secretome-based therapies (18, 20).

The increased number of Leydig cells observed in AdMSC secretome-treated groups suggests that secretome-derived factors not only mitigate cellular apoptosis but may also enhance the survival and proliferation of testosterone-producing cells (10-12). This finding is particularly relevant due to the fact that Leydig cell dysfunction can be caused by various chemical agents, either environmental or non-environmental chemical agents (21). This finding is in line with the result from *Prihatno et al.* that damaged the rats testes using cisplatin and administered MSC secretome, finding regeneration in both Leydig and Sertoli Cell (22).

VEGF, one of the growth factors secreted by the secretome of AdMSC appears to be the highlight of this systematic review findings. Study from *Monakova et al.* demonstrated that VEGF depletion from the secretome completely abolished the therapeutic benefits, highlighting its importance as a key paracrine mediator (11). This finding aligns with established research showing that

DECLARATIONS

Ethical approval and consent for participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and/or analysed during the current study are available upon reasonable request from the corresponding author.

Competing interests: No Conflict of interest was declared by the authors.

Funding: The authors would like to thank Directorate of Research and Community Service, Directorate General of Research and Development, Ministry of Higher Education, Science, and Technology for their assistance in supporting this project through funding in BIMA Grant No. 093/C3/DT.05.00/PL/2025, dated May 28, 2025.

Authors' contributions: NNE: Conceptualization, methodology, data curation, formal analysis, writing original draft. IDS: Data curation, screening and selection of studies, writing, review & editing. NS: Supervision, methodology, critical revision of the manuscript. AR: Conceptualization, Supervision, Validation, Writing – review & editing, Corresponding author.

Acknowledgments: The authors acknowledge Universitas Padjadjaran for administrative support and for covering the publication costs through an LPDP-funded reimbursement scheme under the EQUITY Program of the Indonesian Ministry of Higher Education, Science and Technology.

Conference presentation: This article was never presented in any conference before.

VEGF/VEGFR2 signalling promotes testicular regeneration via proliferation and direct action on germ cells, also enhancing testicular vascularization (23). The restoration of hormonal recovery are related to the VEGF content of AdMSC secretome in a dose dependent manner. The restoration of both free and total testosterone was reported in the study from *Atia et al.* in the AdMSC secretome group, even higher when compared to direct AdMSC treatment. The increase in testosterone levels following AdMSC secretome therapy is in line with the recovery and increased proliferation of the Leydig cells (24, 25). Recent studies have shown that AdMSC conditioned medium can protect human sperm from cryoinjury, affecting sperm motility, viability, morphology, and other functional parameters, supporting the broader application of secretome therapy in male reproductive health (26). Despite these promising findings, several limitations should be acknowledged. The overall moderate risk of bias among included studies and the heterogeneity in chemical agents used to induce testicular injury may limit the strength of the conclusions. Furthermore, standardization of secretome composition, potency, and dosing remains a critical challenge for future clinical translation. Additional studies are required to determine the optimal timing of intervention, duration of therapeutic effects, and the potential need for repeated secretome administration.

CONCLUSIONS

This systematic review provides evidence supporting the therapeutic potential of AdMSC secretome for chemically induced testicular injury. The consistent improvements in histological parameters, reduction in cellular apoptosis, and restoration of hormonal profiles across different injury models suggest broad applicability. However, the moderate quality of evidence and limited number of studies highlight the need for more rigorous preclinical research before advancing to clinical trials.

REFERENCES

1. Leslie SW, Soon-Sutton TL, Khan MA. *Male Infertility [Internet]. Treasure Island: Statpearls Publishing; 2024.*
2. Gül M, Russo GI, Kandil H, et al. *Male Infertility: New Developments, Current Challenges, and Future Directions. World J Mens Health. 2024; 42:502.*
3. Punjani N, Alawamlh OA-H, Kim SJ, et al. *Changes in Semen Analysis over Time: A Temporal Trend Analysis of 20 Years of Subfertile Non-Azoospermic Men. World J Mens Health. 2023; 41:382.*
4. Levine H, Jørgensen N, Martino-Andrade A, et al. *Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum Reprod Update. 2017; 23:646-59.*
5. Soleimani MZ, Khorsandi L, Asadi-Fard Y, et al. *Protective Effects of Adipose Mesenchymal Stem Cell Secretome On Oxidative Stress-Induced Bisphenol-A in Isolated Rat Testes Mitochondria and Sperm Quality. JBRA Assist Reprod. 2025; 29:53-60.*
6. Muzes G, Sipos F. *Mesenchymal Stem Cell-Derived Secretome: A Potential Therapeutic Option for Autoimmune and Immune-Mediated Inflammatory Diseases. Cells. 2022; 11:2300.*

7. Sumarwoto T, Suroto H, Mahyudin F, et al. *Role of adipose mesenchymal stem cells and secretome in peripheral nerve regeneration. Ann Med Surg. 2021; 67.*
8. Daneshmandi L, Shah S, Jafari T, et al. *Emergence of the Stem Cell Secretome in Regenerative Engineering. Trends Biotechnol. 2020; 38:1373-84.*
9. Trzyna A, Banas-Zabczyk A. *Adipose-Derived Stem Cells Secretome and Its Potential Application in "Stem Cell-Free Therapy." Biomolecules. 2021; 11:878.*
10. Abdollahifar MA, Azad N, Faraji Sani M, et al. *Impaired spermatogenesis caused by busulfan is partially ameliorated by treatment with conditioned medium of adipose tissue derived mesenchymal stem cells. Biotech Histochem. 2022; 97:107-17.*
11. Monakova A, Sagaradze G, Basalova N, et al. *Novel Potency Assay for MSC Secretome-Based Treatment of Idiopathic Male Infertility Employed Leydig Cells and Revealed Vascular Endothelial Growth Factor as a Promising Potency Marker. Int J Mol Sci. 2022; 23:9414.*
12. Atia MM, Badr EL-Deen AA, Abdel-Tawab HS, Alghriany AAL. *Rehabilitation of N, N'-methylenebisacrylamide-induced DNA destruction in the testis of adult rats by adipose-derived mesenchymal stem cells and conditional medium. Heliyon. 2024; 10:e40380.*
13. Sagaradze GD, Basalova NA, Kirpatovsky VI, Ohobotov DA, et al. *Application of rat cryptorchidism model for the evaluation of mesenchymal stromal cell secretome regenerative potential. Biomed Pharmacother. 2019; 109:1428-36.*
14. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, et al. *SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014; 14:43.*
15. Ajit A, Ambika Gopalankutty I. *Adipose-derived stem cell secretome as a cell-free product for cutaneous wound healing. 3 Biotech. 2021; 11:413.*
16. Sreenivas A, K. Jha D. *Cell-Free Therapies: Revolutionizing the Approach to Cellular Treatments. In: Advances in Regenerative Medicine and Tissue Engineering. IntechOpen; 2025.*
17. Silveira BM, Ribeiro TO, Freitas RS, et al. *Secretome from human adipose-derived mesenchymal stem cells promotes blood vessel formation and pericyte coverage in experimental skin repair. Haque N, editor. PLoS One. 2022; 17:e0277863.*
18. Jiao Z, Ma Y, Wang Y, et al. *Protective Effect of Adipose-Derived Mesenchymal Stem Cell Secretome against Hepatocyte Apoptosis Induced by Liver Ischemia-Reperfusion with Partial Hepatectomy Injury. Arnhold S, editor. Stem Cells Int. 2021; 2021:1-12.*
19. An H-Y, Shin H-S, Choi J-S, et al. *Adipose Mesenchymal Stem Cell Secretome Modulated in Hypoxia for Remodeling of Radiation-Induced Salivary Gland Damage. Camussi G, editor. PLoS One. 2015; 10:e0141862.*
20. Chen Z, Xia X, Yao M, et al. *The dual role of mesenchymal stem cells in apoptosis regulation. Cell Death Dis. 2024; 15:250.*
21. Yang F, Li X, Wang M, et al. *The Role of Environmental Endocrine Disruptors on Leydig Cell Death and Senescen. World J Mens Health. 2025; 43:477.*
22. Prihatno SA, Padeta I, Larasati AD, et al. *Effects of secretome on cisplatin-induced testicular dysfunction in rats. Vet World. 2018; 11:1349-56.*
23. Tian R, Yang S, Zhu Y, et al. *VEGF/VEGFR2 Signaling Regulates Germ Cell Proliferation in vitro and Promotes Mouse Testicular Regeneration in vivo. Cells Tissues Organs. 2016; 201:1-13.*

24. Sagaradze G, Monakova A, Efimenko A. Potency Assays for Mesenchymal Stromal Cell Secretome-Based Products for Tissue Regeneration. *Int J Mol Sci.* 2023; ; 24:9379.

25. Datrianto DS, Budipitojo T, Prihatno SA. Secretome improves testosterone and androgen-binding protein production in testicular

dysfunction rats induced by cisplatin. *J Adv Vet Anim Res.* 2021; 8:687-94.

26. Nafchi HG, Azizi Y, Halvaei I. Effect of Conditioned Medium from Human Adipose-Derived Mesenchymal Stem Cells on Human Sperm Quality During Cryopreservation. *Reprod Sci.* 2024; 31:1586-92.

Correspondence

Nadya Nathalia Evangelista
nadya24022@mail.unpad.ac.id

Indah Dian Shafira
indah24016@mail.unpad.ac.id

Graduate School of Master Program in Anti-Aging and Aesthetic
Medicine, Faculty of Medicine, Universitas Padjadjaran, Jl. Prof Eyckman
No. 38, Bandung, West Java, Indonesia

Nova Sylviana
nova.sylviana@unpad.ac.id

Andri Rezano (Corresponding Author)
andri.rezano@unpad.ac.id

Department of Biomedical Sciences, Faculty of Medicine, Universitas
Padjadjaran, Jalan Ir. Soekarno KM. 21, Jatinangor - Sumedang 45363,
Indonesia