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REVIEW ARTICLE

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Major clinical outcomes of corneal regeneration processes through advanced and nutrological therapy with exosomes and microRNAs: a systematic review

Maria de Lourdes Alves Fávaro[1,*], **Vitor William Favinha**[1]

[1] Irmandade da Santa Casa de Misericórida de Pederneiras, São Paulo, Brazil.

*Corresponding author: Maria de Lourdes Alves Fávaro.
Irmandade da Santa Casa de Misericórida de Pederneiras,
São Paulo, Brazil.
E-mail: favaro.marialourdes@gmail.com
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Abstract

Introduction: The corneal healing process is complex and induces the formation of fibrosis, which is one of the main causes of blindness worldwide. An important therapeutic tool for treating scarred corneas includes those based on exosomes and microRNAs. Protecting and regenerating human corneal endothelial cells (hCECs) should be the main therapeutic goal for corneal endothelial diseases. **Objective:** It was to carry out a concise systematic review to present the main considerations and clinical outcomes of corneal regeneration processes through advanced and nutrological therapy with exosomes and microRNAs. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from August to September 2025 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 124 articles were recruited for the initial evaluation, and 44 articles were evaluated and 18 were included in the results of the present systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 16 studies with a high risk of bias and 32 studies that did not meet GRADE. Most studies showed homogeneity in their results, with X^2=87.2%>50%. It was concluded that exosomes are membrane-bound vesicles released by cells, especially mesenchymal stem cells, into their extracellular space, pointing out a new therapeutic approach to cell-based therapy for the treatment of corneal scars. Exosomes can deliver antifibrotic proteins and miRNAs from stem cells to the ocular surface to modulate the healing cornea's therapeutic signaling pathway. Exosomes appear to be more effective in preventing neutrophil infiltration, reducing the expression of fibrotic markers, and restoring corneal morphology. Corneal stromal stem cells treated with exosomes isolated from adipose tissue-derived stem cells showed optimal proliferation, reduced apoptosis, increased aldehyde dehydrogenase 1 (ALDH1), decreased expression of MMP1, MMP3, and MMP9 and increased collagen I, II, III, IV, and V expression compared to untreated corneal stromal cells.

Keywords: Cornea. Regenerative processes. Endothelial cells. Corneal Stroma. Exosomes.

Introduction

The corneal healing process is complex and induces the formation of fibrosis, which is one of the leading causes of blindness worldwide. The ocular scarring process disrupts the highly organized fibrillar arrangement of collagen in the corneal stroma, making it opaque. The process of recovering this organized arrangement of the extracellular matrix of the stromal layer to restore corneal transparency is complex **[1,2]**.

In this respect, the surface retention capacity of ocular medications is weak, and there is a large gap between suitable corneal donors and clinical

requirements. Therefore, a more efficient way to treat corneal scarring is needed. An important therapeutic tool for the treatment of scarred corneas includes those based on exosomes and microRNAs [1]. Human corneal endothelial cells (hCECs) do not regenerate, and their excessive loss results in corneal decompensation, which requires corneal transplantation [2]. Thus, protecting and regenerating hCECs should be the main therapeutic goal for endothelial corneal diseases [3]. The pathogenesis of hCECs includes oxidative stress, endoplasmic reticulum stress, and RNA toxicity [4,5]. A potential therapeutic strategy could be to inhibit senescence, because cell cycle arrest in the G0/G1 phase, observed in hCECs, resembles senescence [6,7].

For this purpose, mesenchymal stem cells (MSCs) are stromal cells capable of self-renewal and multilineage differentiation [8]. The immunomodulatory and regenerative effects of MSCs are mediated by their paracrine, endocrine, and autocrine activity [9]. MSCs secrete biologically active molecules, including microRNAs, cytokines, and growth factors such as interleukin (IL)-1, IL-10, tumor necrosis factor-stimulated gene 6 (TSG-6), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), which activate multiple signal transduction pathways. These pathways include phosphoinositide 3-kinase (PI3K)/Akt, Janus kinase (JAK)/signal transducer, and mitogen-activated protein kinase transcription activator, which promote survival, proliferation, anti-apoptosis, and extracellular matrix remodeling [9-11].

In summary, exosomes are cell-derived vesicles present in many biological fluids that are supposedly involved in the paracrine effect of MSCs and cell-cell communication [12]. In particular, adipose-derived mesenchymal stem cells (ADSCs) secrete cytokines, growth factors, proteins, and extracellular vesicles and have great potential for tissue regeneration [13,14]. ADSC-derived exosomes containing lipids, microRNAs (miRNAs), DNA, and heat shock proteins can alleviate ischemic injury and regenerate tissues and organs by modulating inflammation, senescence, and oxidative stress [15]. TGF-β or oxidative stress has been found to induce senescence that inhibits hCEC regeneration. Furthermore, evidence is emerging that ADSC-derived exosomes promote hCEC regeneration by inhibiting TGF-β/oxidative stress-induced senescence.

Therefore, the present study conducted a concise systematic review to present the main considerations and clinical outcomes of corneal regeneration processes through advanced and nutrological therapy with exosomes and microRNAs.

Methods

Study Design

This study followed an international model for systematic review, adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: September 9, 2025. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: September 9, 2025.

Research Strategy and Sources

The literature search process was conducted from August to September 2025 and developed using Scopus, PubMed, Science Direct, SciELO, and Google Scholar, encompassing scientific articles from various periods to the present day. The following descriptors were used (DeCS/MeSH Terms): "Cornea. Regenerative processes. Endothelial cells. Corneal Stroma. Exosomes", and using the Boolean operator "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot (Sample size versus Effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

As a corollary to the literature search system, a total of 124 articles were found, which were submitted to eligibility analysis, and subsequently, 18 of the 44 final studies were selected to compose the results of this systematic review. The listed studies presented medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with

X^2=87.2%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 16 studies with a high risk of bias and 32 studies that did not meet the GRADE criteria.

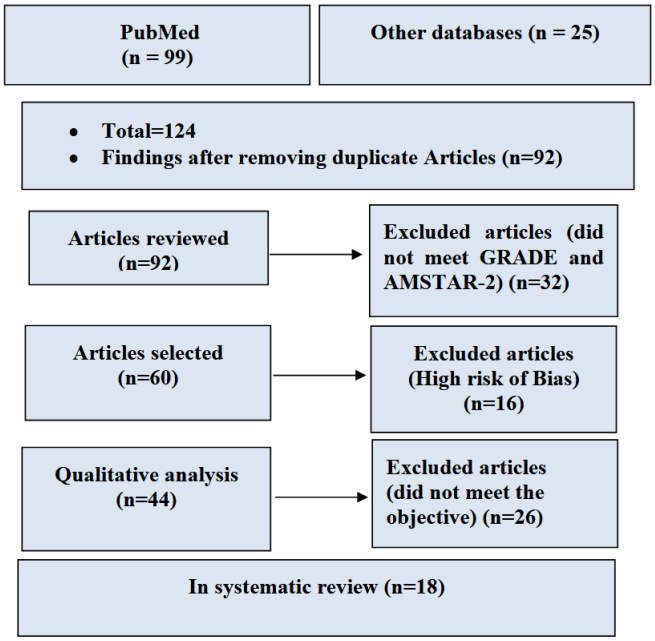

Figure 1. Flowchart showing the article selection process. Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's d test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) shown at the bottom of the graph and in studies with large sample sizes shown at the top.

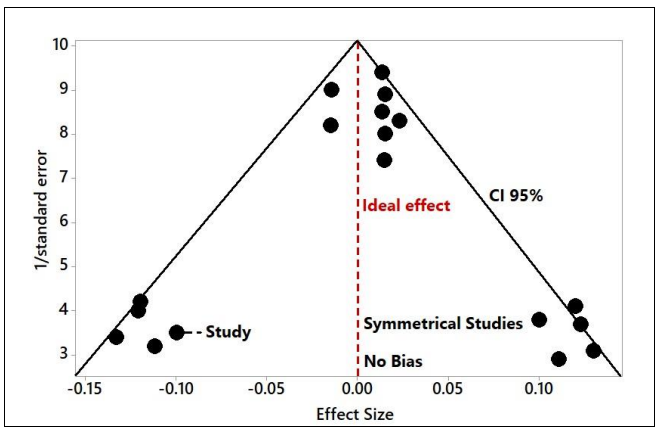

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=18 studies). Source: Own authorship.

Major Scientific Approaches and Clinical Evidence

After recruiting and analyzing the literature results on corneal regenerative processes, it was shown that exosomes are membrane-bound vesicles released by cells into their extracellular space, pointing to a new therapeutic approach in relation to cell-based therapy for the treatment of corneal scars **[16]**. Most stem cell-based therapies face several challenges, such as immunogenicity, high production cost, ethical concerns, stability, and survival. However, exosomes have less stringent regulatory and safety requirements than other stem cell-based therapies.

Exosomes act as biological vehicles that deliver cargo from stem cells to target cells. Exosomes are internalized by target cells by receptor-mediated endocytosis or by simple membrane fusion. Upon reaching the cytoplasm of the target cell, exosomes release their contents, activating various signaling cascades **[17]**. Exosomes can be isolated from stem cells using simple techniques such as ultracentrifugation, ultrafiltration, size exclusion chromatography, and immunity capture. These vesicles can deliver antifibrotic proteins and miRNAs from stem cells to the ocular surface to modulate therapeutic signaling cascades in the healed cornea.

In this scenario, an increase in the concentration of chemokines and cytokines at the site of injury is the hallmark of wound healing. Interleukin 8 (IL-8), a pro-inflammatory cytokine, binds to glycosaminoglycans (GAGs). In this GAG-bound form, IL-8 interacts with the CXC motif chemokine receptor 1 (CXCR1) and CXCR2 of neutrophils that infiltrate the site of injury, leading to oligomerization and a hydrostatic gradient. This hydrostatic gradient directs neutrophil migration to the injured area and seeds the corneal fibrosis process **[18]**. Corneal stromal stem cells (CSSCs) express tumor necrosis factor (TNF)-stimulated gene 6 (TSG-6), a hyaluronan-binding protein, during inflammation **[19]**.

This 35 kDa protein interacts with IL-8 through its binding module domain and disrupts IL-8 and GAG binding, preventing neutrophil migration **[20,21]**. Shojaati et al. **[22]** isolated extracellular vesicles (EVs) from CSSCs, mixed them with fibrin gel, and administered the EV-fibrin gel to the surface of an eye with corneal debridement. After 2 weeks of debridement, the EV-treated cornea showed small corneal scars compared to CSSC-treated and untreated controls. EVs were more effective in preventing neutrophil infiltration, reducing the expression of fibrotic markers, and restoring corneal morphology.

Cultured CSSCs treated with exosomes isolated from adipose-derived stem cells (ADSCs) showed optimal proliferation, reduced apoptosis, increased

aldehyde dehydrogenase 1 (ALDH1), decreased expression of MMP1, MMP3, and MMP9, and increased collagen I, II, III, IV, and V expression compared to untreated CSSCs **[23]**. Therefore, ADSC-derived exosomes can revive the plasticity of transformed corneal keratocytes or stromal cells, increasing keratocyte marker expression and corneal stromal layer production.

The therapeutic effects of ADSCs and ADSC-derived exosomes can be attributed to microRNA-19a, which binds to the 3'UTR of homeodomain-containing serine/threonine kinase 2 (HIPK2). MicroRNA-19a post-transcriptionally suppresses homeodomain-interacting protein kinase 2 (HIPK2), preventing activation of the Jun N-terminal kinase (JNK) pathway and fibrosis **[24]**. Corneal keratocytes, when co-cultured with ADSC-derived exosomes, reduce the expression of HIPK2, phosphorylated SMAD3, and p53, preventing the transformation of keratocytes into myofibroblasts and apoptosis of nearby damaged cells. This condition was reversed by lentivírus-mediated HIPK2 overexpression in keratocytes, confirming the role of miRNA-19a in corneal scar healing **[25]**.

In one study, human corneal epithelial cells (hCEs) were treated with recombinant thrombospondin 1 (TSP1) to evaluate the efficacy of corneal epithelium-derived exosomes in corneal wound healing. They were subjected to the same hypoxic stress found in corneal wound healing. Exosomes with TSP-1 as cargo protein decrease paraptosis (apoptosis caused by hypoxic conditions) **[26]**. EVs derived from human placental mesenchymal stem cells were used to treat alkali-burned mouse corneas. EVs decreased vascular endothelial growth factor (VEGF) expression after 48 hours, and corneal restoration was observed 14 days after treatment. hCEs treated with EVs showed a reduction in the expression of profibrotic genes (IL-10, IL-1β, TNF-α, and NF-κβ) and the apoptosis gene cas8, revealing their anti-inflammatory and anti-apoptotic potential **[27-29]**.

A study developed by the authors Ryu et al. (2023) **[30]** investigated whether exosomes derived from adipose-derived stem cells (Adipose-Derived Stem Cells - ADSCs) could protect and regenerate human corneal endothelial cells hCECs. Cell viability and cell cycle analyses were performed to evaluate the effect of ADSC-derived exosomes on the regenerative capacity of cultured hCECs. Transforming growth factor β (TGF-β) and hydrogen peroxide (H_2O_2) were used to induce biological stress in hCECs. The effect of ADSC-derived exosomes on hCECs was investigated in vivo. ADSC-derived exosomes induced hCEC proliferation and suppressed oxidative stress and senescence induced by TGF-β or H_2O_2. ADSC-derived exosomes protect hCECs against TGF-β or H_2O_2-induced endothelial-mesenchymal transition and mitophagy.

The authors Shojaati et al. (2019) **[22]** investigated the hypothesis that tissue regeneration by CSSCs is mediated by secreted extracellular vesicles (EVs). CSSC produced EVs of 130-150 nm in diameter with surface proteins that include CD63, CD81, and CD9. EVs from CSSCs reduced visual scarring in murine corneal wounds as effectively as living cells, but EVs from human embryonic kidney (HEK) 293T cells lacked regenerative properties. Wound treatment with EVs decreased the expression of the fibrotic genes Col3a1 and Acta2, blocked neutrophil infiltration, and restored normal tissue morphology. CSSC EVs labeled with carboxyfluorescein succinimidyl ester dye rapidly fused with cultured corneal epithelial and stromal cells, transferring microRNA (miRNA) to the target cells. Elimination of mRNA for Alix, a component of the endosomal sorting complex required for transport, using siRNA, resulted in an 85% reduction of miRNA in secreted EVs. EVs with reduced miRNA were ineffective in blocking corneal scarring.

CSSCs with reduced Alix expression also lost their regenerative function, suggesting EVs as a mandatory component in miRNA delivery. The results of these studies support an essential role for extracellular vesicles in the process by which CSSC cells block scarring and initiate regeneration of transparent corneal tissue after injury. Corneal damage forms scar tissue and manifests as permanent corneal opacity, which is the leading cause of visual impairment due to corneal diseases. To treat these diseases, authors developed a novel approach based on exosomes derived from induced pluripotent stem cells (iPSC-MSCs) combined with a thermosensitive hydrogel, which reduces scar formation and accelerates the healing process. It was found that sustained-release iPSC-MSC exosomes from chitosan-based thermosensitive hydrogels (CHI hydrogel) can effectively promote the repair of damaged corneal epithelium and stromal layer by negatively regulating the expression of mRNA encoding the three most enriched collagens (type I alpha 1 collagen, type V alpha 1 collagen, and type V alpha 2 collagen) in the corneal stroma and reducing scar formation in vivo. Furthermore, iPSC-MSCs secrete exosomes containing miR-432-5p, which suppresses translocation-associated membrane protein 2 (TRAM2), a vital modulator of collagen biosynthesis in corneal stromal stem cells to prevent extracellular matrix deposition **[31]**.

Finally, exosomes derived from ADSCs have been shown to improve senescence both in vitro and in vivo by improving mitochondrial function and inhibiting autophagy. Depolarization of the mitochondrial

membrane potential indicates mitochondrial dysfunction, also observed in premature cell death [32]. Mitochondria play a crucial role in the survival and function of hCECs, which require a significant amount of energy to maintain corneal stromal dehydration. In addition, exosomes derived from ADSCs can inhibit autophagy, contributing to the regeneration of hCECs [33].

Conclusion

It was concluded that exosomes are membrane-bound vesicles released by cells, especially mesenchymal stem cells, into their extracellular space, pointing to a new therapeutic approach in relation to cell-based therapy for the treatment of corneal scars. Exosomes can deliver antifibrotic proteins and miRNAs from stem cells to the ocular surface to modulate the therapeutic signaling cascade of the scarred cornea. Exosomes appear to be more effective in preventing neutrophil infiltration, reducing the expression of fibrotic markers, and restoring corneal morphology. Corneal stromal stem cells treated with exosomes isolated from adipose tissue-derived stem cells showed optimal proliferation, reduced apoptosis, increased aldehyde dehydrogenase 1 (ALDH1), decreased expression of MMP1, MMP3, and MMP9, and increased expression of collagen I, II, III, IV, and V compared to untreated corneal stromal cells.

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Author contributions: **Conceptualization**; **Data curation**; **Formal Analysis**; **Investigation**; **Methodology**; **Project administration**; **Supervision**; **Writing - original draft**; **Writing-review & editing-** Maria de Lourdes Alves Fávaro and Vitor William Favinha.

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Ethical Approval

Not applicable.

Informed Consent

It was applicable.

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Data Sharing Statement

All referenced sources are accessible through the respective journals or public repositories.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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