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Review Article

A New Frontier in Dry Eye Management: A Systematic Review of Topical Secretome Therapies

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Abstract
Dry Eye Disease (DED) is a multifactorial ocular surface disorder characterized by tear film instability and chronic inflammation, resulting in discomfort and visual disturbance. Conventional treatments such as artificial tears and anti-inflammatory agents mainly provide symptomatic relief and show limited regenerative potential. Secretome-based therapy, derived from mesenchymal stem cells (MSCs), has recently emerged as a promising cell-free regenerative approach. This systematic review aims to evaluate the efficacy, safety, and mechanisms of topical secretome therapy for DED in animal models. A systematic literature search was conducted in PubMed, Google Scholar, and ScienceDirect for studies published between January 2004 and September 2025. Eligible studies included animal models of DED treated with MSC-derived secretome, exosomes, or conditioned medium administered as topical eye drops. Data extraction followed PRISMA guidelines, and study quality was assessed using the SYRCLE's risk of bias tool for animal research. Eleven animal studies met the inclusion criteria. Topical secretome therapy significantly improved tear break-up time and tear production in most studies and reduced corneal fluorescein staining, indicating enhanced tear film stability and epithelial repair. Histological analyses revealed increased goblet cell density, reduced inflammatory cytokines, and decreased apoptosis markers. No ocular or systemic adverse effects were reported, confirming good tolerability across all animal models. Topical secretome therapy demonstrates strong anti-inflammatory, anti-apoptotic, and regenerative effects in animal models of DED, with a favorable safety profile. Future research should focus on standardizing secretome production and conducting clinical studies to confirm its translational potential as cell-free therapy for ocular surface regeneration..

Keywords: *Secretome, Dry Eye Disease, Topical Therapy, Animal model, Mesenchymal stem cells*
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INTRODUCTION

Dry Eye Disease (DED) is a multifaceted condition of the ocular surface initiated by a loss of tear film homeostasis. This imbalance manifests as tear instability and causes a range of ocular symptoms, including discomfort and visual impairment, while also carrying the risk of inflicting damage upon the ocular surface.[1] The pathophysiology of DED is complex and self-perpetuating, primarily driven by chronic

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inflammation and hyperosmolarity, which lead to apoptosis of epithelial cells and damage to the underlying corneal and conjunctival tissues.[2] Current management of DED primarily focuses on alleviating symptoms and controlling inflammation. Conventional treatments range from artificial tears and lubricants for symptomatic relief to anti-inflammatory agents like topical corticosteroids, cyclosporine, and lifitegrast. While these therapies can be effective for many patients, they often have limitations.[3] Artificial tears provide only transient relief, and pharmacological agents may have incomplete efficacy, delayed onset of action, or potential side effects. Critically, most existing treatments do not adequately address the underlying need for ocular surface regeneration and tissue repair.

In response to these therapeutic gaps, regenerative medicine has offered new avenues, with cell-free therapies emerging as a particularly promising frontier. Among these, topical secretome therapy holds considerable promise. The secretome refers to the rich milieu of paracrine factors including growth factors, cytokines, chemokines, and extracellular vesicles secreted by various kind of stem cells, particularly mesenchymal stem cells (MSCs).[4] This cocktail of biomolecules orchestrates a multi-pronged therapeutic effect, demonstrating potent anti-inflammatory, immunomodulatory, anti-apoptotic, and pro-regenerative properties. By delivering these factors directly to the ocular surface via a non-invasive topical application, secretome therapy aims to not only control inflammation but also actively promote the healing of damaged tissues and restore ocular homeostasis.[5]

Given the burgeoning body of preclinical and early clinical research in this area, a comprehensive synthesis of the existing evidence is required to clarify the therapeutic potential and current standing of this novel approach. Secretome-based therapy may be particularly relevant in non-infectious dry eye disease characterized by ocular surface inflammation, epithelial damage, reduced tear production, and goblet cell loss. Therefore, this systematic review aims to critically evaluate the efficacy, safety, and proposed mechanisms of action of topical secretome therapy for the treatment of DED.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria. A systematic search of the published literature was conducted from January 2004 to September 2025. The search was performed using PubMed, Google Scholar, and ScienceDirect databases. The search items consisted of the following terms: (“dry eye syndrome” OR “dry eye disease” OR “keratoconjunctivitis sicca” OR “ocular surface disease”) AND (“stem cell secretome” OR “mesenchymal stem cell secretome” OR “MSC secretome” OR “stem cell conditioned medium” OR “conditioned media” OR “stem cell exosome” OR “exosomes” OR “extracellular vesicles”) AND (therapy OR treatment OR intervention OR “topical application” OR eyedrops OR “eye drops”)

Inclusion criteria for this systematic review were studies involving animal models with dry eye syndrome, including subgroups with Sjögren’s syndrome and aqueous deficient dry eye (ADDE). Eligible studies included preclinical animal studies without restriction on animal species, sex, or age. In which the intervention consisted exclusively of MSC secretome–based eye drops (conditioned medium, exosomes, or extracellular vesicles derived from adipose tissue, bone marrow, umbilical cord, Wharton’s jelly, iPSC, etc.). Studies were required to include a comparison with standard therapy (such as artificial tears or placebo) and report outcomes including tear break-up time (TBUT), Schirmer test, or histopathological parameters (epithelial integrity, goblet cell density, inflammation).

Exclusion criteria were in vitro or ex vivo studies, stem cell therapies without secretome isolation, non-MSC secretome studies, secretome delivered via injection routes (subconjunctival or periocular), review articles, theses, and books, abstract-only publications (conference proceedings, editorials, author responses), and studies with unreliable, duplicate, or overlapping data.

The primary outcomes were tear film stability and tear production, assessed by tear break-up time (TBUT) and Schirmer test or Phenol Red Thread test, respectively, when reported. Secondary outcomes included ocular surface integrity assessed by corneal fluorescein staining scores or other reported epithelial damage grading methods, histopathological parameters such as goblet cell density and epithelial changes, inflammatory markers, apoptosis-related markers, and safety outcomes.

Duplicates were removed using Rayyan software. Title and abstract screening were performed to exclude studies that did not meet the eligibility criteria. After data extraction, risk of bias assessment of the included animal studies was performed using the SYRCLE’s Risk of Bias tool, which is specifically adapted for preclinical animal intervention studies. Final full-text review was performed by the first and second authors to determine the study design, population, sample size, type, frequency, and duration of intervention, and study results. Relevant data were extracted to Microsoft Excel and reviewed by the third author, and any disagreements were clarified in consultation with the fourth author.

We assessed the methodological quality of the included animal studies using SYRCLE’s risk of bias tool. Each study was judged as having a low, high, or unclear risk of bias across the following domains: selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding of caregivers and investigators), detection bias (random outcome assessment, blinding of outcome assessor), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential

Figure 1. PRISMA Flow Diagram of the Systematic Review Search Process

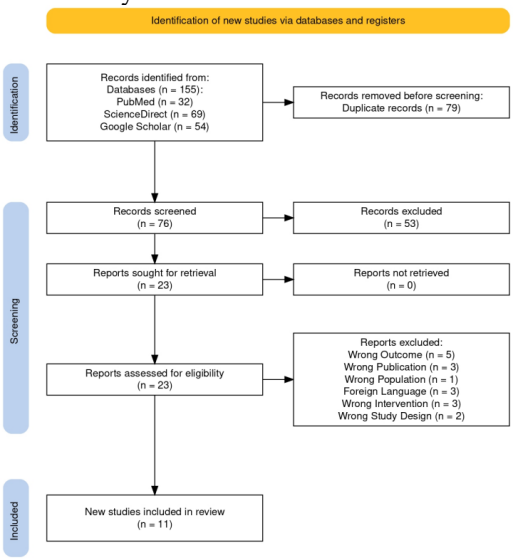
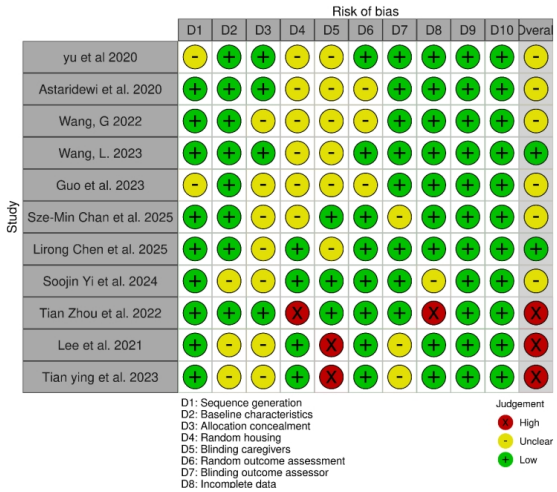


Figure 2. Risk of Bias



sources of bias.[6] A summary of the risk of bias assessment is presented in Figure 2.

RESULTS

Study Selection and Characteristics

A total of 155 records were identified through database searches (PubMed, Google Scholar, and ScienceDirect) covering publications from January 2004 to September 2025. After removing duplicates, 79 unique records remained. Screening of titles and abstracts led to the exclusion of 53 records due to irrelevant topics, study designs not meeting the inclusion criteria including reviews, editorials, or conference abstracts, non-MSC secretome or exosome sources, and non-topical administration routes. After full-text assessment, several studies were excluded because of lack of targeted outcomes such as TBUT, Schirmer, or histopathological data and different population targets including in vitro or non-DED models. The final selection included 11 studies that met all eligibility criteria and were incorporated into the qualitative synthesis (Figure 1). All were experimental animal studies evaluating topical MSC-derived secretome, conditioned medium, or extracellular vesicle therapy for dry eye disease. The study selection process is illustrated in Figure 1, and the main characteristics of included studies are summarized in Table 1.

Risk of Bias Assessment

The methodological quality of the included animal studies was evaluated using the SYRCLE's Risk of Bias tool. Overall, the reporting quality and experimental design were moderate. Across all domains, five were judged as unclear risk, three as high risk, and two as low risk of bias. Most studies demonstrated low risk in baseline comparability, selective reporting, and data completeness, whereas domains related to sequence generation, allocation concealment, and blinding procedures frequently showed unclear or high risk of bias due to insufficient methodological detail. These findings suggest that while the overall internal validity of the included studies was acceptable, improved transparency in randomization and masking would further strengthen future preclinical evidence. A summary of the risk of bias assessment is presented in Figure 2.

Tear Film Stability

Four studies evaluated tear film stability using tear break-up time (TBUT), and all reported significant prolongation following topical secretome

therapy compared with untreated or standard control groups. These findings suggest that secretome therapy may improve tear film stability in experimental dry eye disease.[7-9,11]

Tear Production

Tear production was assessed in ten studies using the Schirmer test or Phenol Red Thread test. Most studies demonstrated increased tear secretion after topical secretome administration, although one study reported only minimal improvement. Overall, these findings indicate that secretome therapy may support aqueous tear production in experimental dry eye disease. [5,7–16]

Corneal and Conjunctival Integrity

Eight studies reported a significant reduction in corneal fluorescein staining scores, suggesting improved epithelial healing and decreased ocular surface damage.[7,8,10–14,16] Histopathological analysis showed that seven studies demonstrated increased goblet cell density, reflecting enhanced mucin secretion and epithelial regeneration. One study also reported reduced corneal neovascularization following secretome administration.[5] Collectively, these findings support the regenerative role of secretome therapy on the corneal and conjunctival epithelium.

Inflammatory and Apoptotic Markers

Seven studies assessed inflammatory or cytokine-related outcomes. Most consistently showed downregulation of pro-inflammatory mediators, including IL-1β, IL-6, TNF-α, and IL-17A, along with suppression of inflammasome components (NLRP3, ASC).[5,7,9,10,12,14,16] Several studies also reported increased expression of anti-inflammatory and reparative factors such as IL-13, TIMP-1, and TIMP-2.[10] These immunomodulatory effects were associated with reduced epithelial apoptosis, as evidenced by a decrease in TUNEL-positive cells. Collectively, topical secretome administration produced broad anti-inflammatory and anti-apoptotic effects without any evidence of immune activation or ocular irritation. A detailed summary of cytokine modulation in individual studies is provided in Table 2.

Safety Outcomes

Although all included studies reported good tolerability, only two explicitly evaluated ocular and systemic safety parameters in detail. Both confirmed the absence of histopathological abnormalities in ocular and visceral tissues and stable intraocular pressure following secretome administration. Collectively, these findings suggest that secretome-based eye drops are generally well tolerated in preclinical dry eye models and demonstrate a favorable short-term safety profile. However, formal safety evaluation was limited to a small number of studies, and long-term safety data remain insufficient.

Table 1. Summary of Preclinical Studies Using Mesenchymal Stem Cell–Derived Secretome for Dry Eye Disease

Author	Type of intervention	Follow up	Administration	Total population	Dose	Adverse effect
Yu C. et al.7	hADSC-derived extracellular vesicles (EVs)	5 days (mouse model); 24h in vitro HCECs	four times daily	24 mice	5 µg of EVs per eye	None significant
Astaridewi D. et al.8	Resveratrol-preconditioned secretome from Wharton's Jelly mesenchymal stem cells (cell-free therapy)		eye drop, every 8 hours for 7 days	15 rabbit	The secretome was packaged into a single-dose application in a sterile Eppendorf tube at 50 µl volume	
Wang, G et al.9	Mouse adipose-derived mesenchymal stem cell-derived exosomes (mADSC-Exos)	14 days BAC induction + 7 days treatment	Topical instillation, 5 µL, 3 times daily	36 mice	12.5, 25, 50 mg/mL mADSC-Exos	No adverse effects reported in mice

Author	Type of intervention	Follow up	Administration	Total population	Dose	Adverse effect
Yu C. et al.7	hADSC-derived extracellular vesicles (EVs)	5 days (mouse model); 24h in vitro HCECs	four times daily	24 mice	5 µg of EVs per eye	None significant
Astaridewi D. et al.8	Resveratrol-preconditioned secretome from Wharton's Jelly mesenchymal stem cells (cell-free therapy)		eye drop, every 8 hours for 7 days	15 rabbit	The secretome was packaged into a single-dose application in a sterile Eppendorf tube at 50 µl volume	
Wang, G et al.9	Mouse adipose-derived mesenchymal stem cell-derived exosomes (mADSC-Exos)	14 days BAC induction + 7 days treatment	Topical instillation, 5 µL, 3 times daily	36 mice	12.5, 25, 50 mg/mL mADSC-Exos	No adverse effects reported in mice
Wang et al.10	Human umbilical cord-derived MSC extracellular vesicles (hucMSC-EVs)	21 days	Topical eye drops, 5 µL, 4times daily	56 mice	0.5, 1.0, 2.0, 3.0, 5.0 mg/m	
Guo et al.11	Human umbilical cord MSC-derived extracellular vesicles (hUC-MSC-EVs)	14 days	Topical eye drops, 4 times a day	32 mice	1 µL (1 µg/µL) per eye	No adverse effects
Sze-Min Chan et al.5	Umbilical Cord MSC-Derived Exosomes (UCMSC-exos)	56 days	topical eye drops, twice daily	Not stated		
Chen et al.12	human umbilical cord mesenchymal stem cells (HUCMSCs)-derived exosomes		eye drop	30 SPF C57BL/6 mice(5 groups, 6 mice each); HCEC cell line assays	HUMSC-EXO (2.5 × 1010 particles/ml in 5 µl) with or without miR146a-inhibitor was added to the droplets	

Author	Type of intervention	Follow up	Administration	Total population	Dose	Adverse effect
Yi et al.13	extracellular vesicles (EVs) derived from human amniotic epithelial cells (hAEC-EVs)		eye drop	50 mice	Topical eye drops (3 times daily)25 μg/mL (in vitro), Concentration in vivo not explicitly stated	
Tian Zhou et a.l14	Mesenchymal Stromal Cell-derived Exosomes (MSC-exo) / miR-204-enriched exosomes	Mice: 7 days	Topical eye drops	12 mice	Mice: 2.5×10^10 particles/ml in 5 μl per drop, twice daily	
Lee et al.15	low-molecular-weight adipose-derived stem cell-conditioned medium (LADSC-CM)		topical eye drops	5 mice per group	Twice daily application	
Tian et al.16	MSC-derived exosomes loaded with cerium oxide nanocrystals (MSCExo-Ce)	7 days treatment	Topical eye drops, twice drop	12 mice (efficacy) 20 mice (safety)	100 μg/mL MSCExo-Ce	No significant local or systemic adverse effects. Stable intraocular pressure; no histological abnormalities in heart, liver, kidney, spleen, or lungs. High ocular tolerance.

EVs, extracellular vesicles; MSC, mesenchymal stem cells; hADSC, human adipose-derived stem cells; mADSC, mouse adipose-derived stem cells; hUC-MSC/hucMSC/HUCMSC, human umbilical cord mesenchymal stem cells; hAEC, human amniotic epithelial cells; LADSC-CM, low-molecular-weight adipose-derived stem cell-conditioned medium; BAC, benzalkonium chloride; HCEC, human corneal epithelial cells; SPF, specific pathogen-free.

Table 2: Therapeutic Outcomes of Mesenchymal Stem Cell–Derived Secretome in Experimental Dry Eye Disease.

Study	Tear Break Up Time (TBUT)	Tear Production	Histo pA				Cytokines marker
			Ocular Surface*	Epitelieal deffect	Goblet cell	Inflamation	
Yu C. et al.7	Significantly increased	Significantly increased	Significant reduction	NR	Increased (Restoration of cells)	Significantly decreased	Decrease in of NLRP3, ASC, IL-1β and IL-18
Astaridewi D. et al.8	Significantly increased	Significantly increased	Significant reduction	NR	Increased (Restoration of cells)	Significantly decreased ($p<0.05$)	NR
Wang, G et al.9	Significantly increased	Significantly increased	NR	Significantly decreased ($p<0.05$)	Increased (Restoration of cells)	Significant decrease in TUNEL-positive cells (apoptosis)	Significantly reduced the levels of IL-6, TNF-α, and IL-1β.
Wang et al.10	NR	Significantly increased	Significant reduction	NR	Increased goblet cell density	Significantly decreased CD4+ T cell infiltration($P < 0.05$)	(IL-2, IL-6, IL-7, IL-11, IL-12p70, IL-15, IL-17, TNF-α, IFN-γ, IL-5, IL-8, TGF-β1) significantly reduced ($P < 0.05$); protective cytokines (IL-13, TIMP-1, TIMP-2) significantly increased ($P < 0.05$)

Study	Tear Break Up Time (TBUT)	Tear Production	Histo pA				Cytokines marker
			Ocular Surface*	Epitelieal deffect	Goblet cell	Inflamation	
Guo et al.11	Significantly increased	Significantly increased	Significant reduction	NR	Increased goblet cell density	Significantly decreased neutrophil infiltration and dendritic cell number/maturation ($p<0.05$)	NR
Sze-Min Chan et al.5	NR	Minumum (not stated)	Significant reduction	NR	NR	Significantly less neutrophil infiltration	(IL-1β and TNF-α) were downregulated.
Chen et al.12	NR	Significantly increased	NR	Reduced keratopathy (H&E staining)	NR	NR	- IL-1β, IL-6, and IL-17a reduced significant ($p<0.001$) - level of apoptosis cell reduced (TUNEL)
Yi et al.13	NR	Significantly increased)	Significant reduction	NR	Higher Density ($p<0.0001$) in 14Days	NR	NR
Tian Zhou et a.l14	NR	Significantly increased	Significant reduction	Corneal thickness increased ($p<0.01$)	NR	NR	- reduced pro inflamatory cytokine Il-6, IL-1β, and Il-17a. ($p<0.01$) - Decreased apoptotic cell (TUNEL+) increased Ki-67+ less CD11b+ all above($p < 0.001$)
Lee et al.15	NR	Significantly increased	NR	protected the microvilli best from dry damage.	Significantly increased	NR	NR

Study	Tear Break Up Time (TBUT)	Tear Production	Histo pA				Cytokines marker
			Ocular Surface*	Epitelieal deffect	Goblet cell	Inflamation	
Tian et al.16	NR	Significantly increased	Significant reduction	NR	NR	NR	IL-1β significantly decreased ($p<0.0001$)

TBUT, tear break-up time; NR, not reported; IL, interleukin; TNF-α, tumor necrosis factor-alpha; ASC, apoptosis-associated speck-like protein containing a CARD; NLRP3, NOD-like receptor family pyrin domain containing 3; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; H&E, hematoxylin and eosin; Ki-67, marker of cellular proliferation; CD, cluster of differentiation; IFN-γ, interferon-gamma; TIMP, tissue inhibitor of metalloproteinase; TGF-β1, transforming growth factor beta 1.

DISCUSSION

In this review, four preclinical studies specifically evaluated TBUT following topical secretome therapy. All consistently demonstrated a significant prolongation of TBUT compared with untreated or standard control groups, indicating that secretome-derived formulations effectively enhance tear film stability. Similarly, tear production, as measured by Schirmer or Phenol Red Thread tests, was significantly increased in ten of the included studies, reflecting improved lacrimal gland function and aqueous secretion. These findings suggest that topical secretome therapy may improve both tear film stability and tear production, thereby contributing to restoration of ocular surface homeostasis in experimental dry eye disease. Mechanistically, MSC-derived secretome contains soluble factors and extracellular vesicles with anti-inflammatory and regenerative properties, and topical application has been reported to attenuate corneal inflammation, reduce pro-inflammatory cytokines and inflammatory cell infiltration, and support ocular surface healing. Similar parameters have been evaluated in clinical meta-analyses of sodium hyaluronate eye drops, which demonstrated modest improvements in TBUT and Schirmer scores compared with saline or artificial tears.[17,24] However, unlike conventional lubricants that primarily act through physicochemical hydration, secretome-based formulations promote biological restoration of the ocular surface through anti-inflammatory and regenerative mechanisms, resulting in more sustained stabilization of the tear film.[7]

Eight of the eleven included studies demonstrated a significant reduction in corneal fluorescein staining scores following topical secretome administration, including one study that also reported a marked decrease in corneal neovascularization. Comparable improvement in epithelial integrity was also observed in clinical settings utilizing other biologically active regenerative formulations. In a randomized controlled trial, lacrimal-gland injection of allogeneic adipose-derived mesenchymal stem cells in Sjögren-associated dry eye resulted in significant enhancement of tear stability and reduction of ocular surface staining compared with observation, indicating restoration of ocular surface homeostasis through paracrine immunomodulatory effects.[18] Similarly, autologous platelet-rich plasma (PRP) monotherapy produced a significant reduction in corneal fluorescein staining in 76% of patients with moderate-to-severe dry eye, demonstrating the epithelial-healing potential of growth factor–enriched secretions.[19] These convergent findings reinforce that cell-free secretome or biologically derived growth-factor preparations share comparable regenerative and anti-inflammatory mechanisms that promote epithelial repair and reduce corneal fluorescein staining across both preclinical and clinical contexts.[5]

Seven of the eleven included studies reported cytokine-related outcomes, consistently demonstrating marked suppression of pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, and IL-17A, along with downregulation of inflammasome components NLRP3 and ASC. This inhibition disrupts the NF-κB–dependent cascade driving epithelial injury, while concurrent upregulation of IL-13, TIMP-1, and TIMP-2 supports epithelial differentiation and matrix stabilization. Collectively, topical secretome therapy rebalances the ocular cytokine milieu toward a regenerative state. In contrast, MSC administration by subconjunctival or lacrimal gland injection, as demonstrated by Shin et al., produced similar cytokine suppression (IL-6, IL-1β, TNF-α, IFN-γ, IL-17A) through combined paracrine and cellular effects, whereas secretome therapy achieves comparable

immunomodulatory benefits via a cell-free and less-invasive approach.[20]

Across all included animal studies, no adverse effects were reported following topical secretome administration. Two studies explicitly evaluated safety outcomes and confirmed the absence of ocular or systemic toxicity, with stable intraocular pressure and normal histopathological findings in both ocular and systemic organs.[14,16] Similarly, Sgrignoli et al. reported that topical administration of mesenchymal stem cells in dogs with keratoconjunctivitis sicca caused no clinical signs of rejection or ocular discomfort, supporting the ocular safety of stem-cell–based therapies in immune-mediated dry eye.[21] In a comparable regenerative approach, Alió et al. observed that PRP was also well tolerated in human dry-eye patients, with only mild transient discomfort and no systemic complications.[19] While both MSC and PRP formulations contain cellular or protein components that may elicit transient irritation, secretome-derived preparations are entirely cell-free, eliminating donor cell variability and minimizing potential immunogenicity. Collectively, these findings indicate that topical secretome therapy demonstrates a favorable and consistent safety profile across preclinical models, in line with other biologic ocular-surface treatments, though clinical validation in humans remains warranted to establish long-term ocular and systemic safety.[7]

The present synthesis of preclinical evidence indicates that the secretome exerts a robust anti-inflammatory effect within the ocular surface microenvironment of experimental DED. Several studies consistently demonstrated suppression of key inflammasome components, notably NLRP3 and ASC.[7] These molecules act as upstream regulators of inflammasome assembly and are central to the activation and release of IL-1β and IL-18, both of which drive the amplification of downstream inflammatory cascades.[5,12] Inhibition at this proximal level effectively disrupts the NF-κB–dependent signaling axis, thereby curbing the production of other pro-inflammatory cytokines such as IL-6, TNF-α, and IL-17A that perpetuate corneal epithelial damage and tear film instability.[9,10] Notably, decreased infiltration of $CD4^+$ T cells, neutrophils, and dendritic cells, signifying that secretome therapy modulates both innate and adaptive arms of ocular immunity. This multifaceted immunoregulation contrasts with conventional anti-inflammatory treatments, which generally target single cytokines or specific immune cells. The coordinated suppression of multiple inflammatory mediators alongside cellular infiltration underscores the potential of the secretome as a systems-level immunomodulator, capable of restoring immune balance rather than merely silencing inflammation.

A second major finding across the included studies is the ability of the secretome to attenuate ocular surface apoptosis. A significant reduction in TUNEL-positive cells, indicating decreased apoptosis within the corneal epithelium and stromal layers.[12,14,16] Mechanistically, this anti-apoptotic effect likely arises from both direct and indirect mechanisms. The reduction in pro-inflammatory cytokines mitigates oxidative stress and immune-mediated cytotoxicity, while the secretome's content of trophic and anti-apoptotic molecules such as TIMP-1, TIMP-2, and IL-13 supports cell survival and extracellular matrix stabilization. This dual action interrupts the self-perpetuating cycle characteristic of DED, wherein chronic inflammation induces apoptosis, and apoptotic debris further fuels inflammation. By dampening this feedback loop, secretome therapy preserves corneal integrity and promotes a more quiescent cellular state. Furthermore, the presence of neuroprotective and anti-oxidative molecules within the secretome (as reported in other models) suggests that the observed benefits may extend beyond epithelial preservation, potentially contributing to the maintenance of sensory nerve homeostasis essential for reflex tearing and ocular surface health.

Beyond the suppression of inflammation and apoptosis, evidence strongly supports a pro-regenerative effect of secretome therapy on the corneal and conjunctival epithelium. Multiple studies demonstrated restoration of epithelial continuity, increased goblet cell density, and enhanced Ki-67 expression following treatment.[8,16] These findings point toward augmented cellular proliferation and mucin synthesis as key determinants of tear film stability and ocular surface lubrication. The upregulation of IL-13 within the secretome milieu is particularly relevant, as this cytokine promotes epithelial differentiation, mucin gene expression, and barrier recovery. Simultaneously, increased TIMP-1 and TIMP-2 levels contribute to extracellular matrix remodeling by modulating matrix metalloproteinase (MMP) activity, thereby preventing tissue degradation and supporting structural integrity. Collectively, these molecular and cellular effects establish a reparative environment that facilitates corneal epithelial regeneration rather than mere suppression of inflammatory damage.

One of the major findings across studies is the considerable heterogeneity of the secretome profile reported in different experimental and clinical contexts. Variability may arise from differences in cell sources, donor characteristics, culture conditions, isolation methods, and analytical platforms.[22] This diversity makes direct comparisons between studies challenging and complicates the establishment of standardized reference profiles.[22] While such heterogeneity reflects the dynamic and adaptive nature of secretory activity, it also raises questions regarding reproducibility and consistency of observed effects, especially when translating preclinical findings into therapeutic applications. In addition to biological variability, several limitations were consistently noted in the available literature. Many studies employed small sample sizes, lacked standardized methodologies, or provided incomplete characterization of the secretome.[22] Moreover, differences in reporting practices and limited follow-up data further restrict the ability to draw robust conclusions about efficacy and safety. These limitations highlight the need for harmonized protocols, larger multicenter studies, and more rigorous methodological standards in order to advance the clinical utility of secretome-based approaches.

Taken together, the convergent evidence from animal studies supports a coherent mechanistic model in which secretome therapy rebalances the ocular surface microenvironment through coordinated modulation of inflammation, apoptosis, and regeneration. Rather than acting via isolated cytokine blockade, the therapeutic benefits appear to emerge from the complex interplay of tropal recovery.[23]

Future investigations into secretome-based therapies should prioritize the development of standardized protocols for both production and administration. At present, studies vary widely in how secretomes are harvested, processed, and delivered, leading to substantial variability in outcomes. Standardizing dosage, culture conditions, purification methods, and storage stability would not only improve comparability between studies but also provide a more reliable framework for determining therapeutic thresholds. Clear consensus on methodological standards would also make it possible to establish dose response curves, assess pharmacokinetics, and define optimal delivery routes for specific disease indications. Such progress is a prerequisite for moving from animal model type experiments toward reproducible, evidence-based applications.

CONCLUSION

Preclinical evidence suggests that topical secretome therapy may be particularly beneficial in non-infectious dry eye disease characterized by ocular surface inflammation, epithelial damage, reduced tear production, and goblet cell loss. Available animal studies indicate its potential to improve tear film stability, reduce inflammation and apoptosis, and promote epithelial regeneration, with generally favorable short-term tolerability. However, its efficacy across all dry eye subtypes remains uncertain and requires further subtype-specific investigation. Further standardization and clinical trials are needed to confirm its efficacy and support translation into clinical practice.

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