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Unlocking the potential of exosomes 'extracellular vesicles': drug delivery advancements and therapeutics in ocular diseases

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Overcoming the ocular barriers, such as the corneal, blood-retinal, and conjunctival membranes, poses a significant challenge in ophthalmic drug delivery and therapy. These barriers serve a natural protective function and limit drug access into the eye. In recent years, interest has increasingly centered on exosomes, a subclass of extracellular vesicles with a diameter of 30 to 150 nm. Encapsulated within a lipid bilayer, exosomes naturally carry a variety of bioactive molecules, including proteins, lipids, and nucleic acids, and play a crucial role in cell–to–cell communication and pathophysiology. Nonetheless, their ability to transfer cargos (proteins, lipids, and nucleic acids) to recipient cells provides an exclusive approach to the delivery of various therapeutic agents, such as small molecules or nucleic acid drugs, to target ocular tissues due to their remarkable biocompatibility, stability, low toxicity, and minimal immunogenicity. This review aims to discuss the research in progress on the advantages of exosome-guided drug delivery and ongoing clinical trials for ocular diseases and therapy. This work aspires to bridge the gap between bench research and clinical application, fostering treatments that remarkably enhance patient outcomes in ocular disorders.

1. Introduction

Worldwide, more than 2.2 billion people suffer from vision impairment, with nearly half of these cases being preventable or treatable.[1] The principal causes include uncorrected refractive errors, cataracts, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy. Uncorrected refractive errors affect all regions, while cataracts are especially prevalent in low- and middle-income countries due to limited access to surgery; in higher-income countries, glaucoma and AMD are more common.[1] In children, congenital cataracts and retinopathy of prematurity are significant concerns.[1] Overall, eye diseases account for approximately 61.4 million disability-adjusted life years (DALYs)—about 4.0% of total DALYs—with East Asia, the Pacific, and South Asia bearing the highest burden.[2] The burden is not evenly distributed; East Asia, the Pacific, and South Asia experience the highest number of DALYs, followed by sub-Saharan Africa and high-income economies.[2] The annual global productivity loss of US$411 billion further underscores the economic impact, far outweighing the estimated US$25 billion required to meet vision-related needs.[1]Vision impairment also adversely affects quality of life, employment, and educational outcomes.[1]

Effective treatment is held back by the eye's unique anatomical and physiological barriers.[3] Static barriers—including the corneal epithelium, blood-aqueous barrier, sclera, retinal pigment epithelium, and capillary endothelia.[4,5] Dynamic ocular barriers consist of tear drainage, conjunctival blood, lymph clearance, and choroidal blood and lymphatic circulations that limit drug absorption and bioavailability.[4] The corneal epithelium, with its tight junctions and negative charge, hampers paracellular drug permeation, while reflex blinking, increased tear secretion, and nasolacrimal drainage reduce the available drug, resulting in typical topical bioavailability of only 1–5%.[3,6,7] Additionally, drug metabolism in ocular tissues and the action of efflux pumps (*e.g.*, P-glycoprotein and multidrug resistance protein) further hinder absorption.[3,7] These challenges are even more pronounced for drugs targeting the posterior segment, where conventional eye drops fail and invasive intravitreal injections—associated with risks such as infection and retinal detachment—are often required.[8] Although various administration routes

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(*e.g.*, topical, intravitreal, intraocular, juxta-scleral, subconjunctival, intracameral, and retrobulbar) are employed to overcome these barriers, traditional methods still suffer from low bioavailability, off-target effects, and toxicity.[9,10]

In recent years, Extracellular Vesicles (EVs), particularly exosomes, have emerged as promising vehicles for drug delivery owing to their intrinsic role in cell-to-cell communication.[11] These nanoscale, lipid bilayer-enclosed structures carry proteins, nucleic acids, lipids, and even organelles, enabling them to influence recipient cells.[12] Although the terms "exosomes" and "microvesicles" are often used interchangeably, they differ in their biogenesis. Exosomes, the smallest subgroup, bud from multivesicular bodies and carry specific cargo reflective of their cellular origin,[13,14] whereas microvesicles are larger, shed directly from the plasma membrane, and typically contain cytoskeletal components that mirror the cell's overall state.[15] In addition, apoptotic bodies and other less-characterized EV subtypes further contribute to the heterogeneity of the EV landscape.[16] The molecular cargo within EVs is selectively compiled, representing the donor cell's physiological state through proteins, DNA, RNA, and metabolites.[17,18] This cargo selection remains an active area of research, shedding light on the mechanisms underlying targeted intercellular communication. Moreover, EVs play critical roles in physiological processes such as immune response, tissue repair, and development, while their dysregulation can contribute to disease states.[19] For instance, tumor-derived EVs may promote tumor growth, metastasis, and immunosuppression; conversely, EVs hold promising therapeutic potential as drug-delivery and immunomodulatory agents.[20] Advancements in EV isolation, characterization, and functional studies continue to expand our understanding, paving the way for applications in diagnostics, prognostics, and personalized therapeutics[21] Nonetheless, challenges remain, including the standardization of isolation techniques, clarification of complex cargo-recipient interactions, and addressing ethical considerations.

Given that, exosomes as naturally occurring membranous structures, are highly attractive as drug carriers due to their unique properties.[22] Firstly, their optimal size, surface charge, and inherent homing effects confer superior targeting ability.[23] Secondly, their biocompatibility and reduced immunogenicity—unlike synthetic carriers—minimize toxicity and potential side effects. Thirdly, EVs can cross biological bar-

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riers, including the blood–brain barrier, thereby facilitating targeted delivery for neurological and other disorders.[24] Additionally, their superior stability in circulation allows for prolonged drug delivery, which may reduce dosing frequency, extend drug half-life, and improve overall efficacy.[25,26] Furthermore, EVs can encapsulate a broad spectrum of therapeutic molecules, including proteins, nucleic acids, and small molecules, allowing for tailored delivery strategies.[27,28] Various loading methods further enhance their potential as drug carriers.[29] In summary, exosomes possess unique properties that make them highly promising nanosized vehicles for drug delivery and therapy related to eye diseases.

In this review, we emphasize the emerging potential of exosomes as drug-delivery platforms for treating ocular conditions. We also discuss engineering strategies that can enhance the targeting capabilities of EVs, allowing them to act like guided missiles that "home in" on diseased ocular tissue. Additionally, we highlighted the exosome-mediated clinical trials focused on ocular diseases that are being registered with the National Clinical Trials database.

2. Biological background and characteristics of EVs

EVs are heterogeneous, membrane-bound particles released by various cell types into the extracellular environment, playing crucial roles in intercellular communication, biomarker identification, and therapeutic applications. The biogenesis of EVs occurs through different pathways, primarily classified into three major categories: exosomes, microvesicles, and apoptotic bodies, each distinguished by their cellular origin and size.[30] Exosomes typically range from 30–150 nm and originate through the inward budding of the endosomal membrane, leading to the creation of intraluminal vesicles (ILVs) within

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Dr Jahangir Ahmed holds a B. Ed. from KCEF Law College (University of Kashmir), a B.Sc. in Zoology, Botany, and Sericulture (University of Jammu), an M.Sc. in Biotechnology (Central University of Rajasthan), and a Ph.D. from B.S. Abdur Rahman Crescent Institute of Science & Technology. His doctoral research, defended in October 2024, developed microfluidizer-based nanoemulsion-infused feed to mitigate Vibrio parahaemolyticus infections in Pacific white shrimp. This interdisciplinary work combined in silico phytochemical docking against Photorhabdus PirA/B and ToxR/TDH toxins, in vitro antimicrobial assays, and in vivo shrimp trials, yielding a patent and ten peer-reviewed articles in journals such as Applied Biochemistry and Biotechnology, BioNanoScience, and Microbial Pathogenesis. He also led an ICMR-funded project on nano-ointment formulations targeting multidrug-resistant Klebsiella pneumoniae and demonstrated silver nanoparticle biosynthesis using Cicer arietinum leaf extract during his master's research. Currently a Scientific Officer at Clinigenome Delhi Ltd, he oversees molecular diagnostics—from DNA extraction and PCR to NGS library preparation and bioinformatics analysis—and mentors undergraduate and graduate students. His expertise in nanobiotechnology, molecular microbiology, and computational analysis drives innovative solutions in aquaculture and clinical genomics.

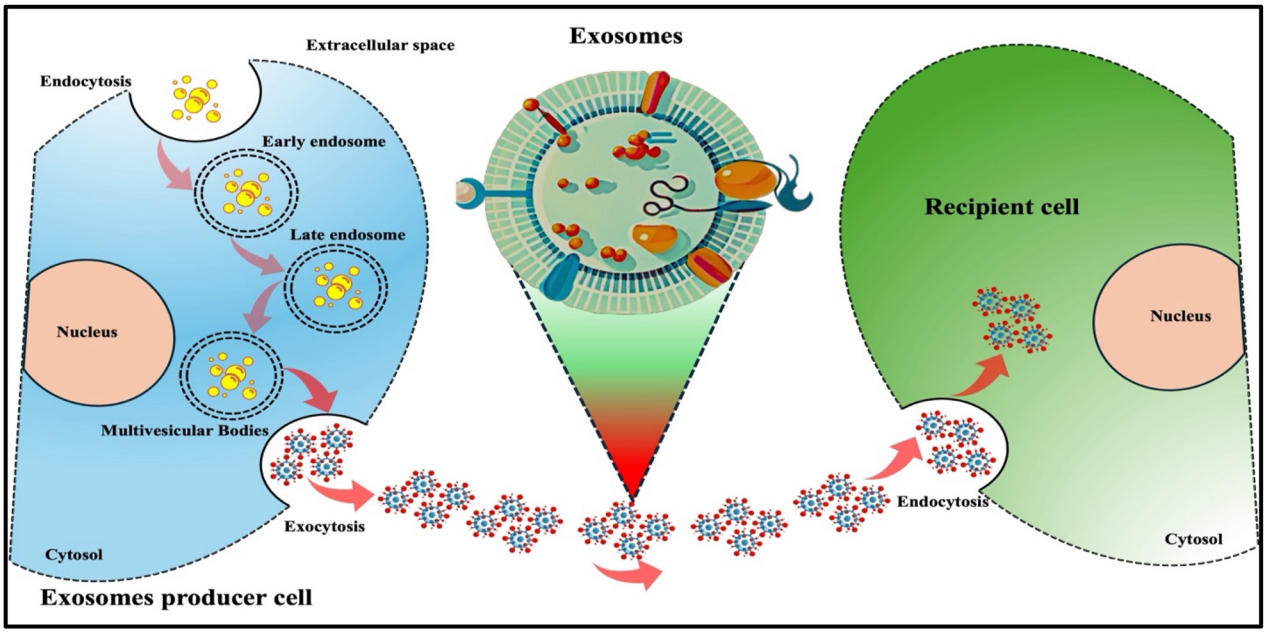

Fig. 1 Illustration of exosome biogenesis and intercellular communication: endocytosis begins with the inward budding of the cell's plasma membrane, forming early endosomes. The early endosomes mature into multivesicular bodies (MVBs), which create intraluminal vesicles (ILVs). These ILVs are precursors to exosomes. MVBs fuse with the plasma membrane, resulting in the release of mature exosomes into the extracellular space through exocytosis. Exosomes' intercellular communications depend on the interactions between ligands and receptors. When exosomes encounter the appropriate recipient cells, they can directly fuse with cell membranes or be endocytosed by recipient cells, releasing their cargo into target cells.

multivesicular bodies (MVBs). The fusion of MVBs with the plasma membrane subsequently releases exosomes into the extracellular space[31] (Fig. 1), while microvesicles (100–1000 nm) are generated *via* exocytosis, where the plasma membrane protrudes and buds off to form larger vesicles.[32] Several proteins, including the Endosomal Sorting Complex Required for Transport (ESCRT) machinery and various small GTPases, are known to be crucial for these processes and are released through direct budding from the plasma membrane.[33] There is growing evidence that tetraspanins, a class of membrane proteins, are involved not only as markers but also in the functional processes of EV biogenesis, including cargo selection and targeting.[34] The secretion mechanisms of EVs are complex and can vary based on cell type and physiological situations. They are influenced by numerous external signals, which can alter the mechanisms driving EV formation and release.[30] The physicochemical properties of EVs, including their size, morphology, surface charge, and molecular composition, play a significant role in determining their biological function and stability. This has important implications for their utility in clinical diagnostics and therapeutics.[33]

Isolation and characterization of EVs are critical steps in understanding their function and potential therapeutic applications. Various methods, such as differential centrifugation, ultrafiltration, and size-exclusion chromatography, are used for isolation, though each method has advantages and limitations regarding yield and purity[35] (Fig. 2). Characterization techniques include nanoparticle tracking analysis (NTA), dynamic light scattering (DLS), and electron microscopy, which collectively provide insights into the size distribution, morphology, and biological content of EVs.[36] Stick to the guidelines set by the International Society for Extracellular Vesicles (ISEV) ensure consistency and reliability in EV research, promoting standardized protocols for characterization.[37] Overall, understanding the biology, characteristics, and functional potential of EVs is vital for harnessing their applications in disease diagnosis and targeted therapy. Ongoing research focuses on clarifying the physiological roles of EVs and developing improved methods for their isolation and characterization, which will facilitate their inclusion into clinical practice.[38]

2.1. Novel insight

Applying single-vesicle multi-omics alongside machine-learning enables the identification of discrete EV subtypes with distinct functions, transforming heterogeneity from a hurdle into an asset for selecting vesicles tailored to specific diagnostic or therapeutic needs.

2.2. Proposed solution

We propose a microfluidic immunoaffinity platform—driven by AI-chosen surface markers and coupled with real-time

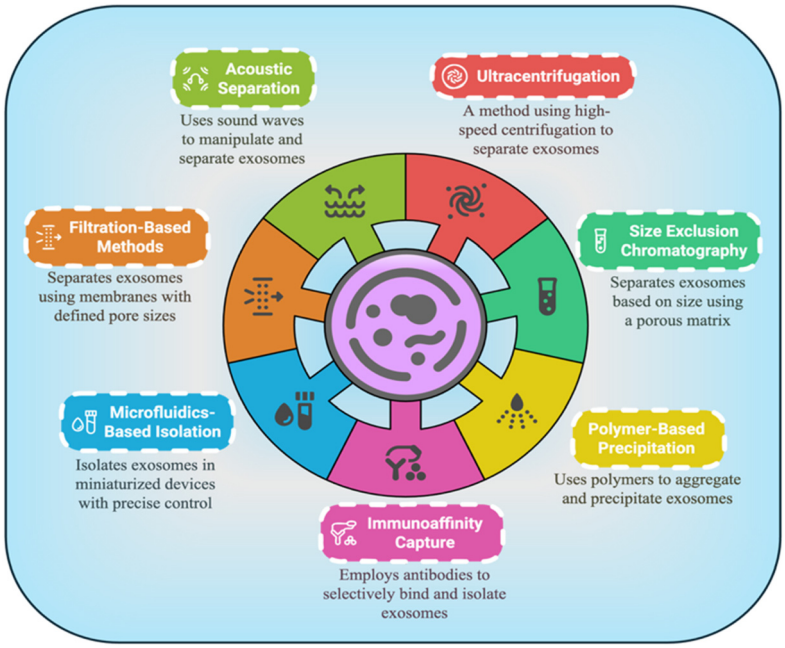

Fig. 2 Schematic overview of extracellular vesicle isolation methods, including differential ultracentrifugation, size-exclusion chromatography, polymer precipitation, immunoaffinity capture, microfluidics, filtration, and acoustic separation.

nanoparticle tracking—to standardize the isolation of high-purity EV subsets optimized for ophthalmic applications.

3. Therapeutic advantages of EVs in ocular diseases

EVs, containing a diverse range of nano-scale carriers derived from cells—particularly exosomes—represent a promising solution for treating ocular illnesses. In the context of ocular drug delivery and therapy, EVs offer several notable advantages.[39] Indeed, exosomes have emerged as a transformative approach over traditional methods. Their inherent attributes, such as exceptional biocompatibility and low immunogenicity, not only enhance safety profiles but also minimize adverse immune responses. Furthermore, their targeted delivery capabilities ensure that therapeutic agents are efficiently directed to specific ocular cells. In addition, exosomes are proficient at encapsulating a wide variety of therapeutic molecules, and their ability to cross the blood-ocular barrier further underscores their superiority in enhancing drug delivery to the ocular tissues (Fig. 3).

EVs, including exosomes, overcome anatomical and physiological barriers that impede conventional ocular therapies.[40,41] These nanoscale vesicles, naturally secreted by most cells, encapsulate proteins, lipids and nucleic acids to facilitate intercellular communication and modulate physiological and pathological processes;[40,42] moreover, they combine low immunogenicity and superior biocompatibility—vital for minimizing adverse immune responses in the sensitive ocular environment[40,43]—with the capacity to traverse the blood-retinal barrier, thereby enhancing delivery efficiency to retinal ganglion cells in glaucoma.[44,45] Mesenchymal stem cell-derived EVs further exhibit anti-inflammatory, anti-apoptotic and neuroprotective activities, promoting nerve regeneration and ameliorating conditions such as optic nerve injury, glaucoma, and diabetic retinopathy.[45,46] Additionally, EVs can be engineered to carry neurotrophic factors, cytokines, and diverse therapeutics—hydrophilic, hydrophobic and macromolecular—enabling co-delivery strategies that improve drug stability, prolong retention at the target site, and reduce off-target effects, thus maximizing efficacy while mitigating systemic side effects.[41,46–48] For instance, EV-mediated delivery of nicotinamide has demonstrated neuroprotection in retinal ganglion cells[49] and platelet-derived EVs have successfully delivered anti-angiogenic agents to inhibit corneal neovascularization.[50] However, clinical translation remains constrained by the need to standardize production, isolation and characterization protocols and to ensure adequate yield, purity and consistency of EV preparations;[42,46,48,51] nevertheless, ongoing preclinical studies and early clinical trials continue to underscore the transformative potential of EVs for targeted, effective and safe ocular drug delivery.[51]

In summary, exosomes offer the combined low immunogenicity and superior biocompatibility, traverse ocular barriers to deliver anti-inflammatory, anti-apoptotic, and neuroprotective cargos, and enhance drug stability, retention, and targeting. Preclinical efficacy in retinal ganglion cell neuroprotection and corneal neovascularization inhibition underscores their therapeutic promise, while efforts to standardize production and characterization are driving clinical translation.

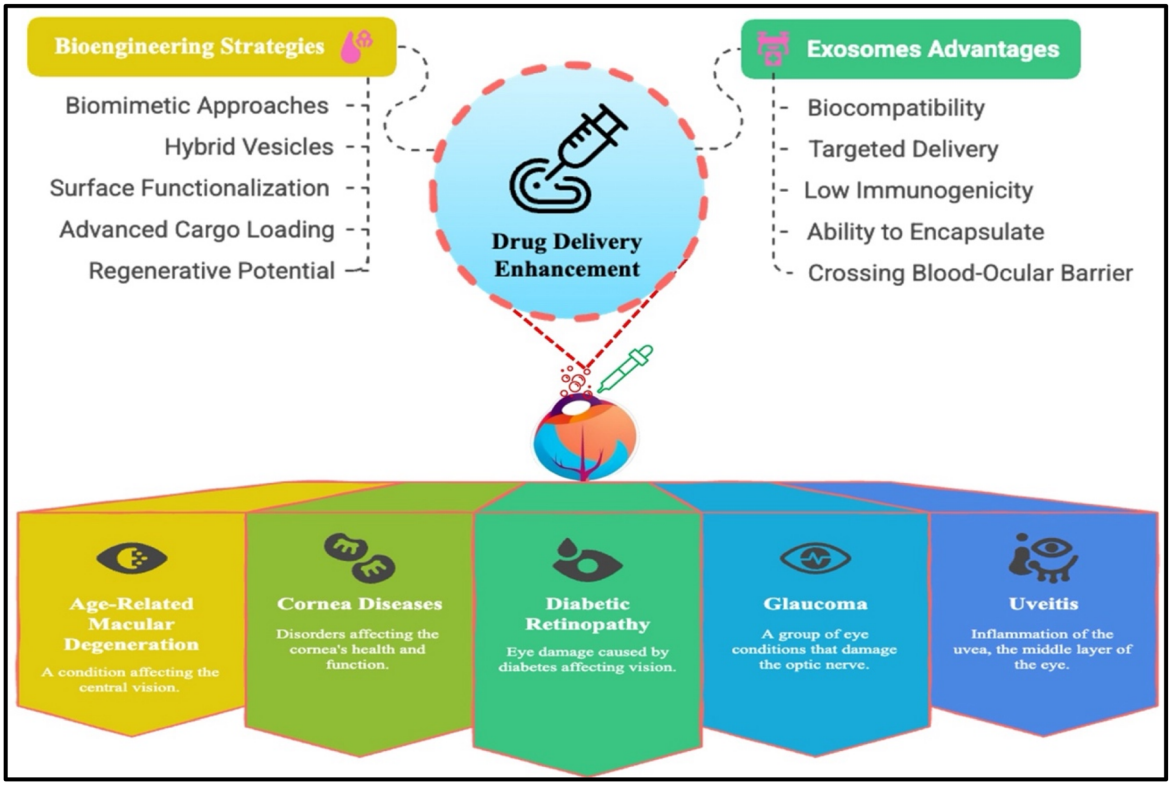

Fig. 3 Illustration of exosomes for advantages in drug delivery and bioengineering strategies in ocular diseases: exosomes, considered subsets of "Extracellular Vesicle (EV)" offer various benefits in drug delivery and bioengineering approaches to improve the efficacy of exosome-targeted delivery to affected ocular diseases.

3.1 Biocompatibility and low immunogenicity

One of the foremost advantages of using exosomes for drug delivery is their intrinsic biocompatibility and low immunogenicity.[40] As natural nanoparticles derived from various cells, exosomes are readily recognized by the body, thereby minimizing adverse immune responses. Research has shown that exosomes exhibit substantially lower immunogenicity compared to liposomes and virus-based vectors, which can provoke significant inflammatory responses.[51,52] Consequently, the low immunogenicity of exosomes permits repeated administrations without triggering anti-drug antibodies—a common drawback of synthetic delivery systems—thus facilitating sustained therapeutic effects.[52–55]

3.1.1. Novel insight. Exploiting donor-cell glycoengineering to display "stealth" sialylated glycans on exosome surfaces can further mask residual allo- or xeno-antigens, pushing immunogenicity below that of even autologous cell products.

3.1.2. Proposed solution. Use CRISPR/Cas9 to upregulate key sialyltransferases in mesenchymal stem cells, harvest the resulting exosomes, and compare their cytokine-release profiles against unmodified vesicles in human peripheral blood mononuclear cell assays.

3.2 Targeted delivery to specific ocular cells

Exosomes exhibit a notable capacity for selective targeting of cells and tissues, advantageous for ocular drug administration. Engineering their surface proteins can optimize targeting to ocular-specific cells, enhancing therapeutic effectiveness while minimizing systemic adverse effects.[56–58] In addition, their nanoscale size enhances their capacity to traverse biological barriers, allowing them to navigate the complex ocular architecture efficiently.[57,58] Studies have demonstrated that exosomes can successfully deliver therapeutics directly to targets within ocular tissues, including the retina and cornea, yielding superior outcomes compared to conventional systems that often lack tissue specificity.[56,59,60]

Corneal epithelial cell-derived exosomes traverse the disrupted basement membrane to fuse with keratocytes, induce myofibroblast transformation, and stimulate endothelial proliferation and aortic ring sprouting, thereby promoting corneal wound healing and neovascularization.[61] Moreover, hybrid exosome vehicles (HEVs) generated by fusing anti-NFKBIZ siRNA-loaded liposomes with corneal epithelium-derived exosomes leverage exosomal homing to deliver siRNA specifically to the cornea in dry eye disease models, significantly reducing pro-inflammatory cytokines and reshaping the ocular inflammatory microenvironment.[62] However, the posterior segment presents complex physical and biochemical barriers;[63,64] in this context, *exo*-AAV2 demonstrates enhanced penetration into the inner nuclear and outer plexiform layers—and to a lesser extent the outer nuclear layer—thereby enabling transduction of ganglion, bipolar, Müller cells and photoreceptors.[64,65]

Additionally, mesenchymal stem cell-derived exosomes transport miRNAs to inner retinal layers to exert neuroprotective and neuritogenic effects on retinal ganglion cells in traumatic optic neuropathy and glaucoma models,[66] while exosomal delivery of the neuroprotective peptide PACAP, enhances tissue penetration and half-life for ophthalmic applications.[67] Furthermore, arginine-rich, PEG2000 lipid-anchored cationic-motif-modified exosomes improve transport and retention within the vitreous humor and retina.[65] Finally, exosome-mediated delivery of miR-205 suppresses pathological retinal and choroidal neovascularization by inhibiting endothelial proliferation, migration and tube formation without cytotoxicity.[68] Overall, exosomes achieve targeted delivery to corneal epithelial cells, stromal keratocytes, vascular endothelium, retinal ganglion cells, bipolar cells, Müller cells, and photoreceptors—underscoring their versatility as engineered carriers for advanced ophthalmic therapies.[62,64,65,69]

3.2.1. Novel insight. Combining phage-display-derived peptide ligands with bispecific aptamers on the same exosome surface can create a dual-lock mechanism that selectively homes in on two mutually exclusive ocular cell markers (*e.g.*, RPE and Müller cell receptors).

3.2.2. Proposed solution. Develop a modular click-chemistry toolbox for orthogonal conjugation of peptide and aptamer moieties onto CD63 scaffolds, then quantify uptake specificity and off-target binding in 3D retinal organoid co-culture models.

3.3 Ability to encapsulate various therapeutic molecules

Another significant advantage is the ability of exosomes to encapsulate diverse therapeutic molecules. Exosomes can carry a broad spectrum of agents, including small molecules, proteins, and nucleotides such as miRNAs and siRNAs.[55,70,71] This versatility permits the integration of multiple therapies within a single delivery system. For instance, exosomes have been utilized to co-deliver anti-inflammatory drugs and neuroprotective agents in models of diabetic retinopathy, thereby enhancing treatment outcomes through synergistic effects.[72,73] Furthermore, the lipid bilayer of exosomes provides a protective environment that preserves the integrity of these therapeutic molecules, enhancing their stability and bioavailability compared to free drugs.[70,74]

Studies have demonstrated successful encapsulation and intracellular delivery of microRNA-494 (miR-494) into exosomes using nanofluidic platforms.[75] moreover, their hydrophilic core makes them well suited for transporting water-soluble synthetic drugs.[69] In the context of neovascularization, exosomes loaded with miR-205 inhibit endothelial cell functions critical to pathological vessel formation, thus offering a novel strategy for treating vision-threatening vascular diseases.[68] For dry eye disease, exosomes conjugated with ascorbic acid have been formulated into therapeutic nano-eyedrops, which significantly improve corneal epithelial recovery and anti-inflammatory capacity.[76] Similarly, a hybrid exosome vehicle (HEV)—created by fusing liposomes encapsulating anti-NFKBIZ siRNAs with corneal epithelial cell-derived exosomes—effectively delivers siRNA payloads to the cornea, reducing pro-inflammatory cytokine secretion and ameliorating dry eye in a mouse model.[77] Additionally, cationic-motif-modified exosomes facilitate topical mRNA delivery to retinal photoreceptors, exhibiting enhanced diffusion and uptake in retinal explants.[78] In myotonic dystrophy type 1 (DM1) and Fuchs endothelial corneal dystrophy (FECD), a small molecule that binds toxic r(CUG) repeat expansions reverses molecular defects.[79] In FECD specifically, this molecule further promotes excision and degradation of a retained intron *via* the exosome complex exonuclease.[79] Furthermore, exosomal delivery of miR-29b activates autophagy to reduce fibrosis and inflammation in corneal injury models;[80] and retinal pigment epithelial cell-derived exosomes rescue photoreceptors during retinal degeneration, underscoring their therapeutic potential in degenerative retinal diseases.[81]

3.3.1. Novel insight. Coupling endogenous ESCRT-binding domains fused to therapeutic cargo (small RNAs or proteins) can drive selective partitioning into intraluminal vesicles, enabling co-loading of multiple payloads without exogenous perturbation of membrane integrity.

3.3.2. Proposed solution. Engineer fusion constructs in donor cells that link cargo to Alix- or TSG101-interacting motifs, then isolate exosomes *via* size-exclusion chromatography and measure dual-cargo loading efficiency and bioactivity *in vitro*.

3.4 Potential to cross the blood-ocular barrier

In addition, the potential of exosomes to cross the blood-ocular barrier (BOB) is a critical asset. The BOB poses a significant challenge to conventional ocular therapeutics; however, exosomes—owing to their small size and lipid bilayer composition—can more readily traverse this barrier.[82–84] This enhanced penetration facilitates the delivery of therapeutic agents to intraocular targets, thereby improving the bioavailability of treatments in the ocular environment.[83,85]

3.4.1. Novel insight. Surface display of short receptor-mediated transcytosis peptides such as angiopep-2 or TAT derivatives on exosomal tetraspanins can actively engage endothelial transporters to shuttle vesicles across the blood-ocular barrier.

3.4.2. Proposed solution. Generate stable cell lines expressing CD9-angiopep-2 fusion proteins, collect their exosomes, and validate barrier penetration using a microfluidic blood-retina barrier chip, followed by quantification of delivered reporter cargo in the "retinal" compartment.

Furthermore, the integration of nanoparticle drug delivery systems, including EVs, has markedly enhanced the effectiveness of advanced therapeutic modalities. For example, the incorporation of photosensitizers into EV-based platforms has improved the precision of photodynamic therapy (PDT) by enabling targeted delivery to specific lesion sites.[86] Similarly, exosome-associated adeno-associated viral (AAV2) vectors have been shown to facilitate robust gene delivery into the murine retina through intravitreal injection. These exosome-associated vectors exhibit superior retinal penetration—targeting the

inner nuclear and outer plexiform layers—and effectively transduce various cell types such as ganglion, bipolar, Muller, and photoreceptor cells.[87]

Moreover, exosome-associated AAV vectors have enhanced the delivery of the retinoschisin 1 (RS1) gene in mouse retina models, as evidenced by the co-expression of a green reporter gene, suggesting potential applications in gene therapy for retinal diseases.[88] In parallel, researchers have developed innovative delivery systems that leverage the unique properties of exosomes. Thermosensitive hydrogels loaded with mesenchymal stem cell (MSC-Exo)-derived exosomes have been designed to promote corneal regeneration by enhancing epithelial cell proliferation, migration, and extracellular matrix synthesis.[89] Additionally, exosome-functionalized intraocular lenses (IOLs) loaded with the anti-proliferative drug doxorubicin (Dox) have demonstrated improved cellular uptake by lens epithelial cells, resulting in a pronounced therapeutic effect against posterior capsular opacification (PCO) while ensuring excellent intraocular biocompatibility.[90]

Moreover, exosomes play a crucial role in retinal diseases by enabling cell-to-cell communication and mediating the delivery of bioactive molecules with anti-inflammatory, neuroprotective, and anti-apoptotic effects.[91] Their capacity to traverse the blood-retinal barrier—together with their physicochemical stability and excellent biocompatibility—positions them as promising candidates for regenerative medicine, facilitating a cell-free approach to tissue repair and precise therapeutic interventions.[39] For instance, studies have demonstrated that hyperglycemia-induced inflammation in diabetic retinal models can be mitigated by miR-126 derived from MSC exosomes, which suppresses the HMGB1 signaling pathway in human retinal endothelial cells (HRECs).[92] Although EVs have been widely investigated for drug delivery in oncology, their application in ocular pharmacology remains relatively underexplored. Therapeutic loading into EVs can be achieved through active techniques—entailing transient disruption of the EV membrane—or passive diffusion methods. Prior research has successfully loaded chemotherapeutic agents such as curcumin and paclitaxel into EVs from various cell sources, thereby enhancing their bioactivity and cytotoxicity. Nonetheless, further studies are required to explore and validate the stability and efficacy of drug-loaded EVs in ocular settings.[93]

Pathological angiogenesis is a distinguishing feature of various vision-threatening ocular ailments. Within this framework, Dong and colleagues, established a treatment approach by utilizing exosomes (EXOs) loaded with the anti-angiogenic peptide KV11. Their findings revealed that administering KV11 *via* EXOs was more effective than using KV11 alone, as it successfully prevented the formation and leakage of new blood vessels in mouse retinal models. This exosome-based therapy shows considerable promise as a less invasive alternative to traditional intravitreal injections for the treatment of proliferative retinopathy.[94] Furthermore, intravitreal delivery of exosomes derived from regulatory T cells conjugated with an anti-VEGF antibody has effectively suppressed ocular neovascularization in experimental choroidal neovascularization models in both mice and non-human primates. These modified exosomes specifically accumulate at sites of neovascularization, suggesting a unique ability to target affected regions and potentially support combined therapies involving both therapeutic antibodies and anti-inflammatory agents.[95]

In parallel, several other studies have underscored the potential of EVs in addressing a range of eye diseases, including dry eye disease and inflammatory ocular disorders. For instance, EV-based strategies have shown therapeutic benefits by inducing apoptosis in human donor corneal endothelial cells, while the identification of thirteen specific miRNAs in EV samples has provided further insight into the molecular mechanisms underlying corneal endothelial dysfunction.[96] Additionally, ocular fluid-derived EVs have been associated with both ocular health and disease, offering a promising platform for monitoring disease phenotypes and evaluating therapeutic outcomes in eye-related disorders.[97] Likewise, MSC-derived EV loaded with anti-VEGF agents have been shown to reduce the necessity for frequent intravitreal injections in diabetic retinopathy treatment, with therapeutic effects lasting beyond two months.[98] Complementarily, EVs released by retinal organoids have been extensively characterized and display promising potential for both diagnostic and therapeutic applications in ocular diseases.[99] The intravitreal administration of MSC-EVs not only offers a convenient delivery route but also mitigates the risks associated with direct MSC transplantation.[100] Beyond ocular applications, exosomes derived from MSC have shown notable immunomodulatory effects in managing treatment-resistant graft-*versus*-host disease (GvHD). Preclinical models of chronic GvHD revealed that these exosomes can extend survival, alleviate clinical and pathological scores, reduce fibrosis, suppress pathogenic T cells, and enhance regulatory T cell (Treg) phenotypes, partly through the action of miR-223, which reduces donor T cell migration and alleviates acute GvHD symptoms, thereby improving overall survival.[101–104] Advances in engineering EVs further broaden their applicability. Engineered EVs can be tailored to incorporate proteins, small molecules, and nucleic acids by methods such as fusing target proteins or miRNAs with tetraspanin, CD63, or by using poly A-binding proteins to selectively load mRNAs. Such strategies enable the production of consistent EV populations with targeted cargoes for specific cell types. Although the delivery of EVs is feasible in various tissues, the blood-retinal barrier complicates retinal drug delivery. Notably, MSC-derived exosomes have demonstrated the capacity to cross the inner limiting membrane, thereby transporting nucleic acid cargoes to multiple retinal layers. By treating parent cells *in vitro* with cytokines, growth factors, or small molecules, it is possible to stimulate the release of EVs enriched with desired therapeutic cargoes.[105]

Not only that, Zhou *et al.* demonstrated that administering MSC-Exo eye drops loaded with miR-204 ameliorated dry eye disease associated with GVHD. The treatment induced a shift in macrophage phenotype from the pro-inflammatory M1 to the anti-inflammatory M2 state, underscoring the therapeutic potential of miR-204-laden exosomes for GVHD-related dry eye

disease.[106] In a related approach, curcumin—a compound effective against oxidative stress, inflammation, and angiogenesis in exudative AMD through modulation of the Wnt/β-catenin signaling pathway—shows enhanced stability, solubility, and bioavailability when encapsulated in exosomes. Likewise, exosomal curcumin not only achieves higher organ concentrations but also exhibits superior antiproliferative and anti-inflammatory effects compared to its free form.[107–109] The blood-eye barrier, like the BBB, poses challenges for drug delivery. Exosomes offer potential as drug carriers due to their tissue-targeting capability, biocompatibility, and permeable membranes, making them promising for innovative topical therapies to treat posterior eye diseases.

In summary, the intrinsic advantages of exosomes—such as their biocompatibility, low immunogenicity, precise targeting capabilities, versatile encapsulation of therapeutic molecules, and ability to traverse both the blood-ocular and blood-retinal barriers—establish them as superior candidates for ocular drug delivery (Fig. 3). Furthermore, by integrating EV-based platforms with advanced therapeutic approaches, exosomes effectively overcome many limitations of conventional methods and significantly enhance treatment efficacy for retinal and other ocular diseases. Moreover, their capacity for repeated administration with minimal adverse effects, combined with the precision in targeting affected ocular cells, highlights their potential as less invasive and highly effective treatment modalities. Ultimately, these findings underscore the need for continued research focused on optimizing, standardizing, and clinically translating exosome-based drug delivery, thereby advancing the field of ocular therapeutics.

4. Engineering strategies for enhanced drug delivery

Exosomes offer distinct advantages as drug delivery systems, including natural cargo transport, targeted delivery, and compatibility with nanoparticle incorporation, which enable precise personalized therapies and imaging capabilities. In ocular drug delivery, exosomes represent a shift toward more biocompatible and efficient strategies.[110] Advances in methods of engineering for exosomes—pre-loading in exosome donor cells and post-loading isolated exosomes through diverse cargo loading, either actively or passively, and surface modifications approaches—have significantly enhanced the efficacy and specificity of ocular treatments (Fig. 4).

4.1 Advanced cargo loading strategies

One primary method for enhancing exosomal drug delivery is the efficient loading of therapeutic cargo—such as siRNAs,

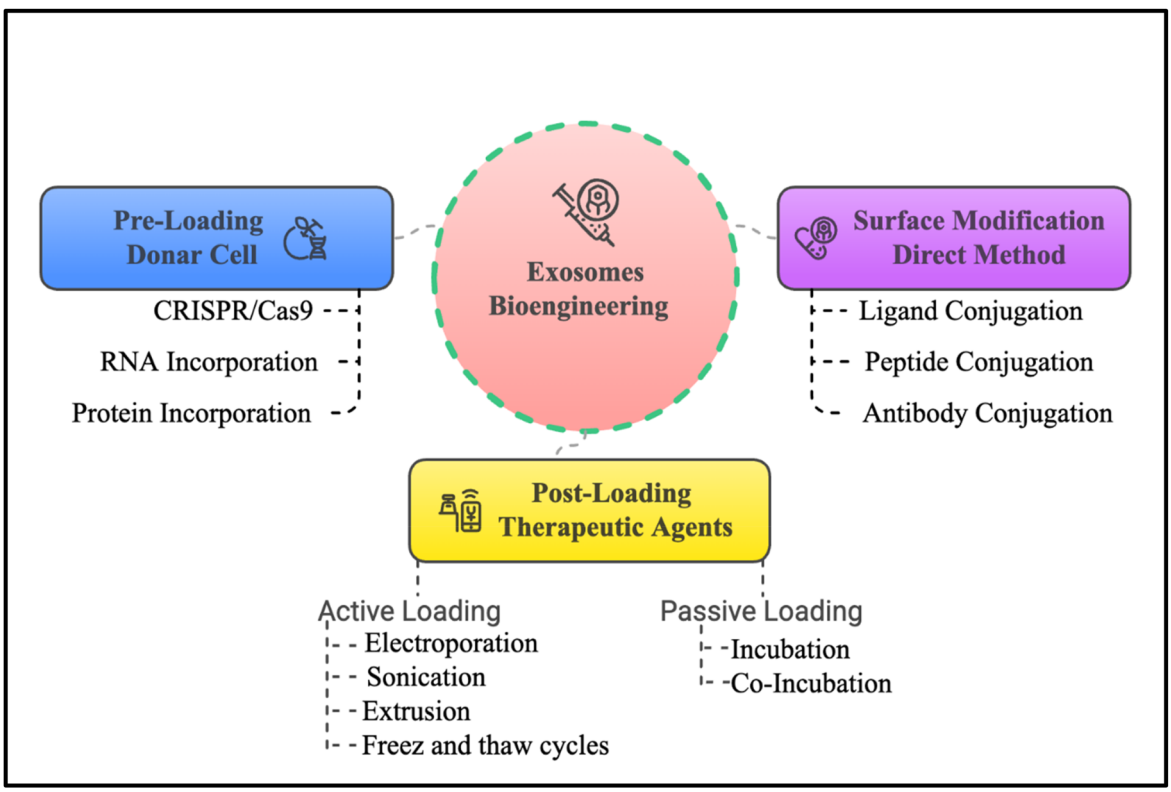

Fig. 4 Schematic representation of exosomes modification methods to enhance drug delivery: in pre-loading: genetically modify the donor cells so that, during exosome biogenesis, the desired cargo is naturally incorporated into the exosomes. Post-loading: modify exosomes after they have been isolated by loading them with therapeutic agents (drugs, siRNAs) using techniques (active loading and passive loading). Surface modifications: apply chemical modifications to attach specific ligands or antibodies to the exosomes surface for targeted delivery.

proteins, or small molecules—into exosomes. Although traditional approaches face challenges, including limited loading capacity and inefficient encapsulation, recent techniques such as electroporation and lipid-based transfection have significantly improved cargo delivery efficiency.[111] Specifically, active loading methods like electroporation and sonication transiently enhance membrane permeability, resulting in higher loading efficiencies than passive approaches.[112] In contrast, passive loading occurs naturally during exosome biogenesis when therapeutic agents are introduced to producer cells, ensuring their entrapment within the secreted EVs.

Moreover, EVs have garnered significant interest as drug delivery platforms due to their unique intrinsic properties; however, efficiently loading them with cargo remains a major challenge.[113] Current approaches are broadly classified into two categories. Pre-loading methods manipulate parental cells —either by co-incubating them with the desired cargo or by transfecting them with cargo-encoding DNA—to ensure that secreted EVs contain the therapeutic agents.[114] In contrast, post-loading methods directly incorporate cargo into isolated EVs by using techniques such as (passively) incubation, (actively) electroporation, sonication, freeze–thaw cycles, transfection, extrusion, the chimeric exosome method, and endogenous loading[70,115] (Fig. 4). Han *et al.* (2021) and Weng *et al.* (2021) present comprehensive overviews of these techniques for transporting siRNA, miRNA, mRNA, CRISPR/Cas9 components, proteins, and various medications into EVs, while also discussing recent progress in engineered EVs for drug delivery.[29,116] The selection between pre-loading and post-loading depends on factors such as cargo type, targeting specificity, and overall loading efficiency. Furthermore, innovative approaches such as nanofluidic channels use transient nanopores on the EV membrane to load exogenous cargo efficiently.[117] Notably, electroporation has exhibited higher cargo incorporation efficiency than passive loading, while preserving EV surface protein integrity.[118] In addition, the Esterase-responsive Active Loading (EAL) platform has shown a significant increase in drug loading and encapsulation efficacy relative to passive techniques.[119] Owing to the distinctive bioactive components within EVs, nano-drug formulations based on these vesicles may display biodistributions that differ from conventional free drugs or liposomal formulations. Nevertheless, a challenge remains in identifying the specific bioactive component—whether lipids, miRNA, proteins, or glycans—responsible for targeting recipient cells and determining therapeutic efficacy.[120] Consequently, the biomanufacturing processes for EVs must be adapted beyond established protocols for biologics, liposomes, and cell-based therapies. This adaptation necessitates additional quality control measures, including assessments of EV dimensions, surface charge, protein markers, drug loading efficiency, and the use of chromatography techniques to purify EVs from impurities.

Moreover, incorporating nanoparticles into exosomes can further augment cargo capacity and control drug release kinetics, seamlessly combining the benefits of both exosome-mediated and nanoparticle-based delivery systems. In addition, disease-specific cargo loading is emerging as a frontier, wherein exosomes derived from particular cell types or disease models serve as vehicles for diagnostic biomarkers and targeted therapeutics, including combination therapies for diseases such as age-related macular degeneration and diabetic retinopathy.[40,121] Collectively, these advanced cargo loading strategies and quality control adjustments are critical for realizing the full potential of exosome-based drug delivery in clinical applications.

4.1.1. Novel insight. Leveraging exosomes' own sorting signals together with gentle acoustic forces can boost cargo uptake without harming vesicle integrity.

4.1.2. Proposed solution. Tag therapeutic RNAs or proteins with ESCRT-binding peptides in donor cells, then use a microfluidic acoustic loader to encapsulate and verify high cargo levels.

4.2 Surface functionalization

Surface functionalization of exosomes is pivotal for enhancing their targeting capabilities and therapeutic potential in ocular drug delivery. Diverse strategies—such as genetic modification of parental cells and post-isolation chemical modifications—have been employed to engineer exosomal surfaces to express specific ligands that bind to receptors on target ocular cells[55,122,123] (Fig. 3). This modification not only improves drug delivery specificity but also reduces off-target effects and systemic toxicity, rendering exosomes a safer alternative to synthetic nanoparticles.[40] Additionally, various surface modification techniques, including the chemical conjugation of ligands, antibodies, or peptides, further promote receptor-specific binding on ocular cells.[112] Polymer coating, particularly with polyethylene glycol (PEG), is another valuable approach used to enhance the stability and circulation time of exosomes in biological systems.[124] Moreover, similar surface functionalization applied to lipid nanoparticles—owing to their structural resemblance to exosomes—has demonstrated significant improvements in penetration and retention of ocular small molecule therapeutics.[125] These modifications also enhance the mucoadhesive properties of exosomes, thereby increasing precorneal residence time and improving transmembrane permeation across the ocular surface. Finally, advanced surface engineering enables the creation of stimuli-responsive exosomes that release their cargo in response to specific environmental cues, further optimizing targeted drug delivery to ocular tissues.[126]

4.2.1. Novel insight. Using enzyme-cleavable linkers to mask targeting ligands means exosomes only "switch on" in diseased ocular tissues.

4.2.2. Proposed solution. Fuse a targeting peptide to CD63 *via* a protease-sensitive linker in donor cells, then confirm selective ligand exposure and uptake in protease-treated ocular cultures.

4.3 Hybrid vesicles and biomimetic approaches

Hybrid exosomes that combine the unique properties of different vesicles—such as lipid nanoparticles and exosomal

membranes—offer a promising strategy to overcome existing limitations in drug delivery.[127] By leveraging the intrinsic biocompatibility and targeting abilities of exosomes, these hybrid vesicles can be engineered to carry larger payloads while preserving the physiological functionality of EVs.[128] Furthermore, biomimetic approaches that coat exosomes with specific proteins or antibodies can facilitate targeted interactions with ocular cells, thereby enhancing therapeutic efficacy by ensuring that drugs reach their intended site of action.[127,129] In addition, one notable biomimetic strategy is the use of stem cell-derived exosomes. Owing to their inherent regenerative and immunomodulatory properties, these exosomes have beneficial effects on damaged ocular tissues, particularly in treating dry eye syndrome and ocular surface injuries.[130] Moreover, engineering exosomes to target specific cellular components—such as mitochondria in brain cells, an approach that could be adapted for ocular cells—further broadens their potential for precise intracellular delivery.[131]

4.3.1. Novel insight. Coating exosome membranes with temperature-responsive nanogels creates carriers that release drugs on demand.

4.3.2. Proposed solution. Gently fuse exosomes with polymeric nanogels, characterize their size and heat-triggered release, and test delivery in an *ex vivo* cornea model.

4.4 Regenerative and therapeutic potential

Stem cell-derived exosomes, particularly those from mesenchymal stem cells (MSCs) and limbal epithelial cells (LECs), have emerged as versatile platforms for ocular regenerative medicine. MSC-derived exosomes exhibit neuroprotective, anti-inflammatory, anti-apoptotic and tissue-repairing functions, making them effective against corneal injuries, glaucoma, retinal diseases, and age-related macular degeneration.[111,132–136] Their therapeutic efficacy stems from direct delivery of proteins, microRNAs, and cytokines to target tissues.[137,138] Notably, they traverse ocular barriers to promote survival and neuritogenesis of injured retinal ganglion cells while attenuating inflammation in autoimmune uveitis.[139] Moreover, exosomes engineered with anti-tumor necrosis factor-α antibodies restore immune homeostasis and enhance corneal regeneration,[140] whereas delivery of anti-angiogenic peptides suppresses pathological neovascularization.[141] Their low immunogenicity, stability and cell-specific targeting further support applications in ocular surface and lacrimal gland repair, such as in dry eye disease.[142]

Human LEC-derived exosomes critically regulate limbal stromal cells (LSCs) in both healthy and diabetic corneas. In non-diabetic conditions, they promote LSC proliferation, accelerate wound closure and modulate stem cell marker expression—effects absent in diabetic LEC-Exos, implicating cargo variations in diabetic dysfunction.[143] Notably, miRNA constituents govern gene expression in pathways linked to diabetes mellitus.[144,145] while in diabetic corneas these exosomal miRNAs delay epithelial wound healing and exacerbate keratopathy.[146] Furthermore, tear film-derived exosomes from diabetic patients exhibit differential miRNA profiles affecting AMPK and ErbB signaling, which are essential for corneal homeostasis.[147] Beyond the cornea, exosomal miRNAs modulate systemic diabetic pathophysiology by influencing insulin resistance and organ function,[145,148] and during corneal repair they facilitate epithelial-stromal cross-talk vital for tissue regeneration.[149] Consequently, the distinct miRNA signatures in diabetic *versus* normal exosomes underscore their potential as diagnostic biomarkers and therapeutic targets for diabetic complications.[148,150]

Despite these advances, clinical translation remains limited by the lack of consensus on scalable, GMP-compliant isolation and purification methods, incomplete understanding of *in vivo* biodistribution and long-term safety, and regulatory uncertainties regarding potency assays and quality control. Addressing these manufacturing, characterization and regulatory challenges—alongside methodological innovations in optimized cargo loading, targeted surface functionalization, hybrid vesicle formation and biomimetic design—will be essential to advance exosome-based ophthalmic therapies from bench to bedside.

4.4.1. Novel insight. Embedding exosome-loaded nanofiber scaffolds on eye wounds can provide prolonged, localized release and structural support for pro-regenerative signaling.

4.4.2. Proposed solution. Co-spin mesenchymal stem cell exosomes into silk fibroin fibers, then assess sustained release and accelerated corneal healing in an animal abrasion model.

5. Engineered exosomes/EVs

Moreover, recent advances in exosome engineering have enhanced their stability, targeting ability, and overall therapeutic efficiency, rendering them versatile tools for mitigating inflammatory situations.[151] Importantly, engineered exosomes offer a novel approach to targeted disease therapy with low toxicity, high engineerability, and the promise of cell-free treatments.[56,152] Engineered exosomes have also demonstrated efficacy in treating neurodegenerative diseases and brain cancer by exhibiting precise targeting and efficient drug delivery.[153] Consequently, understanding exosome biogenesis and refining advanced engineering techniques are critical for developing effective clinical strategies.[154] Contemporary strategies that integrate low immunogenicity, nanoparticle technology, and targeted delivery systems have extended exosome half-life and enabled targeted enrichment—features essential for biomedical research and clinical translation.[155] In parallel, researchers have fused EVs with liposomes using polyethylene glycol (PEG) to incorporate external lipophilic or hydrophilic substances without compromising vesicle integrity, thereby producing hybrid EVs with superior cellular delivery of chemotherapeutic compounds compared to free drugs or standard drug-loaded liposomes.[156] For example, Kooijmans *et al.* (2016) and Dang *et al.* (2020) have emphasized that PEGylated and targeted EVs offer improved cell specificity and prolonged circulation time.[157,158] Findings were corroborated by Photos *et al.* (2003), who observed delayed clearance of PEG-modified

lipid vesicles.[159] Finally, specialized platforms such as the EXOtic device have advanced exosome research by enhancing production yield and packaging specific mRNA molecules. This innovation enables robust transport of mRNA cargo into the cytosol of target cells, as demonstrated by engineered producer cells that consistently deliver mRNA to the brain in live mice.[160] The therapeutic potency of exosomes is largely credited to their cargo—particularly miRNAs—which can be modulated to display specific surface markers (*e.g.*, peptides) for targeted delivery within ocular structures.[161] This strategy shows significant potential for refining both the diagnosis and treatment of corneal diseases, paving the way for more effective and personalized therapies.[162] Moreover, exosomes can encapsulate synthetic therapeutic medications, rendering them suitable carriers for water–soluble drugs. In addition, modifications to their surface not only facilitate *in vivo* visualization and monitoring but also enable the concurrent loading of hydrophobic agents to enhance efficacy and hydrophilic agents, such as RNA, to improve cellular uptake.[163] To further improve cargo loading, researchers have introduced a reversible drug-inducible system that triggers cargo interaction with CD63 alongside the overexpression of syncytin-1.[164] Similarly, engineering fusion proteins such as hCD9.hAGO2 have increased the incorporation of miRNA or shRNA into EVs, thereby enhancing cargo transfer efficiency.[165] Furthermore, genetic modification of membrane protein frameworks—whether *via* endogenous tetraspanins (CD9, CD63, and CD81) or by incorporating exogenous vesicular stomatitis virus glycoprotein (VSVG)—has boosted EV targeting and facilitated therapeutic agent encapsulation, as evidenced by the increased cellular uptake of VSVG-engineered EVs compared to controls.[166] Despite these advances, the inherent tissue and cell-specific targeting limitations of natural exosomes require further customization. For example, MSC-derived EVs genetically altered to express GATA-4 exhibit enhanced pro-angiogenic activity through the transmission of let-7 microRNAs that interact with THBS1 in endothelial cells, suggesting a promising strategy for angiogenesis-related situations.[167] Moreover, the viral oncoprotein LMP1 exploits Hrs, syntenin-1, and elements of the ESCRT-III complex to boost EV production and modulate cargo. Consequently, LMP1-modified EVs promote tumor cell attachment, proliferation, migration, and growth by upregulating ILV budding machinery, thereby offering insights for innovative diagnostic and therapeutic approaches in Epstein–Barr virus-associated cancers.[168,169] In addition, Haney *et al.* (2015) demonstrated that exosomes loaded with catalase (exoCAT) possess significant neuroprotective properties in Parkinson's disease models. The stability of exoCAT formulations at room temperature for over a week—while maintaining size and catalase activity—underscores their practical suitability, with both unaltered and catalase-loaded exosomes effectively reducing reactive oxygen species (ROS) levels in activated macrophages.[170] In sum, exosomes offer substantial promise for ocular drug delivery. Their unique properties, coupled with advanced engineering techniques, pave the way for targeted and efficient treatment strategies. Continued research and development in exosome-based therapies are imperative to fully harness their potential in managing ocular diseases.

Taken as a whole, these data support the view that engineered exosomes offer a transformative approach to ocular drug delivery by combining the biocompatibility and low immunogenicity of natural vesicles with the precision and adaptability of nanotechnology. Consequently, unlike liposomes or viral vectors—both limited by inflammatory responses, poor barrier penetration, and rapid clearance—these vesicles can be modified through PEGylation, surface–ligand conjugation, optogenetic control, or polymeric nanogel hybridization to extend circulation, enable on-demand release, and selectively target retinal or corneal cells. Moreover, platforms such as EXOtic boost production yields and mRNA packaging, while ESCRT-binding motif fusions enhance cargo encapsulation without compromising vesicle integrity. Although challenges in scale-up, standardization, and regulatory approval persist, integrating synthetic-biology tools, microfluidic purification, and stringent quality controls positions engineered exosomes to overcome current delivery barriers and to lead the next generation of personalized, cell-free ophthalmic therapies.

5.1. Novel insight

Incorporating optogenetic control into exosome biogenesis transforms EVs into on-demand nanocarriers: by fusing light-responsive dimerization domains to tetraspanins, cargo loading and surface ligand display can be triggered with precise spatial and temporal resolution, ensuring payload release only at illuminated ocular sites.

5.2. Proposed solution

Generate donor cells expressing a CD63-CRY2 fusion alongside a CIBN-tagged therapeutic miRNA adaptor. Upon blue-light exposure, CRY2-CIBN dimerization drives selective miRNA packaging into intraluminal vesicles. Isolate these "light-programmed" exosomes, then demonstrate controllable cargo release and target engagement in retinal organoid cultures under patterned illumination.

6. Therapeutic applications in ocular diseases

6.1 Cornea diseases

Exosomes have been gradually involved in the development of corneal disorders through multiple mechanisms. First, they can alter the extracellular matrix of the corneal stroma—thereby affecting its composition and organization, which is essential for maintaining transparency—and influence cellular signaling and matrix remodeling.[93,155,171,172] The study demonstrates that EVs derived from human corneal endothelial cells significantly impair the proliferative and regenerative capacity of human corneal endothelial cells (HCEnCs). *In vitro* experiments revealed that EV-treated HCEnCs exhibit a marked reduction in proliferation alongside a higher incidence

of apoptosis compared to untreated controls. Furthermore, *ex vivo* wound-healing assays performed on porcine and rabbit corneas—models that naturally possess robust *in vivo* proliferative responses—showed statistically significant delays in wound closure at days two and three post-treatment. Consequently, these results suggest that increased EV uptake delivers pro-apoptotic factors that not only diminish HCEnC viability but also hinder their migratory and repair processes, thereby restricting proliferative potential and potentially contributing to corneal endothelial dysfunction,[96] and promote excessive scar formation (corneal fibrosis) following injury.[172] Considering that corneal development relies on complex interactions among diverse cell types, including neural crest derivatives that form the endothelium and stromal keratocytes.[173] Also, exosomes could impact disease progression through several pathways, although their exact roles remain under investigation.[174] Moreover, studies have demonstrated that exosomes play a crucial role in corneal tissue biology, particularly in wound healing.[175] Han *et al.* demonstrated that exosomes secreted by corneal epithelial cells mediate intercellular communication by inducing keratocyte-to-myofibroblast transformation, stimulating endothelial cell proliferation, and promoting neovascularization processes that are indispensable for effective wound healing and angiogenesis. Moreover, the authors detected exosome-like vesicles in the interface between the epithelium and stroma during recovery from epithelial debridement and anterior stromal keratectomy, indicating that epithelial-derived exosomes can penetrate the stroma and directly engage fibroblasts. *In vitro* assays confirmed that these vesicles drive myofibroblast differentiation in keratocytes, while *ex vivo* aortic ring experiments revealed enhanced endothelial sprouting and proliferation. Consequently, these findings not only establish epithelial cell-derived exosomes as key regulators of corneal repair and vessel formation but also identify them as promising therapeutic targets for accelerating corneal wound closure and modulating pathological neovascularization by elucidating the underlying signalling mechanisms.[176] Furthermore, the paracrine function of exosomes, including the delivery of miRNAs and the upregulation of signaling pathways, has been associated with enhanced corneal repair, regeneration, and even scar development[172,177] which underscore the potential of exosomal miRNAs as both biomarkers and therapeutic agents in corneal diseases.[162] Notably, EVs are produced by a variety of corneal cell types—such as epithelial cells, stromal keratocytes, fibroblasts, and endothelial cells[178]—which underscores their extensive involvement in corneal biology and their emerging utility as diagnostic and therapeutic tools.[179] Notably, investigations by Han *et al.* have elucidated the role of matrix metalloproteinase 14 (MMP14) in EV-mediated corneal angiogenesis. Their work demonstrated that MMP14-enriched exosomes from corneal fibroblasts incorporate MMP2 in an MMP14-dependent manner.[180] They further revealed that such exosomes can cleave vascular endothelial growth factor receptor 1 (VEGFR1), thereby promoting VEGFA-induced migration and proliferation of vascular endothelial cells.[181] Subsequent studies indicated that MMP14 expression alters the protein composition of EVs from corneal fibroblasts, potentially regulating angiogenesis,[182] and suggested that the proangiogenic function of MMP14 results from its specific interaction with and cleavage of VEGFR1.[183] These findings collectively highlight MMP14 as a promising target for therapeutic intervention in corneal angiogenesis. In parallel, cell-free therapies utilizing EVs derived from MSCs have shown considerable promise in treating corneal diseases. Studies indicate that MSC-derived EVs can accelerate corneal epithelial wound healing, reduce inflammation, and modulate repair dynamics.[93,184–187] Moreover, these vesicles exhibit antifibrotic, anti-inflammatory, and regenerative properties, and they protect corneal endothelial cells from endoplasmic reticulum stress-mediated apoptosis—a critical factor in endothelial dystrophy.[186–188] In addition, the ability of EVs to upregulate signaling pathways and deliver miRNAs further enhances corneal wound healing.[189]

Overall, MSC-derived EVs present a promising alternative to traditional treatments such as transplantation or stem cell therapy. In summary, EVs—particularly exosomes—play a pivotal role in corneal biology by modulating wound healing, fibrosis, inflammation, and cell differentiation. Their paracrine functions and ability to influence cell signaling make them valuable candidates for both diagnostic markers and therapeutic targets in a range of corneal pathologies Table 1.

6.2 Age-related macular degeneration (AMD)

EVs and exosomes have been increasingly implicated in the pathogenesis of AMD, a leading cause of vision loss among the elderly in Western societies.[196] Research reveals that drusen—a hallmark of AMD—contains proteins commonly found in extracellular deposits from other age-related complications, suggesting shared pathological pathways.[197] Moreover, enhanced exosome production and autophagy have been associated with drusen formation.[198] In parallel, genetic studies underscore the critical role of the complement system (including factor B and components C2 and C3) in AMD development.[199,200] while disruption of the autophagy-lysosome pathway—potentially linked to EV function—has also been observed in AMD and similar disorders.[201,202] Notably, exosomes have emerged as key mediators in AMD.[203] Furthermore, AMD is marked by drusen buildup, loss of retinal pigment epithelium (RPE), and subsequent photoreceptor degeneration[204] with oxidative stress further exacerbating these processes.[205] EVs play a dual role by regulating ocular immune functions and facilitating the expulsion of cellular debris, thereby contributing to both local inflammation and peripheral inflammatory responses observed during aging.[206,207] In this context, stressed RPE cells release EVs that increase the secretion of drusen proteins, directly implicating them in AMD pathophysiology.[208] In addition, EVs appear to deliver microRNAs—such as miR-25-3p—that have been linked to protective effects against cellular degeneration.[209] Recent studies further illuminate the role of EVs in AMD. For example, Kurzawa-Akanbi *et al.* (2022) demonstrated that RPE-derived EVs from AMD patients can induce AMD-like characteristics in neighboring cells, while Lin *et al.* (2022) explored the interplay among oxidative stress, EVs, and microRNAs in the disease.[210,211] Moreover, Hadady *et al.* (2021) affirmed the therapeutic potential of EVs by showing that stem

Table 1 Potential uses of exosomes in cornea

Exosome source cells	Exosome content	Target	Ref.
Bone marrow derived MSC	—	p44/42 MAPK pathway	190
Bone marrow derived MSC	—	Antiinflammation	187
Adipose-derived MSC	—	Matrix metalloproteins (MMP)	191
Human corneal MSC	—	—	192
Human umbilical cord MSC	miRNA-21	PI3K/AKT and PTEN	193
Corneal fibroblasts	Matrix metalloproteinase (MMP) 1	MMP2	180
In-growing pig corneal epithelium cells	—	Generate matrix components, promote corneal regeneration	194
Mouse corneal epithelial cells	Thrombospondin-2, latent-transforming growth factor beta-binding protein 1, C–X–C motif chemokine 5, and C–C motif chemokine	Corneal wound healing	176
Normal human cornea limbal keratocytes	Small RNAs	Corneal wound healing	195
Human corneal MSCs	—	Corneal wound healing	192

cells derived from apical papilla—when enriched with EVs *via* a lab-on-chip technique—exert a neuroprotective effect in retinal degeneration models.[212]

In overview, EVs and exosomes significantly contribute to AMD through mechanisms that involve drusen accumulation, immune modulation, disruption of cellular pathways, and the regulation of oxidative stress. Their multifaceted roles underscore both the complex pathogenesis of AMD and the potential of EV-based interventions as a promising therapeutic strategy Table 2.

6.3 Glaucoma

Glaucoma is a group of eye disorders marked by the progressive loss of retinal ganglion cells (RGCs) and their axons, with dysregulation of intraocular pressure playing a crucial role in disease progression.[222,223] Recently, exosomes—a subclass of EVs—have emerged as key mediators of intercellular communication in various ocular diseases, including glaucoma.[224] In this context, bone marrow-derived mesenchymal stem cell (BMSC) exosomes have shown promise by promoting RGC survival, preserving retinal structure, and supporting axonal integrity in animal models.[225,226] Furthermore, these vesicles modulate neuroinflammation, oxidative stress, and apoptosis, all of which are critical factors in glaucoma pathophysiology.[155,227] Additionally, studies examining the uptake and distribution of MSC-derived EVs in the retina suggest a potential role in cell replacement therapies.[228]

Moreover, EVs derived from Müller glia, which are rich in neuroprotective microRNAs, have demonstrated sustained protection of retinal ganglion cells and the optic nerve.[229,230] Similarly, EVs released from oxidative-stressed non-pigmented ciliary epithelium cells protect trabecular meshwork cells by activating antioxidant pathways and attenuating Wnt protein expression, thereby mitigating oxidative damage.[231] In summary, leveraging the neuroprotective, anti-inflammatory, and regenerative properties of these EVs and exosomes offer promising new avenues for developing therapeutic strategies to address the complex pathophysiology of glaucoma Table 3.

Table 2 Potential uses of exosomes in AMD

Exosome source cells	Exosome content	Target	Ref.
MSC	—	Nrf2 signaling pathway	213
Human umbilical cord blood MSCs (hUCMSCs)	—	VEGF-A	214
Human umbilical cord blood MSCs (hUCMSCs)	miR-27b-3p	Reduction of retinal fibrosis	215
Human umbilical cord blood MSCs (hUCMSCs)	miR-126	HMGB1 signaling pathway	92
Retinal astroglial cells (RACs)	Different antiangiogenic factor such as endostatin	Angiogenesis inhibitor	216
Human retinal pigment epithelial ARPE-19 cells; aqueous humor (AH)	Cytokeratin 8, cytokeratin 14, cathepsin D, Hsp70; myosin 9, and actin, aortic smooth muscle	Proteins related to the autophagy-lysosomal pathway and epithelial mesenchymal transition	217
Serum	miR-486-5p, miR-626, miR-885-5	Apoptosis and neovascularization pathways	218
Retinal pigment epithelial (RPE) cells	—	Transport bevacizumab as drug delivery vesicles	219
Cultured ARPE-19 cells under oxidative stress conditions	Signaling phosphoproteins	—	220
ARPE-19	Complement protein C3	Complement pathways	221
ARPE-19	VEGFR2	—	202

Table 3 Potential uses of exosomes in glaucoma

Exosome source cells	Exosome content	Target	Ref.
HEK293T cells	S58 aptame		232
Bone marrow derived (BMSC)	MiRNA cargo such as MIR-106A-5P, MIR-486-5P, MIR-144-5P, *etc.*	miRNA	225
Bone marrow derived (BMSC)	miRNAs	—	233
Bone marrow-derived (BMSC)	—	TNF-α signaling	234
Amniotic membrane mesenchymal (AMMSCs) and epithelial Stem cells (AMESCs)	Higher levels of FGF, EGF, TGF-β, VEGF, BDNF and PDG	NeuN	235
Primary human trabecularmeshwork (TM) cells	miR-182	Retinal ganglion cell	236
Cultured NPCE cells	—	Wnt signaling	236
Bone marrow-derived stem cell (BMSC) sEV	miRNAs	—	237

6.4 Diabetic retinopathy (DR)

(EVs) significantly influence both the development and potential treatment of diabetic retinopathy (DR). For example, plasma exosomes—a specific type of EV—contribute to microvascular damage in DR by activating the classical complement pathway, during which they transport complement proteins and immunoglobulins that induce vascular injury.[238] Moreover, EVs carrying microRNAs (miRNAs) from diabetic individuals further implicate these vesicles in DR pathogenesis.[239] Importantly, the complement activation induced by EVs has been directly associated with damage to retinal endothelial cells.[240] In parallel, vascular endothelial growth factor (VEGF) plays a crucial role in DR progression by promoting the build-up of extracellular fluid in the macula, disrupting the blood-retina barrier, and increasing vascular permeability, which ultimately contributes to diabetic macular edema—a frequent complication of DR.[241–243] Additionally, alterations in the extracellular matrix of retinal vessels in diabetic patients likely contribute to endothelial dysfunction observed in DR.[244,245] Furthermore, EVs have gained recognition as potential biomarkers and therapeutic tools for DR due to their diverse roles in the disease's pathogenesis, detection, and management.[246,247] Notably, EVs derived from MSC have demonstrated the ability to elicit DR-like characteristics under controlled laboratory settings, suggesting their plausible involvement in disease advancement.[248] These emerging roles highlight promising avenues for novel therapeutic interventions targeting diabetes and its ocular complications.[249]

In summary, various EVs—including exosomes and small EVs—exert multifaceted effects on DR by promoting vascular damage, complement activation, and miRNA-mediated processes. A deeper understanding of EV involvement in DR pathophysiology opens new possibilities for innovative diagnostic and therapeutic strategies in managing this serious diabetic complication Table 4.

6.5 Uveitis

Exosomes, nano-sized extracellular vesicles, have emerged as promising therapeutic tools across various medical fields, including ophthalmology. Notably, their immunomodulatory properties and capacity to serve as drug-delivery vehicles render them particularly attractive for treating uveitis, an inflammatory condition of the uveal tract.

Recent studies underscore the therapeutic potential of MSC-derived exosomes in ameliorating experimental autoimmune uveitis (EAU). For example, Bai *et al.* observed that MSC-derived exosomes significantly inhibited EAU in rats by modulating immune responses—decreasing inflammatory cytokines such as IL-17 and IFN-γ, while increasing regulatory T cells marked by $CD25^{+}$ $Foxp3^{+}$.[259,260] Similarly, Jiang *et al.*

Table 4 Potential uses of exosomes in diabetic retinopathy (DR)

Exosome source cells	Exosome content	Target	Ref.
Adipose MSCs	miRNAs	MiRNA-222	250
Human umbilical cord mesenchymal stem cells (hUCMSCs)	Overexpressed level of exosome markers and miRNAs	p38 MAPK signaling	251
Retinal pigment epithelial cell line (ARPE-19)	miRNA-202-5p	TGFβR2	252
Bone marrow-derived MSC (BMSC)	miRNA-486-3p	TLR4 and nuclear factor-kappaB (NF-κB)	253
RGC-5 and HUVEC	—	miRNA-3976	254
Plasma from diabetic mice	Ig-G	—	238
Human umbilical cord-derived mesenchymal stem cells (MSCs)	miRNA-126	HMGB1 signaling pathway	92
Platelet-rich plasma	CXCL10	TLR4 signaling pathway	255,256
Retinal photoreceptors	miRNAs, VEGF	Anti-angiogenic effects of RvD1	257
Plasma	Peroxisome proliferator-activated receptor gamma (PPARγ)	—	258
Pancreatic-β-cells	miR-15a	Inducing oxidative stress	259

Table 5 Potential uses of exosomes in uveitis

Exosome source cells	Exosome content	Target	Ref.
Innate cells	Overexpressed IL-27	IL-27 and Treg/Th17 cells	261
Human umbilical MSC	Overexpressed IL-10	IL-10 and Treg/Th17 cells	263
MSC	miRNAs and proteins	Inflammatory cells, CD4+ T cells and macrophages	266
Mesenchymal stem/stromal cell (MSC)	—	Development of T helper 1 (Th1) and Th17 cells	267
MSCs	—	Inflammatory cell	267 and 268
ARPE-19	—	Proinflammatory cytokines	269

demonstrated that vaccination with circulating exosomes prevented recurrent intraocular inflammation in autoimmune uveitis models.[260] Furthermore, the ability of exosomes to traverse biological barriers, including the blood-retinal barrier, enhances their candidacy as both therapeutic agents and targeted delivery vehicles in ocular diseases.[161,261] Their versatility extends to delivering not only regulatory molecules but also therapeutic agents such as microRNAs and siRNA. For instance, exosomes encapsulating rapamycin (sirolimus) have shown marked efficacy in suppressing uveitis symptoms in preclinical models,[262] a benefit that exploits their innate ability to fuse with target cells and deliver cargo efficiently. Moreover, Kang *et al.* illustrated that exosomes containing interleukin-27 (IL-27) from regulatory B cells dramatically reduced inflammation by promoting Treg expansion while inhibiting Th1 and Th17 activity in a uveitis model.[263] This finding highlights the capability of exosomes to enhance the body's intrinsic regulatory pathways and maintain immune homeostasis in inflammatory situations. In addition, these vesicles facilitate intercellular communication, influence cytokine profiles, and promote tissue repair mechanisms in the eye.[111] Exosomes also show promise as drug delivery systems due to their biocompatibility and low immunogenicity. Batrakova and Kim emphasized their potential as natural nanocarriers for various drugs—including those targeting autoimmune diseases like uveitis.[264] Their intrinsic properties enable effective encapsulation and controlled release of pharmacological agents, a feature particularly beneficial for treating complex ocular inflammatory situations[224,265] (Table 5).

7. Preclinical studies and clinical translation

As exosomes exhibit several unique properties—low immunogenicity, biocompatibility, and the ability to cross biological barriers—that render them promising candidates for targeted drug delivery in ophthalmology. Recent studies underscore their potential in transporting therapeutic agents effectively to ocular tissues. For example, engineered RGD-exosomes have been shown by Pollalis *et al.* to actively target affected tissues in situations like choroidal neovascularization, with a reduced toxicity profile compared to conventional synthetic carriers, thereby offering a safer alternative for intraocular therapies.[270] Moreover, exosomes derived from mesenchymal stem cells possess regenerative properties that could benefit degenerative eye diseases.[161] Tear-derived exosomes have also been explored both as biomarkers and as drug carriers in the treatment of dry eye syndrome.[271,272] Their capacity to encapsulate microRNAs is particularly valuable, as these molecules can modulate inflammatory pathways implicated in diabetic retinopathy and AMD.[224,273] Additionally, the innate cell-to-cell signaling functions of exosomes facilitate precise delivery of therapeutic agents to target cells within ocular tissues.[274] Exosomes are noteworthy not only for their targeting capabilities but also for their versatile cargo-loading potential. Li *et al.* describe efficient methods for incorporating RNA therapeutics —an approach that holds promise for gene therapy in AMD.[275] This is supported by Zeng *et al.*, who emphasize strategies for drug loading that preserve the biological integrity and stability of exosomes.[70]

Clinical investigations are progressively evaluating these platforms. Ongoing trials are testing the safety and efficacy of exosome-based therapies, demonstrating their ability to deliver both small-molecule drugs and biological macromolecules in a regulated manner.[161,276] Exosomes further enhance drug transport across challenging barriers such as the blood-retinal barrier, broadening their applicability in treating retinal disorders.[24,27] Nonetheless, challenges in scalability and reproducibility persist, highlighting the need for standardized isolation and characterization protocols to ensure consistent safety and efficacy.[277] Continued refinement of targeting strategies is also essential for optimizing delivery efficiency to ocular tissues.[278]

In parallel, clinical trials have reported enhanced clinical improvement in symptoms and ocular signs associated with various Illnesses, suggesting that exosomal therapy may represent a viable treatment option for patients with difficult-to-treat eye pathologies.[161] Recent clinical investigations and trials registered in a public database ClinicalTrials.gov have explored the therapeutic application of exosomes in various ocular and systemic disorders (Table 6). For instance, one study on dry eye in chronic graft-*versus*-host disease (cGVHD) patients evaluated UMSC-derived exosomes following an initial two-week period with artificial tears; subsequently, participants received UMSC-Exo eye drops (10 μg per drop, four times daily) for 14 days, with a subsequent 12-week follow-up (NCT04213248). Similarly, a trial assessing limbal stem cell-derived exosome (LSC-Exo) eye drops in approximately 30 patients with dry eye syndrome employed a comparable regimen and follow-up period (NCT06543667). In addition, PSC-MSC-Exo eye drops have been investigated for treating dry

Table 6 A callout table 6 displays all studies focusing on extracellular vesicles in ocular diseases listed on ClinicalTrials.gov, ordered by start year and month

S. no.	NCT number	Conditions	Study status	Exosome source	Start date (YYYY-MM)
1	NCT06771427	Dry Eye Syndrome (DES) Sjogren's syndrome	Recruiting	Plasma	2025-01
2	NCT06188013	Diabetic retinopathy	Not yet recruiting	Plasma	2024-01
3	NCT06198543	Diabetic retinopathy	Not yet recruiting	Intraocular fluid and blood	2024-01
4	NCT06242379	Retinitis pigmentosa	Recruiting	Bone Marrow Mesenchymal Stem cell derived (BM-MSC) sEVs	2024-05
5	NCT06475027	Dry Eye syndrome Sjogren's syndrome	Not yet recruiting	Plasma	2024-07
6	NCT06543667	Dry eye syndromes	Recruiting	Limbal Stem Cell	2024-08
7	NCT05738629	Dry eye disease	Unknown	Pluripotent Stem Cell-derived Mesenchymal Stem Cell Exosome (PSC-MSC-Exo)	2023-03
8	NCT05888558	Myasthenia gravis	Unknown	Serum	2023-07
9	NCT05413148	Retinitis pigmentosa	Unknown	Wharton's jelly mesenchymal stem cells (WJ-MSCs)	2022-08
10	NCT04213248	Dry eye	Unknown	Umbilical Mesenchymal Stem Cells (UMSCs) derived Exosomes	2020-02
11	NCT06883461	Age related macular degeneration Mild Cognitive Impairment (MCI)	Completed	Peripheral serum	2019-04
12	NCT03264976	Diabetic retinopathy	Unknown	Serum	2018-07
13	NCT03437759	Macular holes	Unknown	Mesenchymal Stem Cells derived exosomes (MSC-Exos)	2017-03

NCT stands for National Clinical Trial.

eye diseases following refractive surgery and in cases associated with blepharospasm (NCT05738629).

Concurrently, complementary studies have utilized proteomic and transcriptomic analyses of exosomes to identify diagnostic biomarkers and therapeutic targets in Sjögren's Syndrome (SJS) and Dry Eye Syndrome (DES) (NCT06771427, NCT06475027), while serum-derived exosomal miRNAs are currently being examined as potential diagnostic indicators for ocular myasthenia gravis (OMG) (NCT05888558). Notably, mesenchymal stem cell-derived exosome therapy has shown promising results in enhancing both functional and anatomical recovery in large, refractory macular holes (NCT03437759). Furthermore, in the context of proliferative diabetic retinopathy, analyses of plasma exosome protein profiles aim to identify novel biomarkers and therapeutic targets (NCT06188013, NCT06198543). Additionally, a randomized trial investigating umbilical cord-derived mesenchymal stem cell exosomes in retinitis pigmentosa has demonstrated beneficial outcomes in both functional and structural parameters compared to placebo (NCT05413148, NCT06242379). Finally, proteomic profiling of serum extracellular vesicles in patients with age-related macular degeneration (AMD) and mild cognitive impairment (MCI) (NCT06883461), alongside the evaluation of serum exosomal miRNA as a prognostic biomarker for diabetic retinopathy (NCT03264976), further underscores the broad diagnostic and therapeutic potential of exosome-based strategies.

In brief, exosomes offer considerable promise as advanced drug delivery vehicles in ophthalmology. Their unique biological characteristics, coupled with innovative engineering techniques, position them as a formidable tool in the development of safer and more effective treatments for a wide range of ocular diseases.

8. Challenges and limitations

Exosomes hold significant potential for ocular drug delivery; however, their clinical translation faces interrelated challenges of production and stability. First, the complexity of exosome production stems from their natural secretion and heterogeneous composition, complicating their isolation and characterization. Moreover, current EV isolation methods often result in batch-to-batch variability and require labor-intensive protocols,[279,280] and the scalability of these methods remains limited since reliable large-scale manufacturing techniques are required to produce clinically relevant quantities of exosomes.[55,279] Consequently, the absence of standardized production processes contributes to uncertainties regarding reproducibility and efficacy.[8]

Stability concerns further hamper clinical translation: exosomes are susceptible to storage conditions and may lose functional integrity over time;[111] additionally, systemic clearance can rapidly remove EVs before they reach target tissues,[281] reducing therapeutic retention in retinal and anterior segment disorders.[7,282] Indeed, preclinical studies have quantified this rapid ocular clearance,[283] reporting half-lives of 5–15 minutes in the tear film,[7] 4–6 hours in the aqueous humor, and 24–48 hours intravitreally in rabbit models; these rapid elimination rates necessitate formulation strategies—such as

mucoadhesive hydrogels, surface PEGylation, or receptor-mediated targeting—to prolong ocular residence time and achieve therapeutic concentrations.[161] Although surface engineering approaches have been proposed to enhance specificity toward ocular tissues, optimizing exosome surface properties while preserving biocompatibility remains challenging within the eye's complex microenvironment,[55,281,284] and further insights into exosome–tissue interactions are needed to guide functionalization strategies.[111,285]

Finally, exosome-based therapies are classified as biologics under the biological products provisions of the Public Health Service Act Section 351, requiring extensive safety, efficacy, and quality testing, yet the regulatory pathways for EV therapeutics remain ill-defined;[279,286] for example, the FDA's categorization under Section 351 and the demand for good manufacturing practice compliance pose significant challenges in the absence of clear quality-control standards.[8,282,286,287]

Therefore, until standardized manufacturing protocols, optimized formulation strategies, a mechanistic understanding of exosome–eye interactions, and collaborative dialogue with regulatory authorities are established, exosome therapies will remain confined to the preclinical stage in ophthalmology.

9. Future perspectives and directions

Exosomes represent an exciting frontier in drug delivery and therapeutic strategies for ocular diseases. These nano-sized EVs possess unique properties that make them ideal candidates for targeted delivery systems in the complex environment of the eye. Indeed, emerging research indicates that exosomes can be effectively applied to a range of ocular diseases, including diabetic retinopathy, age-related macular degeneration, corneal injuries, and autoimmune uveitis.

Moreover, the advancement of exosome-based drug delivery holds great promise for improving targeted therapeutic delivery, minimizing side effects, and enabling personalized medicine approaches.[126] Exosomes and their engineered hybrids have demonstrated excellent drug carrier potential and capacity.[288] However, challenges such as scalability, cargo loading efficiency, safety, and regulatory approval remain to be addressed.[126] Notably, stem cell-derived exosomes offer a particularly innovative treatment alternative for various ocular diseases, although further research is necessary to refine delivery methods and assess long-term efficacy in restoring ocular health.[43] As innovative engineering techniques continue to evolve, the future of exosome-based therapies in ocular disease appears increasingly promising.[126] Enhanced targeting, sustained release, and the capacity to carry complex therapeutic payloads are expected to yield more effective strategies for diseases that have historically been challenging to manage.[56] Furthermore, ongoing studies of exosome biology, in concert with advanced engineering solutions, are expected to accelerate the clinical translation of these therapies, thereby providing new hope for patients suffering from ocular diseases.[161] In summary, the future of exosomes as both drug delivery vehicles and therapeutic agents in ocular diseases is bright. Their ability to facilitate targeted delivery, serve as biomarkers, and support regenerative processes could revolutionize treatment paradigms for a variety of ocular disorders.

In addition to that, the authors advocate that exosome–based drug delivery constitutes the next generation of ophthalmic therapeutics because, unlike conventional approaches such as topical drops, nanoparticles, and intravitreal injections which often suffer from low bioavailability, poor tissue specificity, and systemic side effects, exosomes combine nano–sized dimensions with innate tissue tropism and exceptional biocompatibility. Moreover, engineered exosomes and stem cell-derived vesicles can encapsulate a broad array of cargos (small molecules, nucleic acids, proteins) with higher loading efficiency than liposomes or polymeric nanoparticles, thereby enabling personalized treatment regimens while minimizing off–target toxicity. Consequently, exosome platforms hold unique promise for overcoming ocular barriers, achieving sustained drug release, and enhancing therapeutic retention in retinal and anterior segment tissues. Therefore, by addressing longstanding limitations in treating diabetic retinopathy, age-related macular degeneration, corneal injuries, and uveitis and by integrating scalable manufacturing processes, advanced cargo–loading technologies, and evolving regulatory frameworks—exosome–based therapies are poised to fill critical research gaps and lead the field toward more effective, targeted, and patient-specific ocular interventions.

10. Conclusions

In closing, currently, exosomes offer a transformative platform for drug delivery and therapy in ocular diseases. Their innate ability to target specific cells, coupled with immunomodulatory and regenerative properties, positions them as promising agents in overcoming the challenges inherent to ocular pathologies. Although significant advances in exosome engineering and preclinical applications have been achieved, enhanced scalability, optimized cargo loading, and robust regulatory pathways remain essential for clinical translation. Ultimately, continued innovation in this field is poised to revolutionize ocular therapeutics, paving the way for personalized and minimally invasive treatment strategies.

Author contributions

This manuscript was mainly composed by Dr N. Verma and reviewed and edited by Dr S. Arora. Dr A. K. Singh drafted and reviewed the manuscript. Dr J. Ahmed created and reviewed the figures. All authors have examined and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

This review article does not present any primary research findings, nor does it include software or code, and it does not involve the generation or analysis of new data.

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