Journal of Drug Delivery Science and Technology 112 (2025) 107271

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review Article

Nanomedicines for ocular fibrosis

Binapani Mahaling [a,b,*], Aumreetam Dinabandhu [c], Manas R. Biswal [d], Sourabh Ghosh [b]

[a] Schepens Eye Research Institute, Harvard Medical School, Boston, MA, 02114, USA
[b] Department of Textile and Fibre Engineering, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi, 110016, India
[c] Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA
[d] Department of Pharmaceutical Sciences, College of Pharmacy, University of South Florida, Tampa, FL, 33612, USA

ARTICLE INFO

Keywords:
Ocular fibrosis
Nanomedicine
Cornea
Conjunctiva
Lens
Retina
Drug delivery

ABSTRACT

Ocular fibrosis, a common pathological outcome of injury and surgery, is a leading cause of irreversible vision impairment. Existing therapies, such as antimetabolites, often lack precision and pose risks of inflammation, tissue damage, and poor long-term outcomes. This review explores how nanomedicine-based interventions are reshaping the therapeutic landscape by overcoming ocular drug delivery barriers and enabling sustained, targeted, and cell-specific delivery. We provide a comprehensive overview of recent nanotherapeutic advances for treating corneal, conjunctival, capsular, and posterior segment fibrosis. Additionally, we introduce a mechanistic framework where nanomedicines modulate key pro-fibrotic signaling pathways including TGF-β, Wnt/β-catenin, NF-κB, MRTF/SRF, HIF-α, oxidative stress, cell division, and metabolic networks. We also discuss the translational challenges and opportunities in bringing these therapies from bench to bedside. This review aims to serve as a critical reference for designing next-generation anti-fibrotic nanomedicines tailored for ocular applications.

1. Introduction

Ocular fibrosis is a multifaceted biological process that contributes to several clinical conditions, such as corneal fibrosis, conjunctival scarring following glaucoma surgery, capsular fibrosis after cataract surgery, subretinal fibrosis associated with age-related macular degeneration (AMD), fibrovascular proliferation in diabetic retinopathy (DR), and proliferative vitreoretinopathy (PVR), which can cause failure in retinal detachment surgeries [1,2]. This pathological process involves inflammation, activation of fibroblasts, and the transition of epithelial, endothelial, or glial cells into a mesenchymal phenotype. It also includes the accumulation of cellular and extracellular matrix (ECM) components, which are essential for maintaining proper visual function, followed by tissue contraction [1,3]. Fibrosis in ocular tissues can lead to adverse effects by mechanically obstructing the visual axis or altering the fragile tissue microenvironment, ultimately impairing visual acuity [3].

Current strategies to prevent or manage ocular fibrosis largely rely on the topical use of antimetabolites, such as mitomycin-C and 5-fluorouracil, corticosteroids like prednisolone acetate, triamcinolone acetonide, and dexamethasone, and immunosuppressive agents, including azathioprine, cyclosporine, cyclophosphamide, methotrexate, mycophenolate mofetil, sirolimus, tacrolimus, and alongside monoclonal antibodies. However, the effectiveness of these treatments can be limited by the drug properties and their ocular delivery methods. For example, while antimetabolites are effective in addressing ocular fibrosis, they may cause serious side effects such as hypotony, bleb leakage, blebitis, endophthalmitis, and even vision loss [2]. Furthermore, prolonged use of topical steroids can result in elevated intraocular pressure [4,5].

Although immunosuppressive agents are effective in controlling inflammation linked to fibrovascular complications and generally present a safer profile compared to steroids, their overall safety still requires further investigation, as they have been associated with risks such as hypertension, increased susceptibility to infections, cancer, and mortality in various conditions [6]. Antibodies, on the other hand, have short half-lives and are prone to enzymatic degradation. Additionally, drugs administered to the eye face multiple barriers depending on the delivery method. While topical eye drops are favored for their high patient compliance, they are limited by ocular clearance mechanisms like lacrimation, blinking, reflex tearing, and nasolacrimal drainage. These processes rapidly expel the drug from the ocular surface, leading to poor administration efficiency and low bioavailability [7–10].

* Corresponding author. Schepens Eye Research Institute, Harvard Medical School, Boston, MA, 02114, USA.
E-mail addresses: binapanimahaling@gmail.com, bmahaling@meei.harvard.edu (B. Mahaling).

https://doi.org/10.1016/j.jddst.2025.107271
Received 11 March 2025; Received in revised form 8 July 2025; Accepted 11 July 2025
Available online 12 July 2025

Indeed, recent studies have explored topical nanomedicine approaches to overcome ocular clearance and enhance drug retention. For instance, a thiolated gelatin-capped nanoceria system delivering gabapentin significantly improved mucin binding, bioavailability, and therapeutic outcomes in dry eye models, while a structurally engineered gold nano-urchin formulation achieved prolonged ocular retention and potent multi-targeted therapeutic effects including tear stimulation, anti-inflammation, anti-angiogenesis, and nerve regeneration [11,12].

Systemic drug administration is often considered minimally invasive and more convenient; however, it presents challenges related to low bioavailability. This is primarily due to the eye's limited vascularization, which restricts efficient drug delivery. Additionally, systemic delivery can raise concerns about potential toxicity in certain cases [8,13]. Another method, intraocular injections, is more invasive and carries the risk of compromising ocular function [8,14]. Nanomedicine is emerging as a promising alternative to address the limitations of traditional anti-fibrotic drugs and overcome the barriers associated with ocular drug delivery (Table-1) [15–18].

Beyond improved delivery, nanomedicine also enables targeted modulation of pro-fibrotic signaling pathways that are central to the progression of ocular fibrosis. Recent research has focused on engineering nanoscale drug carriers to selectively interfere with molecular pathways such as transforming growth factor (TGF) β1, Wnt/β-catenin, NF-κB, MRTF/SRF, HIF-α, oxidative stress-related cascades, specific stages of cell division, and metabolic regulators. These signaling axes drive fibroblast activation, ECM remodeling, and chronic inflammation in various ocular compartments. By integrating pathway-specific inhibitors into nanocarriers, these therapeutic strategies aim to enhance treatment efficacy, reduce off-target effects, and achieve sustained intraocular bioavailability [20,31–35]. Herein, we discuss the pathophysiology of ocular fibrosis and explore emerging nanomedicine-based strategies, particularly those targeting key pro-fibrotic signaling pathways to improve therapeutic outcomes.

Table-1
Comparison of Nanomedicine vs Traditional Anti-Fibrotic Therapies for Ocular Fibrosis.

Parameters	Traditional Anti-Fibrotic Therapies	Nanomedicine-Based Therapies
Efficacy	- Often limited by poor tissue penetration and wash away by tear fluid [19]. - Non-specific and may lead to toxicity [20].	- Sustained drug release improves therapeutic outcomes [19]. - Enhanced efficacy due to targeted delivery [20,21].
Bioavailability	- Low ocular bioavailability (~1–5 %) due to barriers like cornea, conjunctiva, and tear turnover [14,17].	- Improved ocular bioavailability through nanoparticle penetration, mucoadhesion, and controlled release [14,17].
Safety Profile	- Risk of off-target effects (e.g., cataract, increased intraocular pressure with steroids) [4,22]. - Frequent dosing needed, increasing risks [23,24].	- Lower systemic exposure and off-target effects [22,25]. - Reduced dosing frequency can improve safety profile [23,24].
Administration Route	- Topical (eye drops), periocular, intravitreal injections. - Often needs repeated administration [24,26].	- Versatile delivery: topical nanoformulations, minimally invasive. - Prolonged retention time in ocular tissues [24,26].
Pharmacokinetics	- Rapid clearance from ocular surfaces and short half-life in ocular tissues [23,24].	- Prolonged retention time in ocular tissues and tunable pharmacokinetics via nanoparticle engineering [23,24,27].
Clinical Translation Stage	- Well-established (e.g., antimetabolites, corticosteroids, anti-VEGF agents) [28–30]. - Known long-term outcomes [28,29]	- Mostly preclinical and early-phase clinical trials [31]. - Long-term safety and efficacy needed to be evaluated [31].

2. Ocular fibrosis

Ocular fibrosis, a key contributor to vision loss, is characterized by excessive ECM deposition and myofibroblast activation across different ocular tissues [3,23,36–38]. While conjunctival, corneal, lens, and retinal fibrosis share common profibrotic pathways such as TGF-β signaling and persistent inflammation, the initiating insults and cellular responses vary, conjunctival fibrosis often results from surgical trauma, corneal fibrosis involves stromal keratocyte transformation, lens fibrosis is driven by epithelial-to-mesenchymal transition (EMT) of lens epithelial cells, and retinal fibrosis involves activation of Müller glia and retinal pigment epithelial (RPE) cells. The comparative pathological events are tabulated in Table-2. Comparative insights into these distinct yet overlapping mechanisms are crucial for designing targeted and tissue-specific antifibrotic therapies.

2.1. *Corneal fibrosis*

The cornea is a highly specialized, transparent, and sensory avascular connective tissue that plays a vital role in ocular function. It acts as a mechanical barrier while contributing to nearly two-thirds of the eye's refractive power. Structurally, the cornea is composed of three distinct layers: the outer epithelial cell layer, the central stroma, which makes up 90 % of the corneal thickness and the inner endothelial cell layer [56]. Following corneal injury, immune cells and fibrocytes migrate from surrounding blood vessels to the damaged site to facilitate wound healing and tissue regeneration [39,57]. In cases of minor injuries, such as superficial epithelial abrasions, only limited keratocyte apoptosis is observed. The epithelial or endothelial layers regenerate, the epithelial basement membrane (EBM) and/or Descemet's basement membrane (DBM) are repaired, and myofibroblast precursors originating from keratocytes or fibrocytes either undergo apoptosis or revert to their original cell types. This healing process usually restores the cornea without compromising its transparency [47]. However, deeper stromal injuries initiate an abnormal wound-healing response, marked by excessive deposition of collagen, α-SMA, and vimentin, culminating in corneal fibrosis (Fig. 1) [23,56,58]. In more severe injuries, where significant damage to the EBM and/or DBM occurs, the delayed regeneration of these basement membranes permits the continued influx of pro-fibrotic cytokines, such as TGF-β, TGFβ2, and platelet-derived growth factor (PDGF). These cytokines stimulate the formation of mature alpha smooth muscle actin (α-SMA) positive myofibroblasts, which produce large quantities of disorganized ECM components, ultimately leading to stromal scarring and fibrosis [47].

A variety of *in vivo* models for corneal fibrosis have been established, including alkali burns, chloropicrin-induced ocular toxicity, surgical stromal removal (200–250 μm) combined with rotating-burr polishing, descemetorhexis injury, endothelial keratoplasty, lamellar keratoplasty, and surgical linear corneal incisions at mid-stromal depth for drug screening purposes [23,36,59–61]. These models have greatly enhanced our understanding of the biochemical and biological mechanisms underlying the development and progression of different corneal diseases, identifying potential molecular targets for therapeutic strategies. For example, the alkali burn model is widely used to mimic severe chemical injury and induces a rapid and robust fibrotic response, making it suitable for studying acute inflammation and scar formation [18,23,35]. However, it may not accurately mimic surgical or chronic fibrotic conditions. In contrast, stromal removal combined with rotating-burr polishing offers a more controlled and reproducible model, better suited for evaluating wound healing and therapeutic interventions in post-surgical fibrosis [59,61]. Including a range of models allows researchers to capture the diverse etiologies and progression patterns of corneal fibrosis, facilitating more targeted and translationally relevant studies.

Nevertheless, the high costs associated with developing and

Table-2
Comparison of pathological mechanisms in different types of ocular fibrosis.

Feature	Corneal Fibrosis	Post-Glaucoma Fibrosis	Post-Cataract Fibrosis	Retinal Fibrosis
Primary Trigger	Injury, infection, surgery, chemical burns [39]	Surgery-induced trauma (trabeculectomy, shunt) [2]	Cataract surgery (capsular rupture, lens epithelial cell migration) [40]	Chronic inflammation, ischemia, retinal detachment, CNV [2,3]
Key Cell Types Involved	Keratocytes, fibroblasts, myofibroblasts, fibrocytes, Immune cells [39,41,42]	Tenon's fibroblasts, myofibroblasts Macrophages, neutrophiles, leukocytes [43,44]	Lens epithelial cells (LECs), myofibroblasts [40,45]	RPE, microglia, Müller glia, retinal endothelial cells, myofibroblasts [1,3]
Major Cytokines & Growth Factors	TGF-β1/2, IL-1, IL-6, IL-8, PDGF [41,46,47]	TGF-β2, VEGF, PDGF, IL-1β, IFN-γ [43]	TGF-β1/2, FGF, CTGF [48,49]	TGF-β1/2, VEGF, IL-6, TNF-α [50]
ECM Remodeling	Increased collagen I/III, fibronectin, α-SMA, vimentin [23,36]	Dense ECM containing collagen, α-SMA, vimentin [44]	Increased fibronectin, collagen, I, III [37],	Epiretinal or subretinal fibrous membrane -fibronectin, collagen I/III, α-SMA, vimentin [38,51]
Fibrosis Outcome	Corneal haze, opacification, vision loss [52]	Surgical failure, bleb scarring [44]	Posterior capsule opacification (PCO) [53]	Vision distortion/loss (e.g., macular puckers, scarring) [54,55]
Therapeutic Challenges	Preventing myofibroblast differentiation, anti-scarring without affecting healing	Controlling fibroblast proliferation and ECM without compromising filtration	Inhibiting LEC proliferation and EMT	Balancing inflammation suppression with neuroprotection and anti-fibrotic action

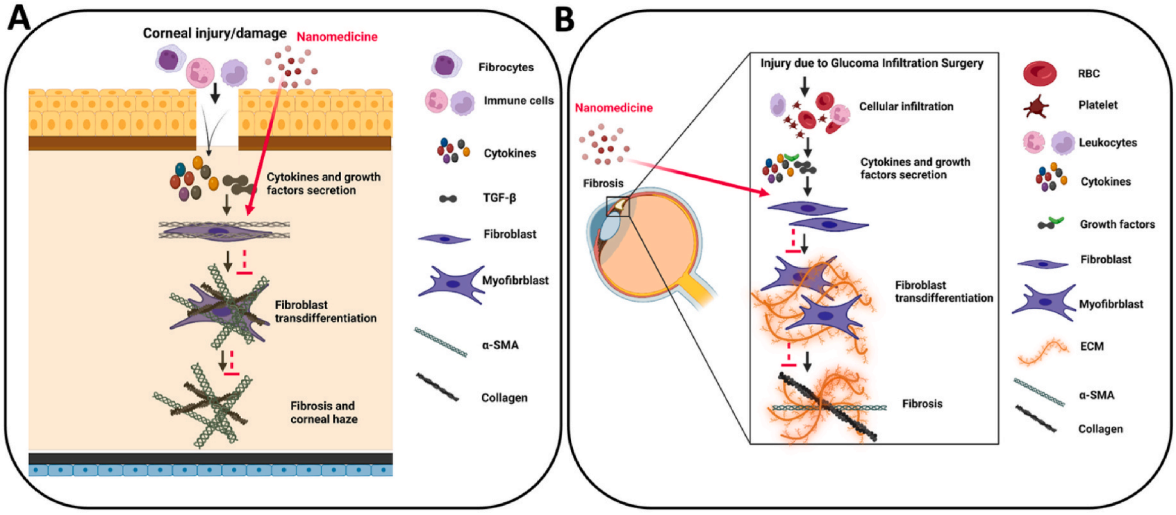

Figure-1. Schematic representation for the treatment of fibrosis by nanomedicine after corneal injury and glaucoma infiltration surgery. (A) Treatment of fibrosis by nanomedicine after corneal injury. The cells from the injured/damaged cornea secrete cytokines and growth factors like TGF-β, which activate fibroblasts to transdifferentiate into myofibroblasts. The myofibroblasts secrete abnormal ECM, leading to fibrosis and corneal haze. The solid black sharp arrows indicate the different stages of corneal fibrosis; the pink sharp and blunt arrows indicate the nanomedicine inhibits corneal fibrosis. (B) Treatment of fibrosis by nanomedicine after glaucoma infiltration surgery. The injury resulting from glaucoma infiltration surgery leads to the infiltration of RBCs and WBCs, which secrete cytokines and growth factors like TGF-β. The secretion of TGF-β leads to fibroblast trans-differentiation into myofibroblasts. The myofibroblasts secrete abnormal ECM and lead to fibrosis and surgical failure. The solid black sharp arrows indicate the different stages of conjunctival fibrosis. The solid pink sharp and dotted pink blunt arrows show the action of nanomedicine inhibiting conjunctival fibrosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

implementing these models, coupled with interspecies physiological differences that influence pharmacokinetic and pharmacodynamic responses, have limited their widespread application. This has driven the shift toward *in vitro* models [59]. Recent progress in corneal *in vitro* fibrosis models has focused on the use of TGF-β, either alone or in combination with other molecules such as ascorbic acid, neuropeptide substance P, interleukin (IL)-6, and IL-8 [46]. These models have shown that interleukins can promote keratocyte-to-myofibroblast differentiation, increase α-SMA expression and matrix contraction, enhance the synthesis and deposition of ECM components, and upregulate pro-fibrotic markers. These cellular processes are vital for understanding corneal scarring mechanisms and serve as valuable tools for screening drugs and nanomedicine-based therapies [46,59,62,63].

Corneal fibrosis can result from infections, injuries, or underlying diseases, obstructing light transmission to the retina and often causing reduced visual acuity. Corneal opacity accounts for approximately 4 % of global blindness cases. At present, corneal transplantation remains the only effective treatment for corneal fibrosis [52]. Various therapeutic agents, including TRAM-34, ascorbic acid, mitomycin-C, pirfenidone, vorinostat, and gene therapies, have been investigated for their potential in treating corneal neovascularization and fibrosis [64]. However, the effectiveness of these treatments is often limited by ocular barriers, such as poor penetration through the corneal epithelium and dynamic barriers like tear turnover and nasolacrimal drainage. These challenges lead to low drug bioavailability, contributing to unwanted side effects and decreased patient compliance [35,56].

2.2. *Fibrosis post glaucoma infiltration surgery*

Glaucoma is characterized by the gradual loss of ganglion cells in the nerve fiber layers, leading to a narrowing of the visual field and eventual blindness. It is often linked to increased intraocular pressure (IOP), which may arise from either excessive production of intraocular fluid or fibrosis in the trabecular meshwork [3]. Glaucoma filtration surgery involves creating a drainage fistula from the anterior chamber to the sub-Tenon space to enhance aqueous outflow and lower IOP.

Additionally, various drainage implants, including subconjunctival, trabecular meshwork, and suprachoroidal pathways, have been clinically explored for managing glaucoma.

In glaucoma filtration surgery, immune cells such as neutrophils, macrophages, and lymphocytes, along with cytokines like IL-1 and Interferon-α2b and growth factors including TGF-β, VEGF (vascular endothelial growth factor), and PDGF, contribute significantly to the fibrotic response [43]. Fibroblasts drive scar formation by inducing crosslinking of collagen type I and elastin, while blood vessels gradually regress. Matrix metalloproteinases (MMPs), produced by macrophages, neutrophils, and fibroblasts, play a critical role in remodeling the ECM and converting granulation tissue into scar tissue [43,65]. A key aspect of fibrosis regulation is the reduction in myofibroblast numbers, as their prolonged presence can result in excessive scarring. Antimetabolites like mitomycin C and 5-fluorouracil are currently the standard adjuvants used in surgery to prevent fibrosis [28,29]. For instance, MMC has been reported to cause shallow anterior chamber (28 %), serous choroidal detachment (22 %), bleb related endophthalmitis (8 %), and complications such as chronic bleb leaks (14.6 %), blebitis (5.7 %), hypotony maculopathy (42.2 %), and scleral thinning or necrosis (rare but vision-threatening) have been documented [28,66]. Additionally, 5-FU has been associated with a range of complications, including epithelial defects (55.5 %), conjunctival wound leaks (36.8 %), suprachoroidal hemorrhage (5.8 %), and rhegmatogenous retinal detachment (2.6 %). Less common but serious adverse events such as endophthalmitis and phthisis (1.9 % each), along with corneal scarring, late-onset bleb leaks, malignant glaucoma, and tractional retinal detachment (1.3 % each), further underscore the urgent need for safer and more targeted anti-fibrotic strategies [67]. To overcome these shortcomings nanomedicine is emerging as an attractive strategy to prevent fibrosis due to glaucoma infiltration surgery.

Several animal models, such as those in rabbits, rats, and mice, have been used for drug and nanomedicine screening in glaucoma filtration surgery. Among these, rabbit models are the most widely employed for *in vivo* testing of drugs and nanomedicines [68–71]. *In vitro* models utilizing human and rabbit tenon fibroblasts, human and rabbit conjunctival fibroblasts, and murine fibroblast cells have also been used to evaluate drugs and nanomedicines [32,72–74].

2.3. Capsular fibrosis post cataract surgery

Posterior capsular opacification is a common long-term complication following cataract surgery and a major cause of non-refractive vision loss [40]. This condition primarily results from the proliferation and migration of residual lens epithelial cells, accompanied by processes such as epithelial-mesenchymal transition, collagen deposition, and lens fiber formation, collectively known as posterior capsular fibrosis (Figure-3) [45].

Posterior capsular fibrosis begins as a wound healing response following cataract surgery, where TGF-β is released by the injured cells, fibroblast growth factor (FGF), leading to the proliferation and migration of residual lens epithelial cells across the posterior lens capsule. These cells undergo epithelial-mesenchymal transition, followed by the deposition of ECM (αSMA, fibronectin, and collagen types I and III) and reduction of expression of vimentin, Snail1/2 and E-cadherin, which leads to fibrosis [40,45,49]. Pharmacological interventions for post-capsular opacification, both *in vitro* and *in vivo*, have been tested using agents such as mitomycin C, H_2O_2, water, EDTA, cinobufagin, and resveratrol [45,75–78]. However, the safety and efficacy of these compounds in the eye still need thorough evaluation, and nanomedicines could be explored as potential therapeutic agents, particularly those targeting the lens.

2.4. Fibrosis during posterior eye diseases

Fibrovascular scarring is a characteristic feature of various posterior eye diseases, including PVR, DR, retinopathy of prematurity, macular degeneration, and neovascular glaucoma. This scarring results from the underlying inflammatory or hypoxia-driven neovascularization and the fibrosis that accompanies these conditions [2,3]. Preventing fibrovascular scarring involves targeting the neovascularization and fibrosis associated with these posterior eye diseases. The activation of retinal pigment epithelium (RPE) cells, Müller glia, microglia, and endothelial cells plays a key role in the fibrosis seen in these conditions (Figure-4) [1,3].

Based on its localization, fibrosis can be characterized into epiretinal and subretinal fibrosis. Epiretinal fibrosis occurs in PVR, DR and ROP (retinopathy of prematurity). Therapeutic approaches investigated for managing subretinal and epiretinal fibrosis are primarily categorized into various classes, including anti-inflammatory, anti-proliferative, anti-neoplastic, anti-growth factor, antioxidant agents, and anti-angiogenic drugs. The anti-inflammatory drugs used are triamcinolone acetonide, dexamethasone; anti-proliferative and anti-neoplastic drugs are 5-fluorouracil (5-FU), daunorubicin, taxol, colchicine, retinoic acid, ribozymes, vincristine; anti-oxidants such as resveratrol, and curcumin and anti-VEGF agents such as pegaptanib, ranibizumab, bevacizumab and aflibercept [13,79,80]. The primary method of administering these drugs is through intravitreal injections. However, due to their short half-lives, multiple administrations are often required. This approach comes with challenges such as the risk of retinal detachment, endophthalmitis, retinal hemorrhage, cataracts, and IOP. Consequently, this regimen can lead to poor patient compliance [13,19].

Though the topical and systemic drug administration are the most acceptable methods for posterior eye diseases, they are hindered by both static and dynamic barriers, leading to low bioavailability [8,13]. Nanomedicine is becoming as emerging possibility for the treatment of epiretinal fibrosis (Figure-4).

3. Nanomedicine for ocular fibrosis

Nanomedicines offer a promising strategy for the treatment of ocular fibrosis by enabling targeted, sustained, and localized delivery of anti-fibrotic agents to specific ocular tissues [21,81,82]. Through the use of nanoparticles, liposomes, polymeric micelles, and dendrimers, therapeutic molecules such as TGF-β inhibitors, siRNAs, and corticosteroids can be efficiently delivered to fibrotic sites while minimizing systemic side effects and improving bioavailability in hard-to-reach ocular compartments [19,35,74,82–84]. These nanoscale carriers can be engineered to overcome ocular barriers, provide controlled drug release, and even respond to microenvironmental cues such as pH or enzymatic activity associated with fibrotic tissue [15,16,21,85]. Emerging preclinical studies have demonstrated the ability of nanomedicines to reduce myofibroblast activation, inhibit epithelial-to-mesenchymal transition, and modulate fibrotic signaling pathways in models of conjunctival, corneal, lens, and retinal fibrosis, supporting their potential as next-generation therapeutics for vision-threatening fibrotic diseases (Table-3).

3.1. Nanomedicine for corneal fibrosis

Nanomedicine is a rapidly advancing field in medical science, offering promising solutions for the prevention and treatment of corneal fibrosis by addressing the limitations of conventional therapies (Fig. 1A). Various nanomedicine platforms, including nanoparticles, liposomes, dendrimers, micelles, nanogels, and extracellular vesicles, have been utilized in experimental *in vivo* and *in vitro* models to assess their antifibrotic potential (Table 3). For example, the topical application of pirfenidone-loaded poly(lactide-co-glycolide) nanoparticles effectively prevented corneal fibrosis in an alkali burn rodent model by inhibiting myofibroblast formation, reducing collagen-I levels comparable to TGFβ-treated control, and accelerating corneal re-epithelialization [23]. Similarly, both albumin nanoparticles and

Table-3
Nanomedicines for ocular fibrosis.

Diseases	Mode of administration	Nanomedicine	Application and mechanism of action
Cornea fibrosis	Topical	Pirfenidone loaded PLGA nanoparticles	Prevents fibrosis by inhibiting myofibroblast formation, decreasing collagen-I levels and corneal haze, and accelerating corneal re-epithelialization in a rodent alkali burn model. [23].
	Topical	Pirfenidone loaded liposomes	Inhibits fibrosis by modulating TGF-β and IL-1β gene expression as compared to pirfenidone in aqueous solution in cornea alkali burn mice model [35].
	Subconjunctival injection	Dexamethasone conjugated PAMAM dendrimer	Shows significant reduction in angiogenesis, inflammation, and corneal opacity and exhibits rapid corneal healing in alkali burn rat model [86].
	Topical	Cabozantinib containing micelles	Enhances bioavailability of the drug by enhanced ocular retention due to their mucoadhesive properties and inhibits corneal neovascularization in mice induced by alkali burn injury [82].
	Subconjunctival injection	Nanohybrid containing bevacizumab-loaded mesoporous silica nanoparticles into a thermogel matrix with anti-inflammation cyclosporine A	Reduces corneal neovascularization by decreasing the CNV area, new vessel length, corneal opacity, inflammation, and abnormal fibrosis through synergistic anti-VEGF and anti-inflammatory effects. The animal model used was rabbit model of CNV induced by in placing sutures in the cornea to stimulate the growth of new blood vessels [87].
	Topical	Extracellular vesicles from corneal stem cells	In a mouse model of corneal injury, where the epithelium, basement membrane, and 10–15 μm of stromal tissue were removed using the AlgerBrush II, microRNA administration inhibited neutrophil infiltration, thereby preventing corneal angiogenesis and fibrosis [88].
Fibrosis after glaucoma infiltration surgery	Topical	Silver nanoparticles	Silver NPs result in reduction of IOP, promote blebs, decrease in fibrosis and myofibroblast formation after glaucoma infiltration surgery in rabbit model because of their anti-microbial and anti-inflammatory properties [71].
	Subconjunctival injection	Homoharringtonine liposomes	Reduces the IOP, inhibited scarring, and promote the formation of filtering blebs in rabbit model of glaucoma infiltration surgery [89].
	Topical	Hyaluronic acid and penetratin modified PAMAM dendrimers loaded with 5-fluorouracil and anti-TGF- β2 oligonucleotide	Inhibits prolonged survival time of filtering blebs and inhibits scar formation by inhibiting myofibroblast proliferation and fibrosis by enhanced cellular uptake in rabbit trabeculectomy models [74].
	Subconjunctival injection	Cyclosporine-A loaded PLGA-PEG-PLGA micelles	Exhibits sustained release of cyclosporin-A and shows antifibrotic properties by inhibition of TGF-β induced myofibroblast differentiation in rabbit model of filtration surgery [81,90].
	Subconjunctival injection	S58 loaded exosomes	Exo-S58 treatment prolongs filtering bleb retention and reduces fibrosis *in vivo* in glaucoma infiltration surgery rat model by binding with TGF-β2 receptor [91].
	Subconjunctival injection	Rapamycin containing injectable hydrogel	The hydrogel enhances autophagy by regulating the PI3K/AKT/mTOR/WIPI2 signaling pathway, which in turn suppresses subconjunctival fibrosis in rat subconjunctival injury model [92].
	Conjunctival implantation	Rosiglitazone loaded poly(3-hydroxybutyric acid-co-3-hydroxyvaleric acid) nanofibers	Prevents scar formation in a rabbit model of glaucoma filtration surgery and minimizes toxicity by exhibiting anti-fibrotic effects through the inhibition of the TGF-β/p38 signaling pathway [73,93].
	Subconjunctival implantation	Core-shell nanofiber polylactic acid and zein to deliver rutin and celastrol in a sequential manner.	It provides a programmed treatment strategy where rutin is released first to suppress inflammation, followed by the sustained release of celastrol to inhibit fibrosis in rat subconjunctival injury model [94].
Posterior capsular opacification (PCO)	Intra ocular lens	5-fluorouracil loaded chitosan nanoparticles coated intraocular lens	Prevents PCO in a rabbit model by inhibiting HLEC proliferation and inducing apoptosis through sustained 5-FU release from chitosan nanoparticle-modified intraocular lenses, without compromising optical transparency or causing significant anterior chamber toxicity [95].
	Subconjunctival delivery	PEG methyl ether-block-poly(ε-caprolactone) (MePEG-PCL) doxorubicin (DOX)-loaded nanoparticles (NPs)	Prevents PCO in a rabbit model by selectively eliminating proliferative lens epithelial cells through sustained release of DOX-loaded MePEG-PCL nanoparticles following a single subconjunctival injection, without inducing toxicity to intraocular structures or impairing retinal function [96].
	Intra ocular lens	Ti3C2 MXene nanosheet-coated IOLs	Prevents PCO in a rabbit model by selectively eliminating proliferative lens epithelial cells through synergistic photothermal therapy and near-infrared (NIR)-controlled rapamycin release from ultrathin Ti_3C_2 MXene nanosheet-coated intraocular lenses, without causing pathological damage to surrounding healthy tissues.
	Intra ocular lens	DOX-incorporated chitosan (CHI) nanoparticle containing polyelectrolyte multilayer with heparin (HEP)	Prevents posterior capsule opacification (PCO) in a rabbit model by inhibiting lens epithelial cell adhesion, proliferation, and migration through sustained release of doxorubicin from chitosan-based polyelectrolyte multilayers on intraocular lenses, without compromising biocompatibility [97].
Fibrosis in posterior eye diseases	Intravitreal injection	Plasminogen kringle-5 loaded nanoparticles	Reduces the fibrosis and the gene expression associated with fibrosis such as TGF-β, CTGF and α-SMA in laser induced epiretinal membrane rat model [98].
	Intraocular	Daunorubicin loaded liposome	Exhibits PVR prevention in experimental rabbit PVR model which can be attributed to inhibition of fibroblastic proliferation and fibroblast collagen synthesis by daunorubicin [99,100].

(*continued on next page*)

Table-3 (*continued*)

Diseases	Mode of administration	Nanomedicine	Application and mechanism of action
	Intravitreal injection	Poly (CEP) micelles	Prevents scar formation in an *in vivo* experimental rabbit PVR model and reduces RPE cell contraction *in vitro* by modulating the Nrf2 signaling pathway [101].
	Intravitreal injections	Dexamethasone palmitate emulsion	Provides sustained delivery of drug without exhibiting any toxicity. Inhibits VEGF-induced vascular permeability diabetic macular edema [102].
	Intravitreal injection	Triamcinolone acetonide conjugated PAMAM-dendrimer	Targets to activated microglia and significantly inhibits neuro inflammation and angiogenesis in oxygen induced ischemic retinopathy mice model [103].

PEGylated albumin nanoparticles loaded with bevacizumab significantly suppressed fibrosis, inflammation, and edema in corneal neovascularization models compared to the free drug [104]. These nanoparticles enhance drug retention on the corneal surface, resulting in superior antifibrotic efficacy over conventional formulations. Additionally, gene therapies utilizing PEI-DNA and gold nanoparticles have been explored to deliver the soluble extracellular domain of TGF–β type II receptor (sTGFβRII), decorin, and BMP-7, effectively reducing myofibroblast formation and fibrosis in *in vitro* corneal fibrosis models. These findings pave the way for innovative nanotechnology-based treatments for corneal fibrosis [105–107].

Liposomes are extensively studied drug delivery systems for treating corneal fibrosis due to their ability to enhance drug penetration, prolong contact time with the ocular surface, and improve the therapeutic efficacy of topical ophthalmic medications, thereby reducing the frequency of administration [35,85]. Liposomal formulations containing pirfenidone, ferrostatin-1, and usnic acid have been investigated for their antifibrotic effects in rodent models of corneal alkali burns [35,108,109]. Pirfenidone-loaded liposomes have shown significant advantages, including reductions in haze size and density, corneal edema, corneal thickness, and inflammatory cell infiltration when compared to pirfenidone in aqueous solution. This liposomal formulation effectively suppresses fibrosis by modulating the gene expression of TGF-β and IL-1β, offering superior outcomes to the aqueous form of pirfenidone [35]. Additionally, ferrostatin-1 encapsulated in liposomes has demonstrated marked inhibition of ferroptosis, inflammation, neovascularization, corneal edema, and fibrosis in alkali burn rodent models compared to the free drug. This enhanced therapeutic effect is largely attributed to improved drug bioavailability provided by the liposomal delivery system [108].

Usnic acid, recognized for its anti-inflammatory and tissue healing properties, is limited by issues such as poor solubility, high toxicity, and difficulty in interacting with cell barriers. However, liposomes encapsulating usnic acid within a gelatin membrane have successfully addressed these challenges and demonstrated promising wound healing effects in chemically-treated rabbit eyes [109]. In a mouse model of alkali burns, cabozantinib-loaded micelles exhibited significant inhibition of angiogenesis, inflammation, and fibrosis. These cationic nanomicelles not only enhanced the drug's bioavailability in the cornea but also demonstrated excellent biocompatibility both *in vitro* and *in vivo* [82]. Additionally, amphotericin-loaded polyhedral oligomeric silsesquioxane micelles showed good biocompatibility and bioadhesiveness, effectively reducing fungal keratitis-induced fibrosis in a mouse model [7].

In an autologous cornea transplantation model, subconjunctival injection of dichloromethylene diphosphonate-loaded liposomes effectively depleted macrophages, resulting in the inhibition of angiogenesis, myofibroblast formation, and inflammation in the cornea [110]. Similarly, subconjunctival injection of dexamethasone-conjugated poly--amidoamine (PAMAM) dendrimers significantly reduced angiogenesis, inflammation, and corneal opacity, while promoting rapid corneal healing in an alkali burn rat model [86]. More recently, extracellular vesicles (EVs) derived from mesenchymal stem cells have shown potential in inhibiting corneal neovascularization, shifting macrophages toward an anti-angiogenic and anti-inflammatory phenotype, and accelerating healing in nonhealing corneas, thus possibly preventing corneal fibrosis [111]. Additionally, EVs that lacked miRNA led to visible scarring and upregulation of genes associated with fibrosis and inflammatory cell infiltration, underscoring the therapeutic potential of EVs from control stem cells in promoting wound healing and reducing fibrosis [88].

Overall, nanomedicines have demonstrated enhanced drug bioavailability, the capacity to bind large therapeutic genes, and potent anti-fibrotic properties, positioning them as promising candidates for therapeutic development in corneal fibrosis. However, further preclinical and clinical trials are required for the successful advancement of nanomedicine in the treatment of corneal fibrosis.

3.2. *Nanomedicine for post glaucoma infiltration surgery*

Nanomedicine is emerging as an alternative with more targeted physiological effects and reduced cytotoxicity (Figure-1B). Various nanomedicine carriers, such as nanoparticles, liposomes, dendrimers, micelles, quantum dots, exosomes, and nanofibers, are being utilized in experimental *in vivo* and *in vitro* glaucoma filtration surgery models (Table-2). In a rabbit model of filtration surgery, the topical administration of silver nanoparticles resulted in sustained reductions in intraocular pressure studied for 6 weeks, leading to blebs with less fibrosis indicated by less α-SMA positive cells and ischemia compared to mitomycin C, suggesting that silver nanoparticles could serve as an appealing alternative to mitomycin C [71]. When paclitaxel-loaded lipid nanoparticles were administered as a subconjunctival injection, they significantly reduced fibrosis, blood vessel formation, and inflammation at the surgical site in rabbits undergoing trabeculectomy, with less conjunctival and ciliary body toxicity compared to mitomycin C. This effect was attributed to the targeting of LDL receptor-overexpressing fibroblasts in inflammatory fibrotic tissue [112]. PEGylated lipid nanoparticles effectively delivered MRTF-B siRNA into conjunctival fibroblasts, reducing fibroblast contraction after a single transfection by targeting ocular fibroblasts via the peptide Y. This nanoformulation holds promise as a therapeutic approach to prevent conjunctival fibrosis after glaucoma filtration surgery [72].

When a disc made of 5-fluorouracil-loaded PLA microspheres was implanted subconjunctivally in the eyes of rabbits undergoing trabeculectomy, it resulted in a reduction in intraocular pressure (IOP), prolonged persistence of the bleb, and a longer-lasting filtration fistula compared to control eyes, with no signs of corneal toxicity [69]. In a rabbit posterior sclerectomy model, subconjunctival injection of homoharringtonine-loaded liposomes reduced IOP, inhibited scarring, and promoted the formation of filtering blebs, providing experimental evidence for its potential clinical use in the future [89]. In another study, subconjunctival injection of liposomal mitoxantrone, an antimitotic drug, in a rabbit sclerectomy model improved surgical outcomes by lowering IOP, with results comparable to mitomycin C [70]. The ocular pharmacokinetics of 5-fluorouracil-loaded liposomes were tested in a rabbit model after subconjunctival injection, showing the highest

bioavailability at 1 and 8 h, with measurable levels remaining up to 96 h. However, the efficacy of this liposomal drug delivery system has not yet been evaluated *in vivo* [113].

Unilamellar cationic liposomes incorporated with Myocardin-Related Transcription Factor (CCG-222740) significantly inhibited ACTA2 gene expression *in vitro* fibroblast cell culture and doubled bleb survival, reduced conjunctival scarring, and showed no local or systemic adverse effects in a rabbit model of glaucoma filtration surgery [32]. The co-delivery of fluorouracil and anti-TGF-β2 oligonucleotide in cationic PAMAM dendrimers, modified with hyaluronic acid and the cell-penetrating peptide penetratin, synergistically inhibited myofibroblast proliferation and achieved comparable fibrosis inhibition to 5-fluorouracil [74]. The PAMAM dendrimers functionalized with glucosamine and glucosamine 6-sulfate, known for their immunomodulatory and anti-angiogenic properties, significantly reduced scar formation in a rabbit model of glaucoma filtration surgery and improved the long-term success of the procedure [114].

Cyclosporin-A, encapsulated within micelles made of poly-(DL-lactic acid-co-glycolic acid)–poly(ethylene glycol)–poly-(DL-lactic acid-co-glycolic acid), underwent gelation after subconjunctival injection. This gel matrix not only enables sustained drug release but also demonstrates antifibrotic properties [81]. Cyclosporin-A inhibits TGF-β-induced myofibroblast differentiation through the degradation of hypoxia-inducible factor-1α (HIF-1α) [90]. Quantum dots, functionalized with cyclo (RGDfC) and covalently attached to their surface, were targeted to cultured trabecular meshwork cells, where they were efficiently internalized through binding to avb3 and avb5 integrins. These cyclo (RGDfC)-quantum dots exhibit a strong affinity for trabecular meshwork cells, while the cyclic RGD peptides reduce CTGF-mediated matrix production and stress fiber formation *in vitro* [115]. Additionally, exosome-mediated delivery of the aptamer S58 significantly reduced cell proliferation, migration, and fibrosis in TGF-β2-induced human conjunctival cells *in vitro*. *In vivo* studies in rats undergoing glaucoma filtration surgery showed that S58-loaded exosomes prolonged filtering bleb retention and reduced fibrosis compared to the direct administration of naked S58 [91]. Poly(3-hydroxybutyric acid--co-3-hydroxyvaleric acid) nanofiber meshes loaded with rosiglitazone, implanted under the conjunctiva, successfully prevented scar formation in a rabbit model of glaucoma filtration surgery, and importantly, it reduced toxicity to the conjunctiva and cornea compared to mitomycin C placement [93]. 5-fluorouracil-loaded chitosan-silk protein nanofibers released the drug over a period of three months, significantly inhibiting fibrosis and myofibroblast formation in a rat subconjunctival injury model, without any ocular toxicity [116]. Although nanomedicines show promise as adjuvants for preventing fibrosis in glaucoma filtration surgery, further safety and efficacy studies in larger animal models are required and should be explored in human trials.

3.3. Nanomedicine for the fibrosis post cataract surgery

The development of polycaprolactone (PCL) nanoparticles represents a significant breakthrough in ophthalmic nanomedicine, especially for addressing lens-related conditions. PCL nanoparticles exhibit enhanced bioavailability in the lens compared to polylactic acid (PLA) and poly(lactic-co-glycolic acid) (PLGA) nanoparticles, making them a promising option for treating capsular fibrosis. PCL particles exhibit comparable physicochemical properties—such as size, surface charge, and mucoadhesiveness to PLA and PLGA nanoparticles, but they are significantly more hydrophilic. However, the precise reason for their higher bioavailability in the lens compared to the other two remains unclear [8]. Additionally, PLGA nanoparticles have shown potential beyond drug delivery by transporting a sumoylation-deficient Prdx6 mutant protein, which boosts cellular defense mechanisms and prevents lens opacity in Shumiya cataract rats. This suggests a novel therapeutic approach to maintain lens transparency and prevent cataract formation. When combined with anti-fibrotic or anti-proliferative drugs, this drug delivery system could offer a comprehensive solution for capsular fibrosis, providing both protective and therapeutic benefits [117]. The use of N-trimethyl chitosan-coated liposomes loaded with Coenzyme Q10 further highlights nanotechnology's potential in ocular treatments. These liposomes effectively penetrate the corneal epithelial barrier, internalize into lens epithelial cells, and significantly reduce oxidative stress, a key factor in cataract development. This makes them a promising intervention for oxidative stress-related conditions affecting the lens [118]. Additionally, liposomal formulations have been shown to enhance the bioavailability of vitamin E and tocotrienol in the lens, which has been linked to the inhibition of cataract progression in diabetic rat models. This underscores the potential of liposomes in delivering essential nutrients and therapeutic agents to the lens, offering a viable strategy for preventing or slowing cataract development [119,120]. Nanoparticles and liposomes targeting lens can be subjected to further research and can be explored for capsular fibrosis (Figure-2A).

3.4. Nanomedicines for retinal fibrosis

Nanomedicines hold significant promise for the treatment of retinal fibrosis, a vision-threatening condition often resulting from injury, chronic inflammation, or degenerative diseases such as PVR, DR, ROP and AMD (Fig. 2B) [21,121–123]. By exploiting the unique properties of nanoscale drug delivery systems such as enhanced permeability, targeted delivery, and controlled release of therapeutic agents can be directed precisely to fibrotic retinal tissues, minimizing off-target effects and improving efficacy [19,21]. These platforms can be engineered to deliver anti-fibrotic molecules, siRNAs, or corticosteroids to modulate fibrotic signaling pathways and inhibit the proliferation of myofibroblasts and extracellular matrix deposition [20,102,124]. Continued development of retina-targeted nanomedicines may offer a transformative approach to managing and potentially reversing retinal fibrosis.

3.4.1. Nanomedicine for proliferative vitreoretinopathy

PVR involves the proliferation, contraction, and fibrotic transformation of cellular membranes within the vitreous cavity, frequently resulting in tractional retinal detachment [125]. In PVR, plasminogen kringle-5 loaded nanoparticles (K5-NP) demonstrated promising results when administered via intravitreal injection in a rat model with laser-induced epiretinal membrane. This intervention significantly reduced fibrosis and the gene expression associated with fibrosis, such as TGF-β, CTGF, and α-SMA. This suggests its potential application in treating fibrosis-related diseases like PVR [98]. The intravitreal injection of liposomal doxorubicin significantly inhibits the severity of experimental PVR and gliosis in rabbit model [121]. Similarly, liposome-encapsulated 5-fluorouracil, when administered intravitreally along with corneal fibroblasts, shows significant reduction in retinal detachment compared to groups injected with fibroblasts alone or fibroblasts and 5-fluorouracil in a rabbit model [124]. Daunorubicin encapsulated in liposomes demonstrated enhanced prevention of PVR when administered as intraocular injection in an experimental rabbit model [99]. Daunorubicin's antifibrotic effect, attributed to inhibition of fibroblastic proliferation and collagen synthesis, contributed to its efficacy [100]. Dasatinib encapsulated in micelles exhibits greater cellular internalization than the free drug and effectively inhibits cell proliferation, adhesion, and migration in ARPE-19 cells, a commonly used *in vitro* model for PVR [126]. Additionally, poly (CEP) micelles exhibit significant inhibition of scar formation in both an experimental rabbit PVR model and an *in vitro* RPE contraction model. This effect was attributed to its action on the Nrf2 signaling pathway, offering a novel therapeutic avenue for PVR [101]. The RGD-modified PLGA nanoparticles when administered intravenously could target to the choroidal neovascularization area, delivered Flt23k and significantly inhibited angiogenesis and subretinal fibrosis in AMD in rodent model [21]. These findings collectively suggest a promising future for nanoparticle and

micelle-based therapies in treating PVR and related fibrotic conditions.

3.4.2. *Nanomedicine for diabetic retinopathy*

In DR, the transition from non-proliferative DR (NPDR) to proliferative DR (PDR) involves increased ischemia, hypoxia, cytokine, and growth factor secretion, ultimately leading to pathological angiogenesis and fibrosis. This progression can result in fibrovascular contraction, retinal detachment, and irreversible blindness [13]. However, current rodent models of DR and ischemic retinopathy primarily exhibit gliosis and vascular complications without developing fibrosis. Therefore, the majority of the nanomedicines developed for DR are focused on gliosis, inflammation, vascular permeability, and retinal neovascularization [19,122].

Topical application of dexamethasone cyclodextrin nanoparticles significantly reduces macular thickness and edema with increase in visual acuity in DR patients [122]. Utilization of protein or peptide nanoparticles has been reported to enhance drug solubility, extend half-life, and reduce toxicity. For instance, PEG-conjugated albumin nanoparticles loaded with apatinib efficiently counteracted VEGF-induced retinal vascular hyperpermeability in both *in vitro* and *in vivo* DR models [127]. Resveratrol-coated gold nanoparticles, possessing anti-oxidant and anti-inflammatory properties, exert their anti-inflammatory effects through the NF-κB signaling pathway, while inhibiting vascular permeability in the retina of DR rats [128]. Functionalization of magnetic nanoparticles with somatostatin analog octreotide, known for its neuroprotective and antiangiogenic properties, exhibits no retinal toxicity and holds promise for DR treatment [129].

In a diabetic retina, topical application of liposomal citicoline formulations demonstrated prevention of glial activation and neural apoptosis. This neuroprotective effect was achieved through down-regulation of synaptophysin and its anti-inflammatory properties by inhibiting the upregulation of NF-κB and TNF-α [130]. Solid lipid nanoparticles or liposomes loaded with siRNA targeting HuR expression proved effective in reducing VEGF and HuR overexpression, mitigating neurodegeneration in DR rats [131].

Emulsions not only increase the stability of the drug but also provide

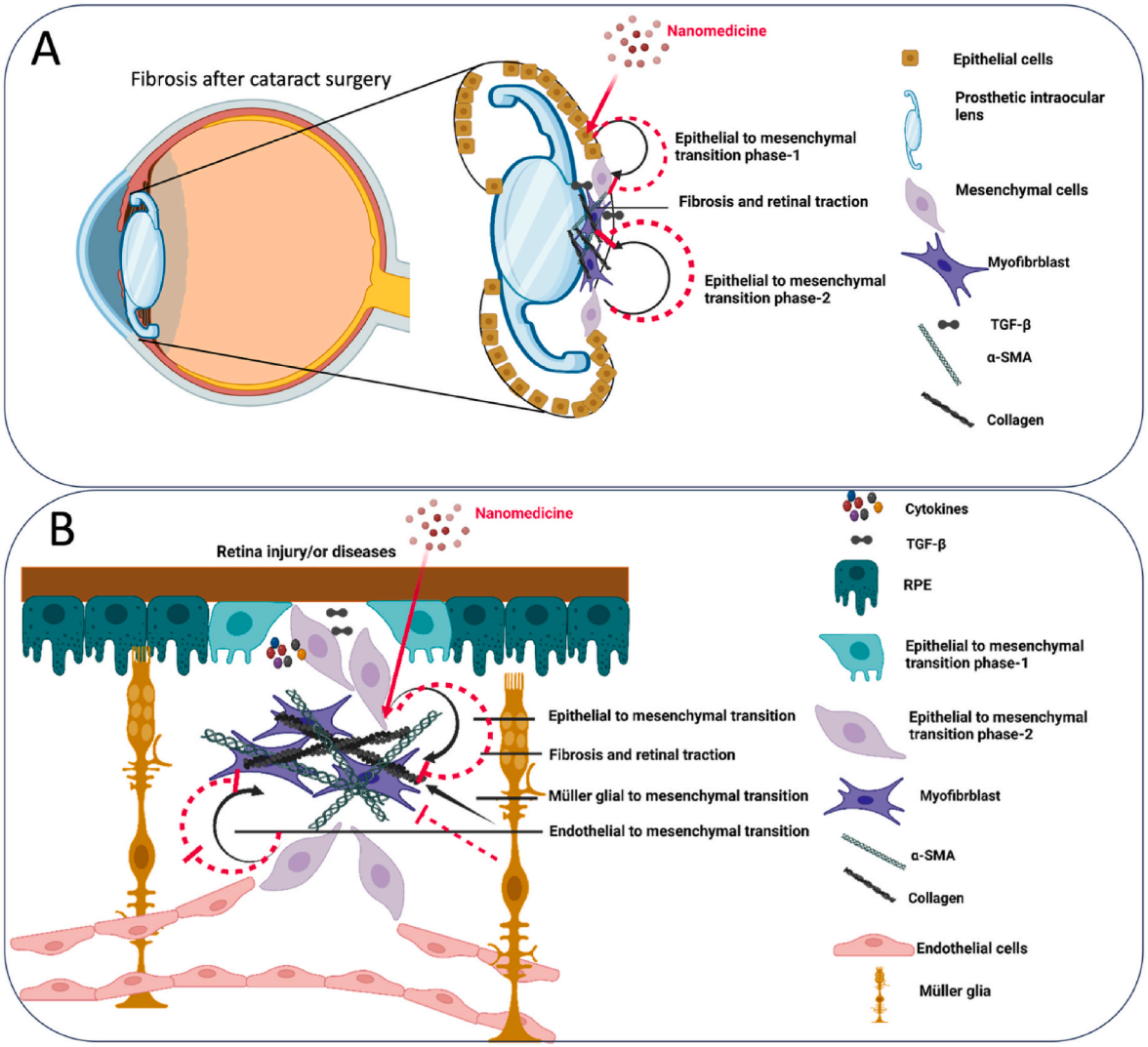

Figure-2. Schematic representation for the treatment of capsular fibrosis by nanomedicine after cataract surgery and post retinal injury or diseases. (A) Treatment of capsular fibrosis by nanomedicine after cataract surgery. The remnant lens epithelial cells under TGF-β secreted by the injured cells proliferate, migrate and undergoes epithelial to mesenchymal transition. The mesenchymal cells differentiate in myofibroblast secrets abnormal ECM resulting capsular fibrosis and opacification represented by solid black sharp arcs. Dotted pink blunt arcs represent the hypothetical action of nanomedicine for inhibiting capsular fibrosis in different phases. (B) Treatment of retinal fibrosis by nanomedicine post retinal injury/diseases/surgery. Nanomedicine application inhibits mesenchymal transition of the various cells in the internal layer after retinal surgery. The solid black sharp arcs indicate stimulation of various cells to mesenchymal transition. The dotted pink blunt arcs indicate inhibition of the transition process by nanomedicine. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

sustained delivery and enhanced ocular bioavailability. Dexamethasone palmitate emulsion, administered via intravitreal injections in various animal models, exhibited sustained drug release without retinal toxicity, effectively reducing VEGF-induced vascular permeability over a 9-month period in macular edema [102]. Similarly, the administration of difluprednate ophthalmic emulsion in diabetic macular edema patients resulted in increased visual acuity and reduced retinal thickness. However, the elevation of ocular pressure poses limitations on its use as an adjuvant therapy [30,132]. Targeting activated microglia, PAMAM-dendrimer-triamcinolone acetonide exhibited significant inhibition of neuroinflammation and angiogenesis in a mouse model of oxygen-induced ischemic retinopathy [103]. In DR rat models, micelles based on an Anti-Flt1 peptide - hyaluronate conjugate notably inhibited angiogenesis in laser-induced choroidal neovascularization (CNV) and vascular permeability [133]. In another study anti-angiogenic peptide modified micelles specifically target avβ3 and inhibits *in vitro* angiogenesis in HUVAC cells [134].

3.4.3. *Nanomedicine for retinopathy of prematurity*

In retinopathy of prematurity (ROP), the presence of hypoxia triggers a sequence of events beginning with pathological angiogenesis, ultimately progressing to fibrosis and retinal detachment at the later stages of the disease. Early intervention methods, such as cryotherapy, laser photocoagulation, and anti-VEGF therapy, are utilized during ROP stages 1–3, characterized by angiogenesis. These interventions aim to enhance visual acuity. However, in the advanced stage of ROP (stage 4), marked by fibrosis, more invasive approaches like vitrectomy or scleral buckling may be employed. It is important to note that such procedures may lead to permanent visual impairment [135].

Vaso-obliteration begins at preterm birth and is marked by delayed or disrupted retinal vascular development, caused by exposure to a relatively hyperoxic environment. This is followed by a subsequent vaso-proliferative stage. To counteract this progression, the intravitreal administration of microparticles encapsulating pro-angiogenic factors (such as VEGF-A165) holds potential. This approach could prove beneficial in preventing and treating ROP at an earlier stage, before the onset of pathological neovascularization [136]. Early-stage delivery of IGF-I might facilitate proper vascular growth and development [137]. Managing ROP during the early stage of proliferative angiogenesis, coupled with measures to forestall fibrosis, could offer an optimal setting for enhancing visual acuity.

In this context, nanomedicine assumes a crucial role. For example,

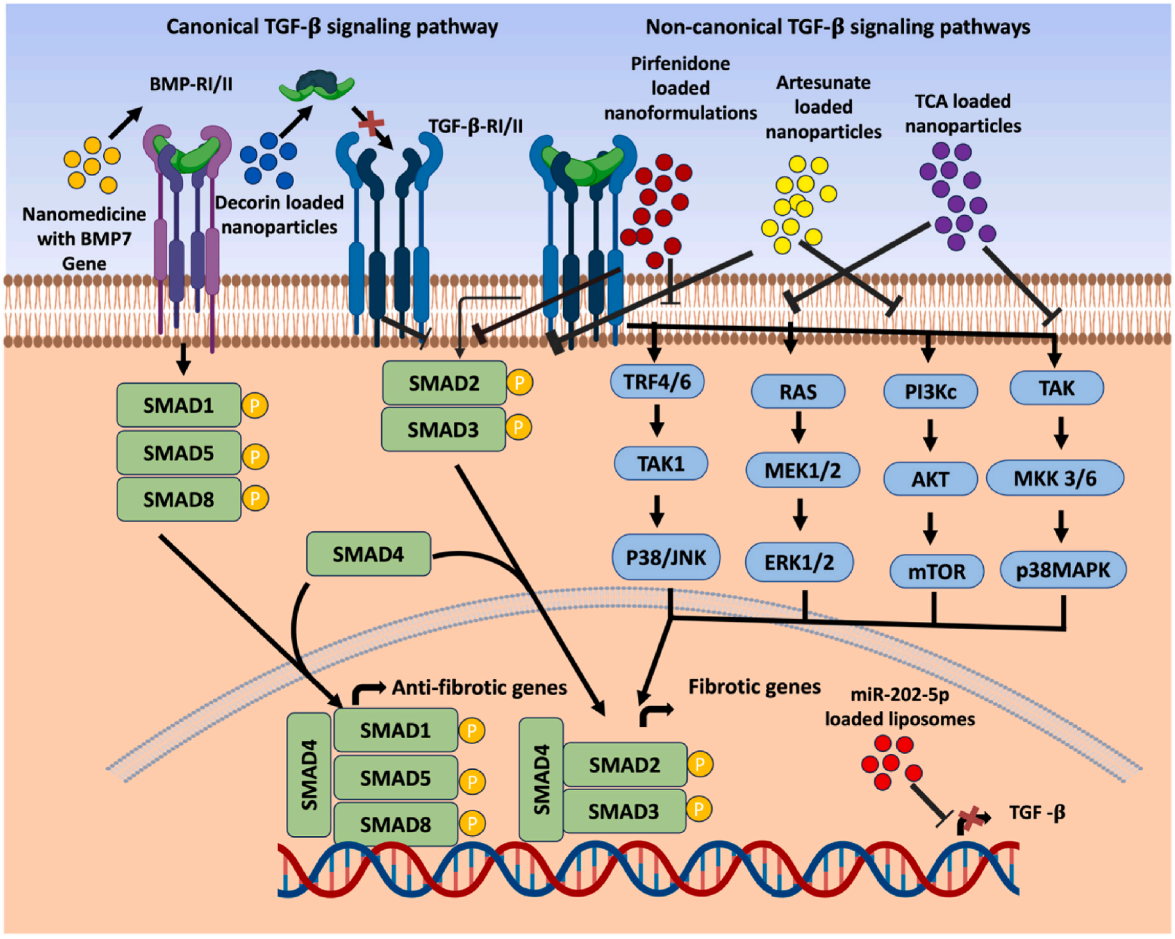

Fig. 3. Schematic illustration showing nanomedicines acting on both the canonical SMAD and non-canonical non-SMAD, TGF-β signaling pathways. The canonical pathway includes TGF-β/SMAD pathway. The non-canonical pathway includes p38MAPK, mTOR, ERK1/2, and p38/JNK signaling pathways. Nanoparticles containing BMP-7 gene inhibit TGF-β/SMAD signaling and inhibit fibrosis. Nanomedicines incorporating decorin inhibit the binding of TGF-β to its receptors, thereby disrupting downstream signaling through both SMAD-dependent and SMAD-independent pathways. Pirfenidone, artesunate, and miR-202-5p-based nanomedicines suppress fibrosis by targeting both SMAD-dependent and SMAD-independent signaling pathways, while TCA-loaded nanomedicines primarily inhibit SMAD-independent signaling. These nanomedicines exert anti-fibrotic effects by downregulating inflammatory cytokines, preventing actin polymerization, and modulating transcription factors involved in extracellular matrix protein expression and mesenchymal differentiation. SMAD: Suppressor of Mothers Against Decapentaplegic, BMP: Bone Morphogenetic Protein, TAK1: Transforming Growth Factor-β Activated Kinase 1, JNK: c-Jun N-terminal Kinase, RAS: rat Sarcoma, MEK: Mitogen-activated protein kinase kinase, ERK: Extracellular Signal-Regulated Kinase, PI3K: phosphatidylinositol 3-kinase, AKT: Protein Kinase B, mTOR: Mammalian Target of Rapamycin.

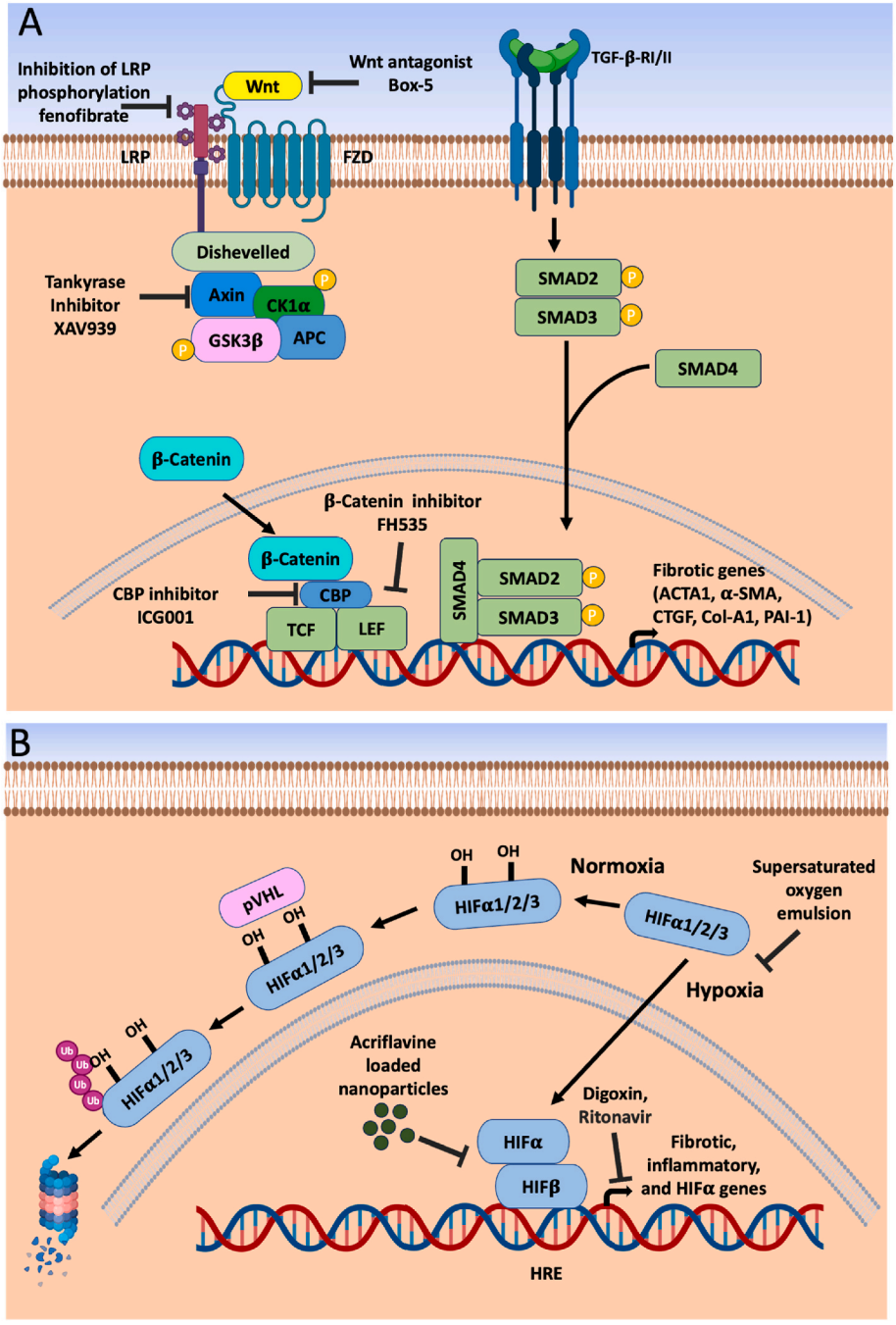

Fig. 4. Schematic illustration showing nanomedicines acting on Wnt and HIF-α signaling pathway. (A) Nanomedicines acting on Wnt signaling pathway: Wnt proteins initiate the Wnt/β-catenin signaling cascade by binding to the FZD receptor, which subsequently forms a complex with the co-receptor LRP5/6 leading to the inhibition of the β-catenin destruction complex through the phosphorylation and inactivation of GSK-3β and CK1α, two key negative regulators. β-catenin is translocated into the nucleus and promotes the transcription of various fibrotic genes. In parallel, TGF-β1 activates its canonical pathway by inducing phosphorylation of SMAD2 and SMAD3, which then associate with SMAD4 and translocate to the nucleus. This SMAD complex further enhances the expression of pro-fibrotic genes and their corresponding proteins, contributing synergistically to fibrotic progression. Fenofibrate acts by inhibition of LRP phosphorylation, Wnt antagonist inhibits Wnt5a signaling and inhibits Wnt5a-mediated Ca2+ release, Tankyrase inhibitors downregulate β-catenin stabilization by inhibiting the poly-ADP-ribosylating enzyme Tankyrase, CBP inhibitor blocks the interaction between CBP and β-catenin preventing transcription of Wnt target genes, β-catenin inhibitor antagonizes β-Catenin/TCF mediated transcription. LRP: Low-density lipoprotein receptor-related protein, FZD: Frizzled, CK1α: casein kinase 1α, GSK3β: glycogen synthase kinase 3β, Axin: axis inhibition protein, APC: adenomatous polyposis coli, (B) Nanomedicines acting on Wnt signaling pathway: Under normoxic conditions, HIFα undergoes hydroxylation at specific proline residues by PHDs, enabling recognition by pVHL, which tags HIFα for polyubiquitination and subsequent degradation via the 26S proteasome. In contrast, under hypoxic conditions, HIFα is no longer hydroxylated, allowing it to escape degradation. It becomes stabilized, translocated to the nucleus, and dimerizes with its partner HIF1β, thereby activating the transcription of various hypoxia-responsive target genes. Supersaturated oxygen emulsions alleviate hypoxia by increasing oxygen availability in tissues. Acriflavine-loaded nanoparticles inhibit HIF-1α and HIF-2α by directly binding to their PAS-B domains, thereby blocking their dimerization with HIF-1β and preventing transcriptional activation. Additionally, compounds such as digoxin and ritonavir suppress HIF-α expression by inhibiting its transcription.

gold nanoparticles have been shown to inhibit retinal neovascularization in a rat model of retinopathy of prematurity (ROP). Additionally, these nanoparticles successfully suppressed VEGF-induced angiogenesis in retinal microvascular endothelial cells *in vitro* by blocking cell proliferation, migration, and the formation of capillary-like structures, which are driven by VEGFR-2 auto-phosphorylation triggered by VEGF [123]. Liposomal superoxide dismutase delivery in an ROP rat model was observed to increase retinal superoxide dismutase activity and reduce oxygen-induced vaso-attenuation, evident through enhanced vessel density and reduced avascular area [138]. At advanced vascular proliferative stages, anti-VEGF therapy's side effects often include fibrosis and retinal detachment. Hence, co-delivering anti--fibrotic agents alongside anti-angiogenic agents may enhance efficacy [139].

3.4.4. Nanomedicine for age-related macular degeneration (AMD)

In AMD, the aged and non-functional RPE lead to deposition of drusen which contains angiogenic lipids and damaged proteins, which finally results thickening of Bruch's membrane. The thickening of Bruch's membrane causes hypoxia followed by pathological angiogenesis, vascular hemorrhage, abnormal wound healing responses and finally to subretinal fibrosis [3]. The advancement in nanomedicine may open up new strategies for the abnormal angiogenesis and subretinal fibrosis. Luo et al. reported that the intravenous administration of RGD-conjugated PLGA nanoparticles encapsulated with Flt23k intraceptor plasmid could be targeted to neovascular lesions in the retina and regresses CNV that suppressed subretinal fibrosis in primate and murine AMD models [140]. The intravitreal injection of PEGylated liposome loaded with triptolide significantly inhibits laser CNV induced subretinal fibrosis by inhibition of infiltration of M2 macrophage, VEGF protein secretion, and molecules associated with TGF-β signaling pathway [141]. The dendrimer-triamcinolone acetonide ameliorates CNV by limiting macrophage infiltration to pathological area, inhibiting cytokines and growth factors after systemic administration [142]. Further it is reported that triamcinolone also acts on TGF-β signaling pathway [143], therefore, these dendrimer-trimconoloane acetonide may be effective for subretinal fibrosis in AMD.

The development of nanomedicines for posterior eye diseases is still in a naïve stage because of unavailability of proper animal model. While various animal models have been employed to investigate fibrotic pathologies in the posterior segment, they often fall short of replicating the full spectrum of human disease [26,144]. Most current models primarily reflect acute injury or short-term responses rather than the chronic, progressive nature of fibrosis in human conditions. For instance, models based on mechanical injury or chemical induction may trigger temporary gliosis or localized membrane formation, but they typically lack sustained inflammation, pathological neovascularization, and progressive extracellular matrix (ECM) remodeling that contribute to irreversible tissue scarring [101,121,144–146]. These human features are driven by complex crosstalk among retinal cells, persistent immune activation, and dysregulated growth factor signaling processes that are either absent or transient in many rodent or rabbit models [50,144,146]. Consequently, preclinical evaluations of anti-fibrotic nanotherapies may not accurately predict long-term therapeutic efficacy or safety in clinical settings. Developing animal models that better recapitulate these chronic fibrotic mechanisms is essential to bridge the translational gap and advance nanomedicine-based interventions toward clinical success.

4. Nanomedicines targeting signaling pathways in ocular fibrosis

Nanomedicines targeting signaling pathways in ocular fibrosis offer a promising therapeutic approach to halt or prevent fibrotic progression in blinding eye diseases. By using nanoscale drug delivery systems, these therapies can selectively modulate key fibrogenic pathways such as TGF-β, Wnt/β-catenin, NFkB, MTRF/SRF, and HIF-1α signaling directly within ocular tissues [20,32–34,147].

4.1. Nanomedicine targeting TGF-β canonical and non-canonical signaling pathways

TGF-β signaling pathway is a central regulator of myofibroblast differentiation and ECM deposition in ocular tissues [43,49,50,147]. Upon binding to its ligand, TGF-β activates it signaling pathway by forming a receptor complex where TGFβRII phosphorylates and activates TGFβRI. Activated TGFβRI then phosphorylates Smad2/3, which forms a complex with Smad4 and translocates to the nucleus to induce transcription of profibrotic genes such as α-SMA, type I collagen, and TIMPs. In contrast, BMP-7, another member of the TGF-β superfamily, activates Smad1/5/8, which also forms a complex with Smad4 and enters the nucleus to promote antifibrotic gene expression by antagonizing Smad3 activity (Fig. 3) [148]. The antifibrotic efficacy of nanomedicine platforms largely stems from their ability to interfere with either canonical or non-canonical TGF-β signaling pathways involved in ocular fibrotic remodeling (Fig. 3) [23,35]. Pirfenidone-loaded nanoparticles and liposomes suppress TGF-β1 induced α-SMA, collagen-I synthesis *in vitro* and fibrosis *in vivo* probably by both TGF-β/SMAD and p38/JNK signaling pathway [23,35,50,149,150]. The chitosan-encapsulated artesunate nanoparticles exert their antifibrotic effects by modulating key signaling pathways involved in fibroblast activation and proliferation. Specifically, they suppress the TGF-β1/SMAD, PI3K/Akt, and Cyclin D1–CDK4/6 pathways which are critical mediators of fibrosis and cell cycle progression. By downregulating these pathways, chitosan-encapsulated artesunate nanoparticles inhibit myofibroblast differentiation, reduce ECM protein expression, and limit inflammatory cytokine release, ultimately preventing postoperative scarring and improving glaucoma filtration surgery outcomes [151]. Similarly, decorin-loaded nanoparticles antagonize TGF-β signaling by sequestering active TGF-β ligands, while gene delivery of BMP-7 restores the balance between profibrotic (TGF-β) and antifibrotic (BMP) cues [106,152]. In another study, plasminogen kringle-5–loaded nanoparticles (K5-NPs) significantly downregulate TGF-β, CTGF, and α-SMA expression in epiretinal membranes, potentially by disrupting the autocrine TGF-β loop and blocking myofibroblast formation in PVR [98]. Exosome containing miR-202-5p secreted from ARPE-19 cells, targets TGF-β2 regulates the TGF-β/SMAD signaling pathway and reduce the growth, tube formation, and migration of human umbilical vein endothelial cells in DR. In addition, it suppresses the EMT, indicating usefulness of exosome-based strategies for fibrosis due to DR [153]. Triamcinolone acetonide-loaded nanoparticles alleviate PVR and PDR by suppressing TGF-β2-induced phosphorylation of Smad2, ERK1/2, and p38 MAPK. Additionally, TA significantly reduces TGF-β2-stimulated VEGF expression by inhibiting p38 signaling activity [19,154]. Together, these findings underscore the therapeutic potential of nanomedicine-based interventions to modulate TGF-β signaling and its associated pathways, offering promising antifibrotic strategies for the treatment and prevention of ocular fibrotic diseases.

4.2. Nanomedicine targeting Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway (Figure-4A) plays a pivotal role in the pathogenesis of ocular fibrosis by regulating EMT, fibroblast proliferation, cell migration, and ECM remodeling [155]. Aberrant activation of this pathway has been implicated in fibrotic disorders of the sclera, conjunctiva, lens capsule, and retina where it often acts synergistically with TGF-β signaling to amplify fibrogenic responses [155–158]. Inhibitors such as FH535 (β-catenin inhibitor), Box5 (Wnt5a antagonist), and fenofibrate effectively attenuate subretinal fibrosis, XAV939 inhibits posterior lens epithelial cell fibrosis, ICG-001 effectively inhibited cell proliferation and migration in TGFβ1-treated in human conjunctival fibroblast by disrupting this signaling axis, offering promising therapeutic potential in ocular fibrosis (Fig. 4A) [155–157,

159]. Nanomedicine-based strategies offer a promising approach to modulate Wnt/β-catenin signaling with high specificity and reduced systemic toxicity. For example, fenofibrate loaded solid lipid nanoparticles or PLGA nanoparticles have been used to provide sustained drug release, enhance drug solubility, and bioavailability to ocular tissues [33,160]. Hence, nanomedicine platform Wnt/β-catenin signaling opens up a new avenue for ocular fibrosis.

4.3. Nanomedicine targeting hypoxia-inducible factor-alpha (HIF-α) signaling pathway

Nanomedicine targeting the HIF-α signaling pathway (Fig. 4B) represents an emerging strategy for combating ocular fibrosis, as HIF-α activation under hypoxic conditions drives EMT transition, fibroblast proliferation, migration, myofibroblast differentiation, and ECM remodeling [161–163]. Several nanomedicine approaches have been developed to modulate HIF-α activity and prevent fibrotic progression in ocular tissues. For example, a supersaturated oxygen nanoemulsion alleviates intraocular hypoxia, decreases cell death, limits leukocyte infiltration, suppresses the production of inflammatory mediators, and inhibits hypoxia-inducible factor 1-alpha (HIF-1α) signaling, thereby accelerating the restoration of normal tissue integrity during the wound healing process following chemical injury [164]. Additionally, acriflavine, an HIF-1α inhibitor that blocks HIF dimerization, has been shown to delay corneal opacity and neovascularization following alkali burn injury, as well as reduce the expression of the myofibroblast marker α-SMA and fibronectin in a mechanical injury cornea model, highlighting its potential as a promising target for controlling corneal fibrosis [165]. Additionally, nanoparticles loaded with acriflavine effectively suppressed choroidal neovascularization after a single suprachoroidal injection [34]. Besides this, digoxin a glycosides and ritonavir an anti-viral drug inhibit HIF-1α mRNA expression, 32-134D inhibits HIFα accumulation, shows potential for nanomedicine development for ocular fibrosis (Fig. 4B) [145,166,167]. These examples highlight how nanomedicine can offer precise, localized control over HIF-α signaling, opening new therapeutic avenue for fibrotic ocular diseases with improved safety and effectiveness.

4.4. Nanomedicine targeting NFkB signaling pathway

Persistent activation of NF-κB has been implicated in the progression of ocular fibrotic diseases, including PVR, epiretinal membrane of DR, fibrosis after glaucoma surgery, and corneal scarring [20,146,168,169]. Nanoparticle-based delivery systems offer the advantage of targeted, sustained release of NF-κB inhibitors, siRNAs, or anti-inflammatory drugs directly to affected ocular tissues, minimizing off-target effects and enhancing therapeutic efficacy [19,20,170]. For example, cationic nano-copolymers delivering IKKβ-targeting siRNA significantly improved bleb survival and reduced subconjunctival scarring in a monkey model of glaucoma filtration surgery. Unlike MMC-treated eyes, siRNA-treated eyes maintained healthy conjunctival epithelium, suggesting enhanced safety and efficacy [20]. Similarly, a single intravitreal injection of cerium oxide nanoparticles in P28 vldlr−/− mice sustained regression of pathological neovascularization, reduced vascular leakage, and inhibited apoptosis for up to six weeks. These effects were mediated through down-regulation of the ASK1-P38/JNK-NF-κB signaling pathway and restoration of photoreceptor gene expression [171]. By precisely modulating NF-κB signaling, nanomedicine approaches can potentially interrupt the vicious cycle of inflammation and fibrosis, promoting tissue repair and preserving ocular structure and function. Continued advances in nanoparticle design and a better understanding of ocular fibrotic mechanisms will be critical for translating these strategies into effective clinical therapies.

4.5. Nanomedicine targeting MRTF/SRF signaling pathway

Nanomedicine offers a promising approach for targeting the myocardin-related transcription factor (MRTF) and serum response factor (SRF) signaling pathway, which plays a crucial role in the development of ocular fibrosis by promoting myofibroblast activation, MMP regulation, and ECM deposition (Fig. 5A) [172]. Recent strategies have focused on delivering small molecule inhibitors, siRNAs, or antisense oligonucleotides using nanoparticle-based systems to enhance therapeutic efficacy and tissue-specific delivery while minimizing systemic side effects. For instance, lipid nanoparticles encapsulating MRTF-B siRNA, have been investigated to suppress trabecular meshwork contractility and proliferation, demonstrating reduced α-SMA expression and collagen-II expression in TM cells and shows promise to prevent fibrosis in post-glaucoma filtration surgery [173]. Similarly, lipid-based nanoparticles carrying CCG-222740, a potent MRTF/SRF pathway inhibitor, have been explored to inhibit conjunctival scarring, enhanced bleb survival in glaucoma infiltration surgery [174]. Other compounds, such as CCG-203971 and CCG-1423, which target the Rho/MRTF/SRF signaling pathway and have shown efficacy in reducing liver and lung fibrosis, present promising candidates for nanomedicine-based approaches in treating ocular diseases [175,176]. These studies highlight the potential of nanomedicine to modulate pathogenic signaling pathways like MRTF/SRF in ocular fibrosis, offering targeted, sustained, and minimally invasive treatment strategies.

4.6. Nanomedicine targeting cell division

Nanomedicines targeting cell division represent a promising approach for managing ocular fibrosis, a major complication following surgeries such as glaucoma filtration or cataract procedures (Fig. 5B). Nanomedicine containing antiproliferative agents like mitomycin C and 5-fluorouracil (5-FU) have long been used to inhibit fibroblast proliferation and scar formation in ocular tissues specifically in glaucoma infiltration surgery [31,74]. Mitomycin C is an alkylating agent that becomes activated under reductive intracellular conditions, leading to the formation of DNA cross-links, particularly at guanine bases. These interstrand and intrastrand cross-links inhibit DNA replication and transcription, ultimately triggering cell cycle arrest in the G1 and S phases and inducing apoptosis in rapidly dividing cells like myofibroblast [177]. 5-Fluorouracil, on the other hand, is a pyrimidine analog that inhibits thymidylate synthase, a critical enzyme for the synthesis of thymidine monophosphate (dTMP), which is required for DNA replication. Its active metabolite, 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP), forms a stable complex with thymidylate synthase and 5, 10-methylenetetrahydrofolate, leading to “thymineless death” in proliferating cells [178]. This effect on DNA metabolism contributes to the inhibition of fibroblast proliferation in the subconjunctival space, helping reduce fibrosis and bleb failure after filtering surgeries. Similarly, paclitaxel inhibits ocular fibrosis by stabilizing microtubules, thereby disrupting mitotic spindle formation and arresting fibroblast proliferation. This inhibition of cell division reduces myofibroblast differentiation and extracellular matrix deposition, key contributors to fibrotic scarring in ocular tissues [112,179]. Exosomes loaded with the anti-proliferative agent daunorubicin and the anti-inflammatory drug dexamethasone have shown promising effects in reducing proliferative vitreoretinopathy (PVR). Daunorubicin exerts its action by targeting the G2-phase-specific enzyme topoisomerase II, leading to cell cycle arrest at the G2 phase [22].

4.7. Nanomedicine targeting oxidative stress related signaling pathway

Nanomedicine offers a promising strategy to target oxidative stress-related signaling pathways involved in ocular fibrosis (Fig. 6). Oxidative stress is a key driver in the progression of fibrotic diseases of the eye, such as PVR, PDR, glaucoma infiltration surgery, and corneal fibrosis

[180–183]. Nanoparticles can be engineered to deliver antioxidants or modulators of oxidative signaling directly to fibrotic ocular tissues, enhancing therapeutic efficacy while minimizing systemic side effects. For example, Hydrogel containing cerium oxide nanoparticles and siRNA for TGF-β have demonstrated potent antioxidant activity by scavenging ROS and reducing progression of corneal fibrosis in pre-clinical models [184]. Similarly, poly(ethylene glycol) (PEG), poly (propylene glycol) (PPG), and poly(ε-caprolactone) (PCL), a bio-functional polymer prevents retinal scarring in a rabbit model of PVR by suppressing RPE cell EMT, proliferation, and migration through clathrin-mediated internalization and NRF2 pathway activation. This study offers a promising non-surgical strategy to modulate aberrant wound healing after retinal detachment [101]. Another approach utilizes VAS2870 a NOX4 inhibitor, which is a major source of ROS, to inhibit fibrosis in experimental models of PVR, which can be developed as nanoformulation [185]. By precisely modulating oxidative stress pathways, nanomedicine strategies hold potential for preventing or reversing fibrosis and preserving vision in ocular diseases. Collectively, these findings emphasize the potential of nanomedicine platforms to selectively interfere with molecular pathways that orchestrate ocular fibrosis. Advancing these formulations toward clinical application will require deeper investigation into ocular biodistribution, immune response, and long-term retinal safety.

4.8. *Nanomedicine targeting metabolic pathway*

Nanomedicine targeting metabolic pathways offers a novel and promising approach for treating ocular fibrosis by disrupting the energy and redox homeostasis that drives fibrotic cell activation and ECM deposition [186,187]. RPE undergo metabolic reprogramming such as enhanced glycolysis, defective fatty acid oxidation, and mitochondrial dysfunction during EMT transition and fibrosis [186,187]. Vitamin

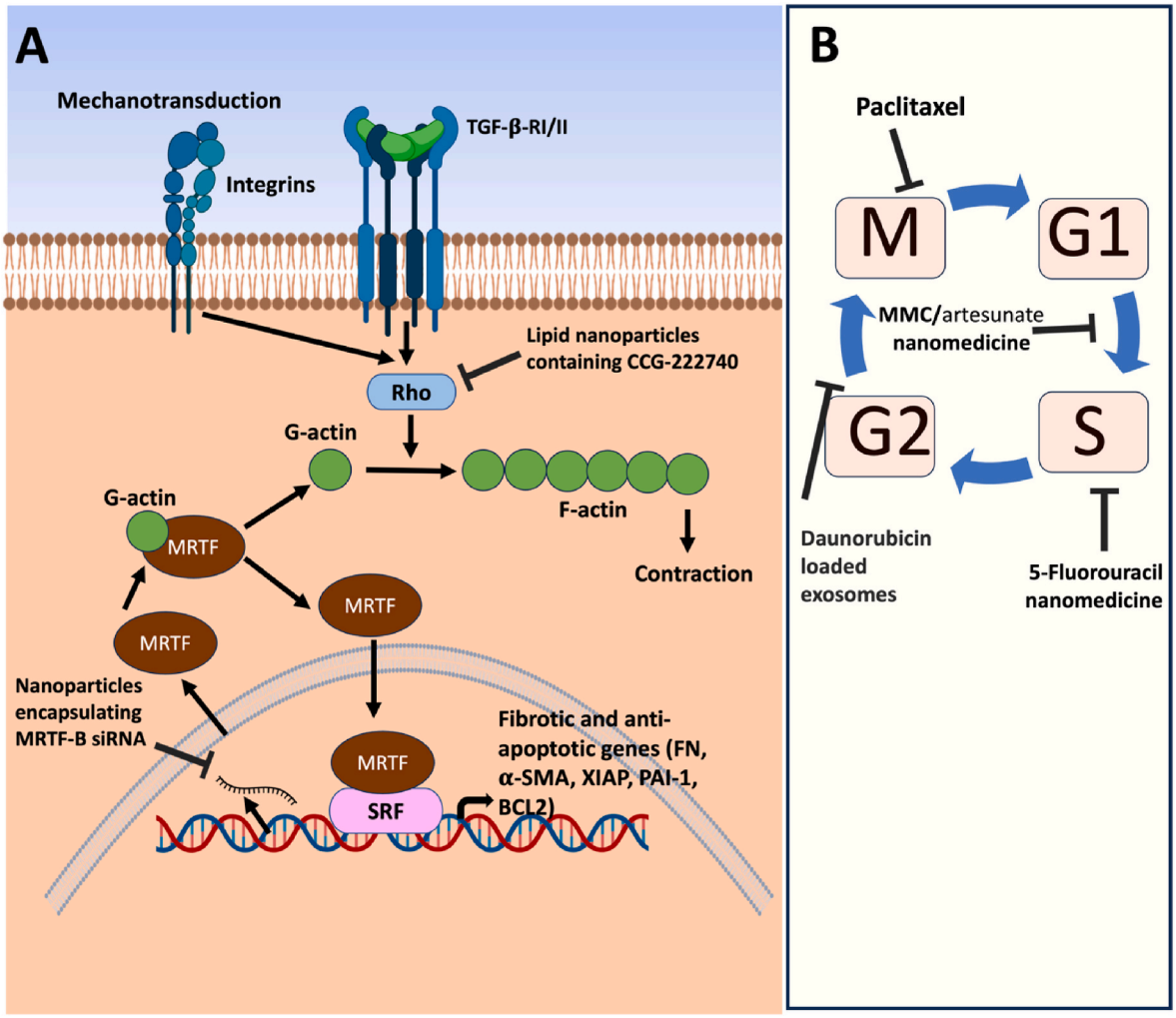

Fig. 5. Schematics of nanomedicines acting on Rho/MRTF/SRF signaling pathway and cell division. (A) Fibroblast-to-myofibroblast differentiation is driven by TGF-β signaling and mechanotransduction through integrins, primarily mediated by the Rho/MRTF/SRF pathway. These signals trigger the polymerization of G-actin into F-actin, leading to the formation of contractile fibers, a hallmark of myofibroblasts. As F-actin forms, the transcription factor MRTF, which is normally bound to G-actin in the cytoplasm, is released and translocated to the nucleus, where it activates the expression of various pro-fibrotic and anti-apoptotic genes. Lipid nanoparticle-based delivery of the Rho-kinase inhibitor has demonstrated anti-fibrotic activity by interrupting this pathway, while nanomedicines carrying MRTF-B siRNA degrade MRTF-B mRNA, thereby preventing the upregulation of fibrotic gene expression. (B) Nanomedicines act on different stages of cell division to inhibit ocular fibrosis. Mitomycin C, an alkylating agent, is activated under reductive intracellular conditions and forms DNA cross-links at guanine residues, which block DNA replication and transcription, leading to cell cycle arrest in the G1 and S phases. In the case of 5-fluorouracil (5-FU), it is metabolized in mammalian cells to fluorodeoxyuridine monophosphate (FdUMP), which binds irreversibly to thymidylate synthase (TS), inhibiting the production of deoxythymidine monophosphate (dTMP) a nucleotide essential for DNA synthesis and repair—thereby inducing cytotoxicity. Daunorubicin acts during the G2 phase by inhibiting topoisomerase II, an enzyme required for DNA unwinding, which results in G2-phase arrest. Meanwhile, paclitaxel binds to β-tubulin, stabilizing microtubules and preventing their depolymerization, which halts cell division by arresting the cell cycle at the G2-M phase.

A-decorated PEG-PCL polymeric micelles loaded with camptothecin selectively target activated hepatic stellate cells, inhibiting HIF-1α--driven glycolysis and reversing their myofibroblastic phenotype to suppress liver fibrosis. This glycolysis-targeted nanotherapy holds promise for treating ocular fibrosis specifically retinal fibrosis by modulating fibrotic cell metabolism in the eye [188]. Similarly, ceria nanoparticles (CeNP-PEG) ameliorate renal fibrosis by restoring mitochondrial function, reducing ROS, and reversing metabolic reprogramming, including downregulation of glycolysis and EMT markers. These findings suggest CeNP-PEG's potential as a redox-modulating nanotherapy for ocular fibrosis, where mitochondrial dysfunction and oxidative stress also drive fibrotic progression [189]. These emerging strategies, although primarily explored for other fibrotic diseases, hold great promise for localized, sustained, and safer interventions in ocular fibrotic disorders.

5. Comparative analysis of nanomedicines for treating ocular fibrosis

Various nanotechnology platforms have been investigated for the treatment of ocular fibrosis, each offering specific advantages and limitations. Polymeric nanoparticles (PLGA, PLA or PCL) provide controlled and sustained drug release, and ocular tissue penetration, with good biodegradability, but may exhibit limited drug loading capacity [14,19,23,34]. Lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles, are advantageous due to their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs, though they can suffer from instability and short time retention ocular tissues [35,112,130,190,191]. Dendrimers offer precise molecular architecture and surface functionalization for targeted delivery; however, concerns remain regarding their cytotoxicity and complex synthesis [74,86,103,114,192]. Nanomicelles are particularly suitable for solubilizing poorly water-soluble anti-fibrotic drugs, penetrating ocular barriers, may act as anti-scarring agent, yet they may be prone to disassembly under physiological dilution and exhibit limited stability [82,101,126,193]. Inorganic nanoparticles (e.g., gold, silica, cerium oxide) enable multifunctional applications such as imaging and therapy, but their long-term safety, biodegradation, and ocular retention remain under investigation [18,87,106,123,128]. Hydrogels, especially in situ forming or stimuli-responsive systems, are highly promising for localized, prolonged drug delivery to ocular tissues, minimizing systemic exposure and improving patient compliance; however, challenges such as burst release, mechanical strength, and scalability must be addressed [83,92,184]. While each nanotechnology brings unique benefits, a thorough understanding of their limitations is essential to optimize therapeutic outcomes and facilitate clinical translation for ocular fibrotic diseases.

6. Challenges in the clinical translation of nanomedicine for ocular fibrosis

Clinical translation of nanomedicine for ocular fibrosis faces several significant challenges. First, achieving targeted and sustained drug delivery to fibrotic ocular tissues such as the conjunctiva, cornea, or retina is difficult due to anatomical barriers (e.g., blood ocular barrier, blood-retinal barrier, tear turnover) and limited vascular access [8,15,16]. Second, the pathological microenvironment of ocular fibrosis, characterized by chronic inflammation, ECM remodeling, and altered cellular metabolism, demands nanocarriers that can respond dynamically and release therapeutics at the right time and site [2,3,23,186,187]. Third, ensuring biocompatibility, minimizing ocular toxicity, and inflammation are critical yet complex, given the eye's immune-privileged but sensitive nature [26,85,194]. Additionally, translating preclinical success into human models is hindered by the lack of physiologically relevant animal models and differences in fibrosis progression between species [26,195]. Regulatory hurdles, manufacturing scalability, and long-term safety data also pose barriers to advancing nanomedicines from bench to bedside in ophthalmic fibrosis [26].

7. Future prospective and concluding remarks

Ocular fibrosis is an irreversible condition that can ultimately result in blindness. At present, there are no approved therapies specifically targeting ocular fibrosis. The limited adjuvant treatments available, such as antimetabolite drugs, carry a high risk of severe, potentially blinding side effects. Therefore, there is a critical need to develop new therapeutic approaches, including the advancement of nanomedicine-based delivery systems, to enhance the safety and efficacy of existing drugs and reduce their associated toxicity in the treatment of ocular fibrosis.

Tissue engineering strategies help to develop *in vitro* disease models of corneal fibrosis and related diseases. The nanomedicine which can directly and indirectly modulate inflammatory, fibrotic, and angiogenic processes at the optimal time, dosage, and locality with reduced toxicity could result in more favorable outcomes. Here we discuss the challenges to the development of nanomedicine for ocular fibrosis, the prospects of nanomedicine development, and recent advancements in the ocular fibrosis model for screening of nanomedicine.

7.1. Toxicity associated with the current adjuvants

The antimetabolites such as mitomycin-C and 5-fluorouracil are associated with toxicity, which can be overcome by encapsulating these drugs in nanostructures such as nanoparticles, liposomes, micelles, emulsions and dendrimers. The nanomedicine can reduce the toxicity as follows-(I) the nanostructures protect the drugs from complete exposure of drug at a time, (II) the sustained and slow delivery overcome the toxicity (III) the targeted delivery of drugs in close proximity to the required cells/tissue minimize the toxicity, (IV) the drug release and degradation rate of nanomedicine can be designed to make same duration and hence the bioaccumulation of ghost nanoparticles will not remain in the eye and may not cause any materials-induced toxicity. For example, paclitaxel-loaded lipid nanoemulsions demonstrated comparable anti-scarring efficacy to mitomycin C in a rabbit trabeculectomy model, while significantly reducing conjunctival and ciliary body toxicity. This highlights how nanocarrier encapsulation can enhance safety without compromising therapeutic outcomes [112]. Nanomedicine from most biodegradable materials is considered safe for drug delivery in eye; however, the majority of the toxicity study has been performed *in vitro* cell culture where cell viability, proliferation and inflammation have been tested. Hence, comprehensive and long-term immunological, biochemical, morphological, and functional evaluations in the eye are essential before these materials can be approved for clinical application.

7.2. Low bioavailability and toxicity associated with mode of drug administration

The eye is a multilayered highly organized structures associated with several barriers. The static and dynamic ocular barriers reduce the bioavailability of the drug both at the anterior and posterior part of the eye [85]. Eye drops are considered the safest and most convenient form of treatment for corneal and conjunctival fibrosis. However, they face challenges related to low bioavailability at the target tissue due to tear fluid flow, nasolacrimal drainage, and the corneal and conjunctival epithelium. Nanomedicines, including nanoparticles, liposomes, micelles, dendrimers, and nanogels, can improve drug retention time, enhance permeability through the epithelial barrier, and ultimately increase the bioavailability of the drugs [26,85,196].

Our studies on the effect of physicochemical properties on ocular biodistribution of the nanoparticles when administered as eye drop indicates that targeting specific tissue layer of the eye is possible by controlling the physicochemical properties of the nanoparticles can be

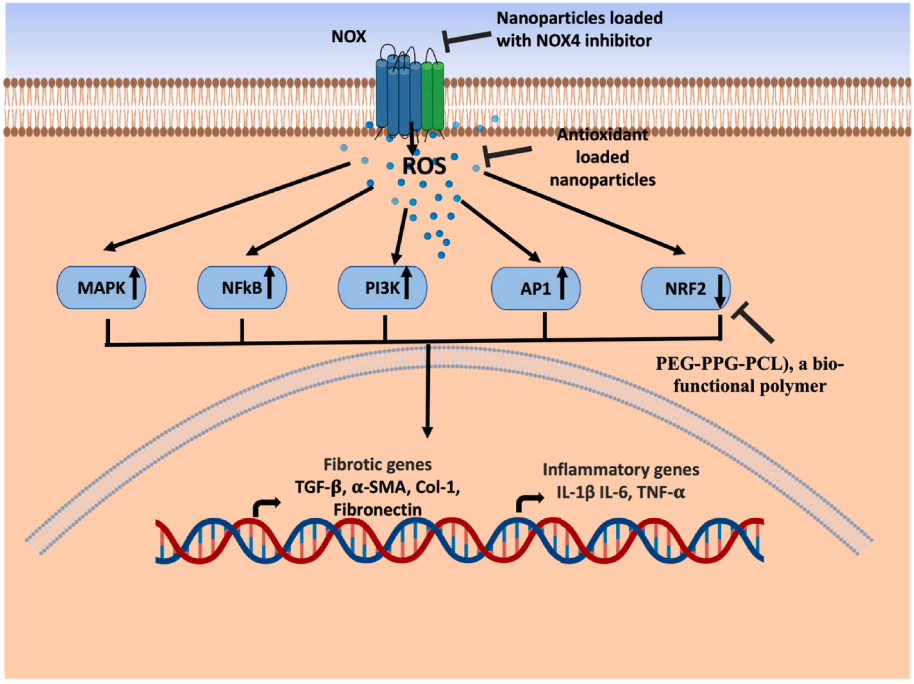

Fig. 6. Schematics of nanomedicines acting on oxidative stress related signaling pathway for inhibition of ocular fibrosis. Increase in NOX4 expression also results in ROS generation, which further activates MAPK, NFkB, PI3K, and AP1. This, in turn, enhances the transcriptional activity of several profibrotic genes, including TGF-β, α-SMA, COL-1, and fibronectin. Nanomedicines incorporating Vas2870, a NOX2 inhibitor, along with antioxidant-loaded nanoparticles, help reduce ROS generation. The subsequent activation of NRF2-target genes suppresses the expression of fibrotic genes, thereby mitigating fibrosis in ocular tissues. NOX: NADPH oxidases, ROS: Reactive Oxygen Species, MAPK: Mitogen-activated Protein Kinase, NFkB: Nuclear factor kappa-light-chain-enhancer of activated B cells, PI3K: Phosphoinositide 3-kinase, AP1: Activator Protein-1, NRF2: Nuclear factor erythroid 2-related factor 2.

harnessed to design nanomedicine for fibrosis in particular of tissue in eye for higher bioavailability [8,27]. Further, nanomedicine can enhance solubility of the drug and increase the bioavailability. For capsular fibrosis, topical administration of the drug may be preferable, although this approach is still in its early stages. However, lens-targeted drug delivery systems also present a promising area for exploration.

Currently, intravitreal injections of drugs are most used method for posterior inflammatory and angiogenic eye diseases associated with fibrosis. Because of short half-lives, repeated injections are necessary which is associated with toxicity [197]. Nanomedicines can provide sustained delivery of drug, and reduce the toxicity with enhanced bioavailability [19,85]. Though topical and systemic administration of drugs for posterior ocular fibrosis is the most convenient method, however, both the administration strategies are associated with blood ocular and retinal barriers and exhibit low bioavailability and needed high dosage of drug, which increase the probability of toxicity. Nanomedicines encompassing nanoparticles, liposomes and emulsions are reported to cross the ocular barriers when applied as eye drops [8,190,198]. In our previous studies core–shell nanoparticles with a hydrophilic, mucoadhesive shell and hydrophobic core are engineered to overcome blood–ocular and blood–retinal barriers while taking via the conjunctival–scleral pathway. Their unique architecture facilitates sustained drug release and targeted therapeutic effects in the retina, making them promising carriers for posterior segment ocular diseases [8,14,19,27]. However, liposomes are primarily delivered via the non-corneal route, involving the trabecular meshwork, iris, and pars plana, with their distribution largely influenced by size and rigidity. Rigid liposomes exhibit higher retinal bioavailability compared to their flexible counterparts [191,199]. These strategies can be used in drugs and gene delivery systems for posterior fibrotic eye diseases.

7.3. Smart nanomedicine addressing multiple complications

Ocular fibrosis especially in cornea and retina is associated with other complications such as inflammation and angiogenesis. To overcome these challenges, the strategic design of inflammation-targeted nanomedicines offers substantial potential. Notably, the pathological microenvironment of inflamed and fibrotic tissues are characterized by factors such as oxidative stress, acidic pH, and elevated enzyme (iNOS, NOX1, NOX4) expression, provides key biochemical cues that can be harnessed for the spatiotemporally controlled release of anti-inflammatory agents [171,180,182]. For example, an oxidative stress-responsive drug delivery system (PMSN-VP@PPCeO$_2$ NPs) was developed to treat neovascular age-related macular degeneration by combining anti-angiogenic, anti-inflammatory, and ROS-scavenging functions. This nanoplatform enabled ROS-triggered verteporfin release, effectively reducing CNV-associated vascular leakage, inflammation, and fibrosis [200]. Similarly, an ROS-responsive nanoparticle system (MPA@Feno), composed of mesoporous silica and polydopamine shell, was developed to improve drug solubility and enable targeted fenofibrate release in inflamed corneal tissue. This system effectively reduced corneal neovascularization and oxidative stress *in vivo*, offering a promising therapeutic strategy [201]. pH and enzyme responsive nanomedicines can be further explored for inflammatory and fibrotic ocular diseases [85]. Nanomedicine with a single or combinatorial drug/gene could be developed to tackle multiple ocular complications. For example, a topically administered polymeric nanoparticle system with a polycaprolactone core and Pluronic® F-68 shell was developed for simultaneous treatment of anterior and posterior eye diseases. Co-delivery of PDTC and TA via this system effectively reduced oxidative stress in the lens and improved retinal outcomes in a diabetic cataract and retinopathy rat model [25]. The sequence, dosage, and duration of the drug delivery system could be designed by selecting the polymer/building block material or by development of hybrid drug delivery systems [25,202,203].

7.4. In vitro and in vivo ocular fibrosis model for drug and nanomedicine screening

Preclinical evaluation of nanomedicine frequently faces hurdles related to its physicochemical properties, concerns regarding sterility/sterilization, as well as safety and efficacy considerations [196,204]. Exploration of 2D and 3D *in vitro* models for ocular fibrosis, as well as *in vivo* animal models, could be conducted to test nanomedicines [46,59]. Screening nanomedicines solely through cell line-based methods and toxicity assays often falls short in predicting efficacy due to the lack of full molecular pathway recapitulation, referred to as "flat biology." Conversely, animal models, while attempting to mimic human pathophysiology, frequently miss crucial effects of drugs [205–207]. For example, while rodents are commonly used in retinal fibrosis research, they lack a macula, and their models cannot fully replicate the complexity of macular fibrosis observed in humans. Nevertheless, they remain valuable models for isolating specific pathways and assessing potential drug candidates [207]. Developing tissue-engineered models for ocular fibrosis is crucial for screening drugs and nanomedicines. These models have enabled significant levels of mimicking disease conditions, particularly in terms of replicating targeted tissue structures, pathophysiological architecture, ECM composition, and interactions between cells and the ECM in fibrotic diseases [59,206,208,209]. Over time, researchers have developed several ocular fibrosis models such as corneal fibrosis, conjunctival, and retina fibrosis models [46,208,210]. Effective *in vitro* models for ocular fibrosis should account for the differentiation of keratocytes, glial cells, and epithelial cells into myofibroblasts, the upregulation of α-SMA resulting in matrix contraction, increased synthesis and deposition of ECM components, and the expression of pro-fibrotic markers, as well as, pathological angiogenesis if associated.

In this context, smart nanomedicine platforms offer a transformative approach for treating ocular fibrosis. For instance, a hypothetical design could involve inflammation-responsive nanoparticles that encapsulate an anti-fibrotic agent and release it selectively in response to pro-inflammatory cytokines (e.g., TNF-α, IL-1β) or oxidative stress signals prevalent in fibrotic microenvironments. Such stimuli-responsive systems could be tested using engineered *in vitro* models that incorporate inflammatory and fibrotic signaling cues, providing a more predictive platform for screening smart, targeted therapies. This approach not only enhances spatiotemporal control of drug release but also improves the translatability of preclinical findings to clinical applications in fibrotic eye diseases.

In this comprehensive exploration of nanomedicines for ocular fibrosis, we have delved into various facets of the condition, from corneal fibrosis to fibrosis post glaucoma and cataract surgeries, as well as fibrosis associated with posterior eye diseases like DR, retinopathy of prematurity, and AMD. Throughout our discussion, we have highlighted the potential of nanomedicine to revolutionize treatment paradigms by addressing challenges such as low bioavailability, toxicity of current adjuvants, and the need for smarter drug delivery systems. Moreover, the development of advanced *in vitro* and *in vivo* models for ocular fibrosis screening underscores the importance of robust preclinical evaluation. As we look to the future, the convergence of nanotechnology with ocular therapeutics holds immense promise for improving patient outcomes and advancing the field of ophthalmology.

CRediT authorship contribution statement

Binapani Mahaling: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Aumreetam Dinabandhu:** Writing – review & editing, Writing – original draft, Visualization. **Manas R. Biswal:** Writing – review & editing, Visualization. **Sourabh Ghosh:** Writing – review & editing, Visualization.

Funding

SG would like to thank funds from Department of Health Research (DHR-1602).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge BioRender (https://www.biorender.com/) and MS PowerPoint that were partly used for the preparation of the figures.

Data availability

No data was used for the research described in the article.

References

[1] F. Mallone, R. Costi, M. Marenco, R. Plateroti, A. Minni, G. Attanasio, M. Artico, A. Lambiase, Understanding drivers of ocular fibrosis: current and future therapeutic perspectives, Int. J. Mol. Sci. 22 (21) (2021) 11748.
[2] P.T. Khaw, Y. Bouremel, S. Brocchini, C. Henein, The control of conjunctival fibrosis as a paradigm for the prevention of ocular fibrosis-related blindness. "Fibrosis has many friends", Eye 34 (12) (2020) 2163–2174.
[3] M. Friedlander, Fibrosis and diseases of the eye, J. Clin. Investig. 117 (3) (2007) 576–586.
[4] S. Shroff, R.K. Thomas, G. D'Souza, S. Nithyanandan, The effect of inhaled steroids on the intraocular pressure, Digit. J. Ophthalmol. 24 (3) (2018) 6–9.
[5] E.R. James, The etiology of steroid cataract, J. Ocul. Pharmacol. Therapeut. 23 (5) (2007) 403–420.
[6] D.M. Hornbeak, J.E. Thorne, Immunosuppressive therapy for eye diseases: effectiveness, safety, side effects and their prevention, Taiwan J Ophthalmol 5 (4) (2015) 156–163.
[7] Y. Han, C. Xu, H. Shi, F. Yu, Y. Zhong, Z. Liu, X.J. Loh, Y.-L. Wu, Z. Li, C. Li, Engineered bio-adhesive polyhedral oligomeric silsesquioxane hybrid nanoformulation of amphotericin B for prolonged therapy of fungal keratitis, Chem. Eng. J. 421 (2021) 129734.
[8] B. Mahaling, D.S. Katti, Physicochemical properties of core–shell type nanoparticles govern their spatiotemporal biodistribution in the eye, Nanomed. Nanotechnol. Biol. Med. 12 (7) (2016) 2149–2160.
[9] H.L. Bui, Y.-H. Su, C.-J. Yang, C.-J. Huang, J.-Y. Lai, Mucoadhesive, antioxidant, and lubricant catechol-functionalized poly(phosphobetaine) as biomaterial nanotherapeutics for treating ocular dryness, J. Nanobiotechnol. 22 (1) (2024) 160.
[10] T.Y. Ger, C.J. Yang, H.L. Bui, S.J. Lue, C.H. Yao, J.Y. Lai, Alginate-functionalized nanoceria as ion-responsive eye drop formulation to treat corneal abrasion, Carbohydr. Polym. 352 (2025) 123164.
[11] C.-J. Yang, A. Anand, C.-C. Huang, J.-Y. Lai, Unveiling the power of gabapentin-loaded nanoceria with multiple therapeutic capabilities for the treatment of dry eye disease, ACS Nano 17 (24) (2023) 25118–25135.
[12] S. Ghosh, Y.-H. Su, C.-J. Yang, J.-Y. Lai, Design of highly adhesive urchin-like gold nanostructures for effective topical drug administration and symptomatic relief of corneal dryness, Small Struct. 6 (2) (2025) 2400484.
[13] M. Silva, T. Peng, X. Zhao, S. Li, M. Farhan, W. Zheng, Recent trends in drug-delivery systems for the treatment of diabetic retinopathy and associated fibrosis, Adv. Drug Deliv. Rev. 173 (2021) 439–460.
[14] B. Mahaling, N. Baruah, N. Ahamad, N. Maisha, E. Lavik, D.S. Katti, A non-invasive nanoparticle-based sustained dual-drug delivery system as an eyedrop for endophthalmitis, Int. J. Pharm. 606 (2021) 120900.
[15] D.D. Nguyen, L.-J. Luo, C.-J. Yang, J.-Y. Lai, Highly retina-permeating and long-acting resveratrol/metformin nanotherapeutics for enhanced treatment of macular degeneration, ACS Nano 17 (1) (2023) 168–183.
[16] L.-J. Luo, D.D. Nguyen, J.-Y. Lai, Dually functional hollow ceria nanoparticle platform for intraocular drug delivery: a push beyond the limits of static and dynamic ocular barriers toward glaucoma therapy, Biomaterials 243 (2020) 119961.
[17] C.-J. Yang, D.D. Nguyen, J.-Y. Lai, Poly(l-histidine)-mediated On-Demand therapeutic delivery of roughened ceria nanocages for treatment of chemical eye injury, Adv. Sci. 10 (26) (2023) 2302174.
[18] T.-Y. Ger, C.-J. Yang, S. Ghosh, J.-Y. Lai, Biofunctionalization of nanoceria with sperminated hyaluronan enhances drug delivery performance for corneal alkali burn therapy, Chem. Eng. J. 476 (2023) 146864.

[19] B. Mahaling, D.A. Srinivasarao, G. Raghu, R.K. Kasam, G.B. Reddy, D.S. Katti, A non-invasive nanoparticle mediated delivery of triamcinolone acetonide ameliorates diabetic retinopathy in rats, Nanoscale 10 (35) (2018) 16485–16498.
[20] H. Ye, Y. Qian, M. Lin, Y. Duan, X. Sun, Y. Zhuo, J. Ge, Cationic nano-copolymers mediated IKKβ targeting siRNA to modulate wound healing in a monkey model of glaucoma filtration surgery, Mol. Vis. 16 (2010) 2502–2510.
[21] L. Luo, X. Zhang, Y. Hirano, P. Tyagi, P. Barabás, H. Uehara, T.R. Miya, N. Singh, B. Archer, Y. Qazi, K. Jackman, S.K. Das, T. Olsen, S.R. Chennamaneni, B. C. Stagg, F. Ahmed, L. Emerson, K. Zygmunt, R. Whitaker, C. Mamalis, W. Huang, G. Gao, S.P. Srinivas, D. Krizaj, J. Baffi, J. Ambati, U.B. Kompella, B.K. Ambati, Targeted intraceptor nanoparticle therapy reduces angiogenesis and fibrosis in primate and murine macular degeneration, ACS Nano 7 (4) (2013) 3264–3275.
[22] P. Zhao, J. Wang, H. Huang, Z. Chen, H. Wang, Q. Lin, Exosomes-based dual drug-loaded nanocarrier for targeted and multiple proliferative vitreoretinopathy therapy, Regen. Biomater. 11 (2024).
[23] S. Chowdhury, R. Guha, R. Trivedi, U.B. Kompella, A. Konar, S. Hazra, Pirfenidone nanoparticles improve corneal wound healing and prevent scarring following alkali burn, PLoS One 8 (8) (2013) e70528.
[24] S. Liu, M.D. Dozois, C.N. Chang, A. Ahmad, D.L.T. Ng, D. Hileeto, H. Liang, M.-M. Reyad, S. Boyd, L.W. Jones, F.X. Gu, Prolonged ocular retention of mucoadhesive nanoparticle eye drop formulation enables treatment of eye diseases using significantly reduced dosage, Mol. Pharm. 13 (9) (2016) 2897–2905.
[25] D.A. Srinivasarao, S. Sreenivasa Reddy, G. Bhanuprakash Reddy, D.S. Katti, Simultaneous amelioration of diabetic ocular complications in lens and retinal tissues using a non-invasive drug delivery system, Int. J. Pharm. 608 (2021) 121045.
[26] B. Mahaling, N. Baruah, A. Dinabandhu, Nanomedicine in ophthalmology: from bench to bedside, J. Clin. Med. (2024).
[27] B. Mahaling, D.S. Katti, Understanding the influence of surface properties of nanoparticles and penetration enhancers for improving bioavailability in eye tissues in vivo, Int. J. Pharm. 501 (1–2) (2016) 1–9.
[28] A.D. Beck, W.R. Wilson, M.G. Lynch, M.J. Lynn, R. Noe, Trabeculectomy with adjunctive mitomycin C in pediatric glaucoma, Am. J. Ophthalmol. 126 (5) (1998) 648–657.
[29] A. Jalil, L. Au, I. Khan, J. Ashworth, I.C. Lloyd, S. Biswas, Combined trabeculotomy-trabeculectomy augmented with 5-fluorouracil in paediatric glaucoma, Clin. Exp. Ophthalmol. 39 (3) (2011) 207–214.
[30] S. Nakano Goto, T. Yamamoto, E. Kirii, S. Abe, H. Yamashita, Treatment of diffuse diabetic macular oedema using steroid eye drops, Acta Ophthalmol. 90 (7) (2012) 628–632.
[31] T. Li, J. Tang, C. Li, G. Liu, Y. Li, S. Guo, Q. Fang, J. Li, X. Qi, X. Liu, Evaluating the efficacy and safety of polyglycolic acid-loading mitomycin nanoparticles in inhibiting the scar proliferation after glaucoma filtering surgery, Ann. Med. 57 (1) (2025) 2436458.
[32] A.D. Tagalakis, S. Madaan, S.D. Larsen, R.R. Neubig, P.T. Khaw, I. Rodrigues, S. Goyal, K.S. Lim, C. Yu-Wai-Man, In vitro and in vivo delivery of a sustained release nanocarrier-based formulation of an MRTF/SRF inhibitor in conjunctival fibrosis, J. Nanobiotechnol. 16 (1) (2018) 1–11.
[33] F. Qiu, T. Meng, Q. Chen, K. Zhou, Y. Shao, G. Matlock, X. Ma, W. Wu, Y. Du, X. Wang, G. Deng, J.-x. Ma, Q. Xu, Fenofibrate-loaded biodegradable nanoparticles for the treatment of experimental diabetic retinopathy and neovascular age-related macular degeneration, Mol. Pharm. 16 (5) (2019) 1958–1970.
[34] S.F. Hackett, J. Fu, Y.C. Kim, H. Tsujinaka, J. Shen, R. Lima e Silva, M. Khan, Z. Hafiz, T. Wang, M. Shin, N.M. Anders, P. He, L.M. Ensign, J. Hanes, P. A. Campochiaro, Sustained delivery of acriflavine from the suprachoroidal space provides long term suppression of choroidal neovascularization, Biomaterials 243 (2020) 119935.
[35] C.D. Diaz-Palomera, I.A. Vidal-Paredes, J. Navarro-Partida, M. Cid-Hernandez, L. C. Rosales-Rivera, R. De la Rosa-Bibiano, H.C. Monroy-Ramirez, A. Santos, J. Armendariz-Borunda, Topical pirfenidone-loaded liposomes ophthalmic formulation reduces haze development after corneal alkali burn in mice, Pharmaceutics 14 (2) (2022) 316.
[36] L.P. Sampaio, T.M. Shiju, G.S.L. Hilgert, R.C. de Oliveira, J. DeDreu, A.S. Menko, M.R. Santhiago, S.E. Wilson, Descemet's membrane injury and regeneration, and posterior corneal fibrosis, in rabbits, Exp. Eye Res. 213 (2021) 108803.
[37] N. Gotoh, N.R. Perdue, H. Matsushima, E.H. Sage, Q. Yan, J.I. Clark, An in vitro model of posterior capsular opacity: SPARC and TGF-beta2 minimize epithelial-to-mesenchymal transition in lens epithelium, Investig. Ophthalmol. Vis. Sci. 48 (10) (2007) 4679–4687.
[38] Y. Kobayashi, K. Tokuda, C. Yamashiro, F. Higashijima, T. Yoshimoto, M. Ota, T. Ogata, A. Ashimori, M. Hatano, M. Kobayashi, S.-H. Uchi, M. Wakuta, K. Kimura, Inhibition of epithelial–mesenchymal transition in retinal pigment epithelial cells by a retinoic acid receptor-α agonist, Sci. Rep. 11 (1) (2021) 11842.
[39] R.C. de Oliveira, S.E. Wilson, Fibrocytes, wound healing, and corneal fibrosis, Investig. Ophthalmol. Vis. Sci. 61 (2) (2020), 28-28.
[40] A.D. Fişuş, O. Findl, Capsular fibrosis: a review of prevention methods and management, Eye 34 (2) (2020) 256–262.
[41] S.E. Wilson, Corneal myofibroblasts and fibrosis, Exp. Eye Res. 201 (2020) 108272.
[42] J. Xu, P. Chen, X. Luan, X. Yuan, S. Wei, Y. Li, C. Guo, X. Wu, G. Di, The NLRP3 activation in infiltrating macrophages contributes to corneal fibrosis by inducing TGF-β1 expression in the corneal epithelium, Investig. Ophthalmol. Vis. Sci. 63 (8) (2022) 15.
[43] C.G. Shao, N.R. Sinha, R.R. Mohan, A.D. Webel, Novel therapies for the prevention of fibrosis in glaucoma filtration surgery, Biomedicines 11 (3) (2023).
[44] Z. Pasvanis, R.C.K. Kong, M.H. Shah, E.C. Chan, J.C. Fan Gaskin, 3′,4′-Dihydroxyflavonol inhibits fibrotic response in a rabbit model of glaucoma filtration surgery, Int. J. Mol. Sci. (2024).
[45] N. Awasthi, S. Guo, B.J. Wagner, Posterior capsular opacification: a problem reduced but not yet eradicated, Arch. Ophthalmol. 127 (4) (2009) 555–562.
[46] S. Chawla, S. Ghosh, Establishment of in vitro model of corneal scar pathophysiology, J. Cell. Physiol. 233 (5) (2018) 3817–3830.
[47] S.E. Wilson, Corneal wound healing, Exp. Eye Res. 197 (2020) 108089.
[48] E.H. Lee, C.-K. Joo, Role of transforming growth Factor-β in transdifferentiation and fibrosis of lens epithelial cells, Investig. Ophthalmol. Vis. Sci. 40 (9) (1999) 2025–2032.
[49] E. Kubo, T. Shibata, D.P. Singh, H. Sasaki, Roles of TGF β and FGF signals in the lens: tropomyosin regulation for posterior capsule opacity, Int. J. Mol. Sci. (2018).
[50] C. Gao, X. Cao, L. Huang, Y. Bao, T. Li, Y. Di, L. Wu, Y. Song, Pirfenidone alleviates choroidal neovascular fibrosis through TGF-β/Smad signaling pathway, Journal of Ophthalmology 2021 (1) (2021) 8846708.
[51] H. Yao, H. Li, S. Yang, M. Li, C. Zhao, J. Zhang, G. Xu, F. Wang, Inhibitory effect of bone morphogenetic protein 4 in retinal pigment epithelial-mesenchymal transition, Sci. Rep. 6 (1) (2016) 32182.
[52] T.B. McKay, A.E. Hutcheon, J.D. Zieske, Biology of corneal fibrosis: soluble mediators, integrins, and extracellular vesicles, Eye 34 (2) (2020) 271–278.
[53] I.M. Wormstone, L. Wang, C.S.C. Liu, Posterior capsule opacification, Exp. Eye Res. 88 (2) (2009) 257–269.
[54] L.O. Hattenbach, S. Grisanti, S.G. Priglinger, A. Chronopoulos, [proliferative vitreoretinopathy (PVR) minimal: same, same but different. Characteristics and surgical treatment of PVR-Associated macular pucker], Ophthalmologe 118 (1) (2021) 24–29.
[55] S. Roy, S. Amin, S. Roy, Retinal fibrosis in diabetic retinopathy, Exp. Eye Res. 142 (2016) 71–75.
[56] S.S. Chaurasia, R.R. Lim, R. Lakshminarayanan, R.R. Mohan, Nanomedicine approaches for corneal diseases, J. Funct. Biomater. 6 (2) (2015) 277–298.
[57] J. Chakraborty, S. Roy, S. Murab, R. Ravani, K. Kaur, S. Devi, D. Singh, S. Sharma, S. Mohanty, A.K. Dinda, Modulation of macrophage phenotype, maturation, and graft integration through chondroitin sulfate cross-linking to decellularized cornea, ACS Biomater. Sci. Eng. 5 (1) (2018) 165–179.
[58] A.V. Ljubimov, M. Saghizadeh, Progress in corneal wound healing, Prog. Retin. Eye Res. 49 (2015) 17–45.
[59] L. Trujillo Cubillo, M. Gurdal, D.I. Zeugolis, Corneal fibrosis: from in vitro models to current and upcoming drug and gene medicines, Adv. Drug Deliv. Rev. 209 (2024) 115317.
[60] O.O. Ebenezar, A. Roney, D.G. Goswami, J.M. Petrash, D. Sledge, A. M. Komáromy, K.T. Liby, N. Tewari-Singh, Ocular injury progression and cornea histopathology from chloropicrin vapor exposure: relevant clinical biomarkers in mice, Exp. Eye Res. 230 (2023) 109440.
[61] V.P. Joshi, K.S. Vaishnavi, S.K. Ojha, V. Singh, S. Basu, A reliable animal model of corneal stromal opacity: development and validation using in vivo imaging, Ocul. Surf. 18 (4) (2020) 681–688.
[62] A. Sharma, M.M. Mehan, S. Sinha, J.W. Cowden, R.R. Mohan, Trichostatin a inhibits corneal haze in vitro and in vivo, Investig. Ophthalmol. Vis. Sci. 50 (6) (2009) 2695–2701.
[63] M. Słoniecka, P. Danielson, Substance P induces fibrotic changes through activation of the RhoA/ROCK pathway in an in vitro human corneal fibrosis model, J. Mol. Med. 97 (2019) 1477–1489.
[64] A.A. Fuchs, P.K. Balne, E.A. Giuliano, N.R. Sinha, R.R. Mohan, Evaluation of a novel combination of TRAM-34 and ascorbic acid for the treatment of corneal fibrosis in vivo, PLoS One 17 (1) (2022) e0262046.
[65] T. Van Bergen, S. Van de Velde, E. Vandewalle, L. Moons, I. Stalmans, Improving Patient Outcomes Following Glaucoma Surgery: State of the Art and Future Perspectives, Clinical ophthalmology, 2014, pp. 857–867.
[66] R. Bindlish, G.P. Condon, J.D. Schlosser, J. D'Antonio, K.B. Lauer, R. Lehrer, Efficacy and safety of mitomycin-C in primary trabeculectomy: five-year follow-up, Ophthalmology 109 (7) (2002) 1336–1341. ; discussion 1341-2.
[67] E.J. Rockwood, R.K. Parrish, D.K. Heuer, G.L. Skuta, E. Hodapp, P.F. Palmberg, M.G. Gressel, W. Feuer, Glaucoma filtering surgery with 5-Fluorouracil, Ophthalmology 94 (9) (1987) 1071–1078.
[68] O. Fernando, A.D. Tagalakis, S. Awwad, S. Brocchini, P.T. Khaw, S.L. Hart, C. Yu-Wai-Man, Development of targeted siRNA nanocomplexes to prevent fibrosis in experimental glaucoma filtration surgery, Mol. Ther. 26 (12) (2018) 2812–2822.
[69] L.-j. Cui, N.-x. Sun, X.-h. Li, J. Huang, J.-g. Yang, Subconjunctival sustained release 5-fluorouracil for glaucoma filtration surgery1, Acta Pharmacol. Sin. 29 (9) (2008) 1021–1028.
[70] P. Tilleul, P. Denis, F. Maignen, P.P. Eléna, J.P. Nordmann, R. Leverge, W. Rostène, Effects of different formulations of mitoxantrone (solutions, nanospheres, liposomes) on glaucoma surgery in rabbits, Ophthalmic Res. 29 (4) (1997) 218–226.
[71] M.R. Butler, C.M. Prospero Ponce, Y.E. Weinstock, S. Orengo-Nania, P. Chevez-Barrios, B.J. Frankfort, Topical silver nanoparticles result in improved bleb function by increasing filtration and reducing fibrosis in a rabbit model of filtration surgery, Investig. Ophthalmol. Vis. Sci. 54 (7) (2013) 4982–4990.
[72] A. Sanghani, K.N. Kafetzis, Y. Sato, S. Elboraie, J. Fajardo-Sanchez, H. Harashima, A.D. Tagalakis, C. Yu-Wai-Man, Novel PEGylated lipid nanoparticles have a high encapsulation efficiency and effectively deliver MRTF-B siRNA in conjunctival fibroblasts, Pharmaceutics 13 (3) (2021).

[73] Y.-H. Luo, P.-B. Ouyang, J. Tian, X.-J. Guo, X.-C. Duan, Rosiglitazone inhibits TGF-β 1 induced activation of human tenon fibroblasts via p38 signal pathway, PLoS One 9 (8) (2014) e105796.
[74] K. Jiang, J. Chen, L. Tai, C. Liu, X. Chen, G. Wei, W. Lu, W. Pan, Inhibition of post-trabeculectomy fibrosis via topically instilled antisense oligonucleotide complexes co-loaded with fluorouracil, Acta Pharm. Sin. B 10 (9) (2020) 1754–1768.
[75] T. Miyamoto, S. Saika, Y. Okada, I. Ishida-Nishikawa, T. Sumioka, N. Fujita, Y. Ohnishi, Topical exposure of mitomycin C reduces opacification of the residual anterior lens capsule and lenticular regeneration after vitrectomy and lensectomy in rabbits, Graefes Arch. Clin. Exp. Ophthalmol. 242 (4) (2004) 327–331.
[76] J.C. D'Antin, R.I. Barraquer, F. Tresserra, R. Michael, Prevention of posterior capsule opacification through intracapsular hydrogen peroxide or distilled water treatment in human donor tissue, Sci. Rep. 8 (1) (2018) 12739.
[77] V. Fernandez, M.A. Fragoso, C. Billotte, P. Lamar, M.A. Orozco, S. Dubovy, M. Willcox, J.M. Parel, Efficacy of various drugs in the prevention of posterior capsule opacification: experimental study of rabbit eyes, J. Cataract Refract. Surg. 30 (12) (2004) 2598–2605.
[78] G.X. Xu, T.T. Wang, Apoptosis of lens epithelial cells induced by cinobufagin in vitro, Int. J. Ophthalmol. 3 (2) (2010) 128–131.
[79] J.C. Pastor, J. Rojas, S. Pastor-Idoate, S. Di Lauro, L. Gonzalez-Buendia, S. Delgado-Tirado, Proliferative vitreoretinopathy: a new concept of disease pathogenesis and practical consequences, Prog. Retin. Eye Res. 51 (2016) 125–155.
[80] A.F. Alex, M. Spitznas, A.P. Tittel, C. Kurts, N. Eter, Inhibitory effect of epigallocatechin gallate (EGCG), resveratrol, and curcumin on proliferation of human retinal pigment epithelial cells in vitro, Curr. Eye Res. 35 (11) (2010) 1021–1033.
[81] J. Sun, X. Liu, Y. Lei, M. Tang, Z. Dai, X. Yang, X. Yu, L. Yu, X. Sun, J. Ding, Sustained subconjunctival delivery of cyclosporine A using thermogelling polymers for glaucoma filtration surgery, J. Mater. Chem. B 5 (31) (2017) 6400–6411.
[82] H. Han, Q. Yin, X. Tang, X. Yu, Q. Gao, Y. Tang, A. Grzybowski, K. Yao, J. Ji, X. Shentu, Development of mucoadhesive cationic polypeptide micelles for sustained cabozantinib release and inhibition of corneal neovascularization, J. Mater. Chem. B 8 (23) (2020) 5143–5154.
[83] L.-J. Luo, D.D. Nguyen, C.-C. Huang, J.-Y. Lai, Therapeutic hydrogel sheets programmed with multistage drug delivery for effective treatment of corneal abrasion, Chem. Eng. J. 429 (2022) 132409.
[84] P.H. Lin, H.J. Jian, Y.J. Li, Y.F. Huang, A. Anand, C.C. Huang, H.J. Lin, J.Y. Lai, Alleviation of dry eye syndrome with one dose of antioxidant, anti-inflammatory, and mucoadhesive lysine-carbonized nanogels, Acta Biomater. 141 (2022) 140–150.
[85] B. Mahaling, N. Baruah, A. Dinabandhu, Drug delivery systems for infectious eye diseases: advancements and prospects, Journal of Nanotheranostics (2024) 133–166.
[86] U. Soiberman, S.P. Kambhampati, T. Wu, M.K. Mishra, Y. Oh, R. Sharma, J. Wang, A.E. Al Towerki, S. Yiu, W.J. Stark, Subconjunctival injectable dendrimer-dexamethasone gel for the treatment of corneal inflammation, Biomaterials 125 (2017) 38–53.
[87] N. Lyu, Y. Zhao, J. Xiang, X. Fan, C. Huang, X. Sun, J. Xu, Z.P. Xu, J. Sun, Inhibiting corneal neovascularization by sustainably releasing anti-VEGF and anti-inflammation drugs from silica-thermogel nanohybrids, Mater. Sci. Eng. C 128 (2021) 112274.
[88] G. Shojaati, I. Khandaker, M.L. Funderburgh, M.M. Mann, R. Basu, D.B. Stolz, M. L. Geary, A. Dos Santos, S.X. Deng, J.L. Funderburgh, Mesenchymal stem cells reduce corneal fibrosis and inflammation via extracellular vesicle-mediated delivery of miRNA, Stem Cells Transl. Med. 8 (11) (2019) 1192–1201.
[89] D. Peng, K. Yu, S. Zeng, Y. Li, J. Lin, Y. Wu, W. Zhou, An experimental study on homoharringtonine liposome and glaucoma filtration surgery, Yan Ke Xue Bao 15 (1) (1999) 51–54, 50.
[90] R. Yamazaki, Y. Kasuya, T. Fujita, H. Umezawa, M. Yanagihara, H. Nakamura, I. Yoshino, K. Tatsumi, T. Murayama, Antifibrotic effects of cyclosporine A on TGF-β1-treated lung fibroblasts and lungs from bleomycin-treated mice: role of hypoxia-inducible factor-1α, FASEB J. 31 (8) (2017) 3359–3371.
[91] Q.-Y. Lin, X.-J. Li, Y. Leng, X.-M. Zhu, M. Tang, Y. Lin, W.-D. Luo, B.-C. Jiang, X. Chen, L. Xie, Exosome-mediated aptamer S58 reduces fibrosis in a rat glaucoma filtration surgery model, Int. J. Ophthalmol. 15 (5) (2022) 690.
[92] X. Sun, H. Cui, J. Li, B. An, R. Liu, Z. Guo, D. Chu, X. Geng, B. Cui, L. Zhu, J. Li, Z. Li, An injectable shape-adaptive hydrogel system for subconjunctival injuries: in situ and permanently releases rapamycin to prevent fibrosis via promoting autophagy, Mater. Today Bio 30 (2025) 101380.
[93] F. Zhang, K. Liu, Z. Pan, M. Cao, D. Zhou, H. Liu, Y. Huang, X. Duan, Effects of rosiglitazone/PHBV drug delivery system on postoperative fibrosis in rabbit glaucoma filtration surgery model, Drug Deliv. 26 (1) (2019) 812–819.
[94] Q. Ning, X. Sun, H. Cui, X. Wang, H. Feng, B. An, Z. Li, J. Shi, J. Li, Dual-corn-derived nanofiber membrane for subconjunctival injury: sequential release of dual-natural products for programmed anti-inflammation and anti-fibrosis, J. Contr. Release 381 (2025) 113577.
[95] X. Huang, Y. Wang, J.-P. Cai, X.-Y. Ma, Y. Li, J.-W. Cheng, R.-L. Wei, Sustained release of 5-Fluorouracil from Chitosan nanoparticles surface modified intra ocular lens to prevent posterior capsule opacification: an in vitro and in vivo study, J. Ocul. Pharmacol. Therapeut. 29 (2) (2013) 208–215.
[96] R. Guha, C. Sushovan, P. Himangshu, M. Akhilesh, B. Samar, M.T. Kumar, H. Sarbani, A. Konar, Doxorubicin-loaded MePEG-PCL nanoparticles for prevention of posterior capsular opacification, Nanomedicine 8 (9) (2013) 1415–1428.
[97] Y. Han, T. Junmei, X. Jiayi, W. Rui, Q. Chen, L. Sihao, Z. Xia, C. Hao, Q. Lin, Anti-adhesive and antiproliferative synergistic surface modification of intraocular lens for reduced posterior capsular opacification, Int. J. Nanomed. 14 (null) (2019) 9047–9061.
[98] Y. Lu, W. Gu, Y. Ren, J. Feng, L. Yang, J. Jin, Anti-fibrosis effect of nanoparticle-mediated delivery of plasminogen kringle 5, Discov. Med. 23 (129) (2017) 343–351.
[99] K. Shinohara, M. Tanaka, T. Sakuma, Y. Kobayashi, Efficacy of daunorubicin encapsulated in liposome for the treatment of proliferative vitreoretinopathy, Ophthalmic Surgery, Lasers and Imaging Retina 34 (4) (2003) 299–305.
[100] E. VuRAL, M. Yilmaz, K. İlbAY, G. İlbAY, Prevention of epidural fibrosis in rats by local administration of mitomycin C or daunorubicin, Turk Neurosurg 26 (2) (2016) 291–296.
[101] B.H. Parikh, Z. Liu, P. Blakeley, Q. Lin, M. Singh, J.Y. Ong, K.H. Ho, J.W. Lai, H. Bogireddi, K.C. Tran, J.Y.C. Lim, K. Xue, A. Al-Mubaarak, B. Yang, S. R, K. Regha, D.S.L. Wong, Q.S.W. Tan, Z. Zhang, A.D. Jeyasekharan, V.A. Barathi, W. Yu, K.H. Cheong, T.A. Blenkinsop, W. Hunziker, G. Lingam, X.J. Loh, X. Su, A bio-functional polymer that prevents retinal scarring through modulation of NRF2 signalling pathway, Nat. Commun. 13 (1) (2022) 2796.
[102] P. Daull, C.A. Paterson, B.D. Kuppermann, J.-S. Garrigue, A preliminary evaluation of dexamethasone palmitate emulsion: a novel intravitreal sustained delivery of corticosteroid for treatment of macular edema, J. Ocul. Pharmacol. Therapeut. 29 (2) (2013) 258–269.
[103] H. Cho, S.P. Kambhampati, M.J. Lai, L. Zhou, G. Lee, Y. Xie, Q. Hui, R.M. Kannan, E.J. Duh, Dendrimer-triamcinolone acetonide reduces neuroinflammation, pathological angiogenesis, and neuroretinal dysfunction in ischemic retinopathy, Adv. Therapeut. 4 (2) (2021) 2000181.
[104] I.L. de Redín, C. Boiero, S. Recalde, M. Agüeros, D. Allemandi, J.M. Llabot, A. García-Layana, J.M. Irache, In vivo effect of bevacizumab-loaded albumin nanoparticles in the treatment of corneal neovascularization, Exp. Eye Res. 185 (2019) 107697.
[105] A. Sharma, J.T. Rodier, A. Tandon, A.M. Klibanov, R.R. Mohan, Attenuation of corneal myofibroblast development through nanoparticle-mediated soluble transforming growth factor-β type II receptor (sTGFβRII) gene transfer, Mol. Vis. 18 (2012) 2598.
[106] A. Tandon, A. Sharma, J.T. Rodier, A.M. Klibanov, F.G. Rieger, R.R. Mohan, BMP7 gene transfer via gold nanoparticles into stroma inhibits corneal fibrosis in vivo, PLoS One 8 (6) (2013) e66434.
[107] K.S. Donnelly, E.A. Giuliano, A. Sharma, A. Tandon, J.T. Rodier, R.R. Mohan, Decorin-PEI nanoconstruct attenuates equine corneal fibroblast differentiation, Vet. Ophthalmol. 17 (3) (2014) 162–169.
[108] K. Wang, L. Jiang, Y. Zhong, Y. Zhang, Q. Yin, S. Li, X. Zhang, H. Han, K. Yao, Ferrostatin-1-loaded liposome for treatment of corneal alkali burn via targeting ferroptosis, Bioengineering & translational medicine 7 (2) (2022) e10276.
[109] F.R. da Silva, R.O. Silva, H.M. de Castro Oliveira, L.F.N. Dourado, B.L. da Costa, B. S. Lima, N.G.L. Santos, C.E.P. Repeke, G.B. Menezes, A.A. de Souza Araujo, Gelatin-based membrane containing usnic acid-loaded liposomes: a new treatment strategy for corneal healing, Biomed. Pharmacother. 130 (2020) 110391.
[110] S. Li, B. Li, H. Jiang, Y. Wang, M. Qu, H. Duan, Q. Zhou, W. Shi, Macrophage depletion impairs corneal wound healing after autologous transplantation in mice, PLoS One 8 (4) (2013) e61799.
[111] R. Samaeekia, B. Rabiee, I. Putra, X. Shen, Y.J. Park, P. Hematti, M. Eslani, A. R. Djalilian, Effect of human corneal mesenchymal stromal cell-derived exosomes on corneal epithelial wound healing, Investig. Ophthalmol. Vis. Sci. 59 (12) (2018) 5194–5200.
[112] M.L. Occhiutto, F.R. Freitas, P.P. Lima, R.C. Maranhão, V.P. Costa, Paclitaxel associated with lipid nanoparticles as a new antiscarring agent in experimental glaucoma surgery, Investig. Ophthalmol. Vis. Sci. 57 (3) (2016) 971–978.
[113] S. Simmons, M. Sherwood, D. Nichols, R. Penne, T. Sery, G. Spaeth, Pharmacokinetics of a 5-fluorouracil liposomal delivery system, Br. J. Ophthalmol. 72 (9) (1988) 688–691.
[114] S. Shaunak, S. Thomas, E. Gianasi, A. Godwin, E. Jones, I. Teo, K. Mireskandari, P. Luthert, R. Duncan, S. Patterson, P. Khaw, S. Brocchini, Polyvalent dendrimer glucosamine conjugates prevent scar tissue formation, Nat. Biotechnol. 22 (8) (2004) 977–984.
[115] R. Hennig, S. Kuespert, A. Haunberger, A. Goepferich, R. Fuchshofer, Cyclic RGD peptides target human trabecular meshwork cells while ameliorating connective tissue growth factor-induced fibrosis, J. Drug Target. 24 (10) (2016) 952–959.
[116] Z. Li, X. Zhang, Z. Guo, L. Shi, L. Jin, L. Zhu, X. Cai, J. Zhang, Y. Zhang, J. Li, Nature-derived bionanomaterials for sustained release of 5-fluorouracil to inhibit subconjunctival fibrosis, Materials Today Advances 11 (2021) 100150.
[117] B. Chhunchha, E. Kubo, U.B. Kompella, D.P. Singh, Engineered sumoylation-deficient Prdx6 mutant protein-loaded nanoparticles provide increased cellular defense and prevent lens opacity, Antioxidants 10 (8) (2021) 1245.
[118] S. Wang, J. Zhang, T. Jiang, L. Zheng, Z. Wang, J. Zhang, P. Yu, Protective effect of coenzyme Q10 against oxidative damage in human lens epithelial cells by novel ocular drug carriers, Int. J. Pharm. 403 (1) (2011) 219–229.
[119] Y. Ohta, T. Yamasaki, T. Niwa, Y. Majima, Preventive effect of vitamin E-containing liposome instillation on cataract progression in 12-month-old rats fed a 25% galactose diet, J. Ocul. Pharmacol. Therapeut. 16 (4) (2000) 323–335.
[120] N.A.A. Nasir, R. Agarwal, S. Vasudevan, M. Tripathy, R. Alyautdin, N.M. Ismail, Effects of topically applied tocotrienol on cataractogenesis and lens redox status in galactosemic rats, Mol. Vis. 20 (2014) 822.

[121] H.-K. Kuo, Y.-H. Chen, P.-C. Wu, Y.-C. Wu, F. Huang, C.-W. Kuo, L.-H. Lo, J. Shiea, Attenuated glial reaction in experimental proliferative vitreoretinopathy treated with liposomal doxorubicin, Investig. Ophthalmol. Vis. Sci. 53 (6) (2012) 3167–3174.
[122] K. Park, Y. Chen, Y. Hu, A.S. Mayo, U.B. Kompella, R. Longeras, J.-x. Ma, Nanoparticle-mediated expression of an angiogenic inhibitor ameliorates ischemia-induced retinal neovascularization and diabetes-induced retinal vascular leakage, Diabetes 58 (8) (2009) 1902–1913.
[123] J.H. Kim, M.H. Kim, D.H. Jo, Y.S. Yu, T.G. Lee, J.H. Kim, The inhibition of retinal neovascularization by gold nanoparticles via suppression of VEGFR-2 activation, Biomaterials 32 (7) (2011) 1865–1871.
[124] B.C. Joondeph, G.A. Peyman, B. Khoobehi, B.Y. Yue, Liposome-Encapsulated 5-fluorouracil in the Treatment of Proliferative Vitreoretinopathy, SLACK, Incorporated Thorofare, NJ, 1988, pp. 252–256.
[125] B. Mahaling, S.W.Y. Low, M. Beck, D. Kumar, S. Ahmed, T.B. Connor, B. Ahmad, S.S. Chaurasia, Damage-associated molecular patterns (DAMPs) in retinal disorders, Int. J. Mol. Sci. 23 (5) (2022).
[126] Q. Li, K.L. Lai, P.S. Chan, S.C. Leung, H.Y. Li, Y. Fang, K.K.W. To, C.H.J. Choi, Q. Y. Gao, T.W.Y. Lee, Micellar delivery of dasatinib for the inhibition of pathologic cellular processes of the retinal pigment epithelium, Colloids Surf. B Biointerfaces 140 (2016) 278–286.
[127] J.H. Jeong, H.K. Nguyen, J.E. Lee, W. Suh, Therapeutic effect of apatinib-loaded nanoparticles on diabetes-induced retinal vascular leakage, Int. J. Nanomed. 11 (2016) 3101–3109.
[128] Y. Dong, G. Wan, P. Yan, C. Qian, F. Li, G. Peng, Fabrication of resveratrol coated gold nanoparticles and investigation of their effect on diabetic retinopathy in streptozotocin induced diabetic rats, J. Photochem. Photobiol. B Biol. 195 (2019) 51–57.
[129] R. Amato, M. Giannaccini, M. Dal Monte, M. Cammalleri, A. Pini, V. Raffa, M. Lulli, G. Casini, Association of the somatostatin analog octreotide with magnetic nanoparticles for intraocular delivery: a possible approach for the treatment of diabetic retinopathy, Front. Bioeng. Biotechnol. 8 (2020) 144.
[130] P. Bogdanov, J. Sampedro, C. Solà-Adell, O. Simó-Servat, C. Russo, L. Varela-Sende, R. Simó, C. Hernández, Effects of liposomal formulation of citicoline in experimental diabetes-induced retinal neurodegeneration, Int. J. Mol. Sci. 19 (8) (2018).
[131] M. Amadio, A. Pascale, S. Cupri, R. Pignatello, C. Osera, G.M. Leggio, B. Ruozi, S. Govoni, F. Drago, C. Bucolo, Nanosystems based on siRNA silencing HuR expression counteract diabetic retinopathy in rat, Pharmacol. Res. 111 (2016) 713–720.
[132] S. Kaur, S. Yangzes, S. Singh, N. Sachdev, Efficacy and safety of topical difluprednate in persistent diabetic macular edema, Int. Ophthalmol. 36 (3) (2016) 335–340.
[133] E.J. Oh, J.-S. Choi, H. Kim, C.-K. Joo, S.K. Hahn, Anti-Flt1 peptide – hyaluronate conjugate for the treatment of retinal neovascularization and diabetic retinopathy, Biomaterials 32 (11) (2011) 3115–3123.
[134] R. Nagaraj, T. Stack, S. Yi, B. Mathew, K.R. Shull, E.A. Scott, M.T. Mathew, D. R. Bijukumar, High density display of an anti-angiogenic peptide on micelle surfaces enhances their inhibition of αvβ3 integrin-mediated neovascularization in vitro, Nanomaterials 10 (3) (2020) 581.
[135] P.K. Shah, V. Prabhu, S.S. Karandikar, R. Ranjan, V. Narendran, N. Kalpana, Retinopathy of prematurity: past, present and future, World J. Clin. Pediatr. 5 (1) (2016) 35–46.
[136] O.J. Mezu-Ndubuisi, Y. Wang, J. Schoephoerster, J. Falero-Perez, I.S. Zaitoun, N. Sheibani, S. Gong, Intravitreal delivery of VEGF-A165-loaded PLGA microparticles reduces retinal vaso-obliteration in an in vivo mouse model of retinopathy of prematurity, Curr. Eye Res. 44 (3) (2019) 275–286.
[137] L.E.H. Smith, Pathogenesis of retinopathy of prematurity, Semin. Neonatol. 8 (6) (2003) 469–473.
[138] M.R. Niesman, K.A. Johnson, J.S. Penn, Therapeutic effect of liposomal superoxide dismutase in an animal model of retinopathy of prematurity, Neurochem. Res. 22 (5) (1997) 597–605.
[139] Y. Yonekawa, W.-C. Wu, C.E. Nitulescu, R.P. Chan, A. Thanos, B.J. Thomas, B. Todorich, K.A. Drenser, M.T. Trese, A. Capone Jr., Progressive retinal detachment in infants with retinopathy of prematurity treated with intravitreal bevacizumab or ranibizumab, Retina 38 (6) (2018) 1079–1083.
[140] L. Luo, X. Zhang, Y. Hirano, P. Tyagi, P. Barabás, H. Uehara, T.R. Miya, N. Singh, B. Archer, Y. Qazi, Targeted intraceptor nanoparticle therapy reduces angiogenesis and fibrosis in primate and murine macular degeneration, ACS Nano 7 (4) (2013) 3264–3275.
[141] K. Lai, Y. Li, L. Li, Y. Gong, C. Huang, Y. Zhang, L. Cheng, F. Xu, H. Zhao, C. Li, X. Zhong, C. Jin, Intravitreal injection of triptolide attenuates subretinal fibrosis in laser-induced murine model, Phytomedicine 93 (2021) 153747.
[142] S.P. Kambhampati, I.A. Bhutto, T. Wu, K. Ho, D.S. McLeod, G.A. Lutty, R. M. Kannan, Systemic dendrimer nanotherapies for targeted suppression of choroidal inflammation and neovascularization in age-related macular degeneration, J. Contr. Release 335 (2021) 527–540.
[143] T.H. Yang, A. Gingery, A.R. Thoreson, D.R. Larson, C. Zhao, P.C. Amadio, Triamcinolone acetonide affects TGF-β signaling regulation of fibrosis in idiopathic carpal tunnel syndrome, BMC Muscoskelet. Disord. 19 (1) (2018) 342.
[144] C. Peterson, Y. Lu, C.P. Santiago, A.C. Price, M.M. McNally, W. Schubert, K. Nassar, T. Zollner, S. Blackshaw, C.G. Eberhart, M.S. Singh, Transition to chronic fibrosis in an animal model of retinal detachment with features of proliferative vitreoretinopathy, Investig. Ophthalmol. Vis. Sci. 64 (15) (2023) 39.
[145] T. Yoshida, H. Zhang, T. Iwase, J. Shen, G.L. Semenza, P.A. Campochiaro, Digoxin inhibits retinal ischemia-induced HIF-1alpha expression and ocular neovascularization, FASEB J. 24 (6) (2010) 1759–1767.
[146] C. Harada, T. Harada, Y. Mitamura, H. Quah, K. Ohtsuka, S. Kotake, S. Ohno, K. Wada, S. Takeuchi, K. Tanaka, Diverse NF-kappaB expression in epiretinal membranes after human diabetic retinopathy and proliferative vitreoretinopathy, Mol. Vis. 10 (1) (2004) 31–36.
[147] C.D. Diaz-Palomera, I.A. Vidal-Paredes, J. Navarro-Partida, M. Cid-Hernandez, L. C. Rosales-Rivera, R. De la Rosa-Bibiano, H.C. Monroy-Ramirez, A. Santos, J. Armendariz-Borunda, Topical pirfenidone-loaded liposomes ophthalmic formulation reduces haze development after corneal alkali burn in mice, Pharmaceutics (2022).
[148] C.H. Park, T.-H. Yoo, TGF-β inhibitors for therapeutic management of kidney fibrosis, Pharmaceuticals (2022).
[149] S.S. Paik, J.M. Lee, I.-G. Ko, S.R. Kim, S.W. Kang, J. An, J.A. Kim, D. Kim, L. Hwang, J.-J. Jin, S.-H. Kim, J.-Y. Cha, C.W. Choi, Pirfenidone alleviates inflammation and fibrosis of acute respiratory distress syndrome by modulating the transforming growth Factor-β/Smad signaling pathway, Int. J. Mol. Sci. (2024).
[150] S.-B. Wu, T.-Y. Hou, H.-C. Kau, C.-C. Tsai, Effect of pirfenidone on TGF-β1-Induced myofibroblast differentiation and extracellular matrix homeostasis of human orbital fibroblasts in graves' ophthalmopathy, Biomolecules (2021).
[151] J. Liu, S. Wang, G. Tan, B. Tong, Y. Wu, L. Zhang, B. Jiang, Chitosan-artesunate nanoparticles: a dual anti-fibrotic and anti-inflammatory strategy for preventing bleb fibrosis post-glaucoma filtration surgery, Drug Delivery and Translational Research (2025) 1–18.
[152] A. Hildebrand, M. Romarís, L.M. Rasmussen, D. Heinegård, D.R. Twardzik, W. A. Border, E. Ruoslahti, Interaction of the small interstitial proteoglycans biglycan, decorin and fibromodulin with transforming growth factor beta, Biochem. J. 302 (Pt 2) (1994) 527–534 (Pt 2).
[153] S. Gu, Y. Liu, J. Zou, W. Wang, T. Wei, X. Wang, L. Zhu, M. Zhang, J. Zhu, T. Xie, Y. Yao, L. Qiu, Retinal pigment epithelial cells secrete miR-202-5p-containing exosomes to protect against proliferative diabetic retinopathy, Exp. Eye Res. 201 (2020) 108271.
[154] C.-C. Hsiao, Y.-C. Chang, Y.-T. Hsiao, P.-H. Chen, M.-C. Hsieh, W.-C. Wu, Y.-H. Kao, Triamcinolone acetonide modulates TGF-β2-induced angiogenic and tissue-remodeling effects in cultured human retinal pigment epithelial cells, Mol. Med. Rep. 24 (5) (2021) 802.
[155] D. Liu, J. Du, H. Xie, H. Tian, L. Lu, C. Zhang, G.-T. Xu, J. Zhang, Wnt5a/β-catenin-mediated epithelial-mesenchymal transition: a key driver of subretinal fibrosis in neovascular age-related macular degeneration, J. Neuroinflammation 21 (1) (2024) 75.
[156] X. Chen, H. Yan, Y. Chen, G. Li, Y. Bin, X. Zhou, Moderate oxidative stress promotes epithelial–mesenchymal transition in the lens epithelial cells via the TGF-β/Smad and Wnt/β-catenin pathways, Mol. Cell. Biochem. 476 (3) (2021) 1631–1642.
[157] X. Wang, K. Chen, Y. Yao, Y. Lin, J. Yang, Y. Zhu, B. Zhou, TGFβ1-Induced fibrotic responses of conjunctival fibroblasts through the Wnt/β-Catenin/CRYAB signaling pathway, Am. J. Pathol. 194 (9) (2024) 1764–1779.
[158] M. Li, Y. Yuan, Q. Chen, R. Me, Q. Gu, Y. Yu, M. Sheng, B. Ke, Expression of Wnt/β-Catenin signaling pathway and its regulatory role in type I collagen with TGF-β1 in scleral fibroblasts from an experimentally induced Myopia Guinea pig model, Journal of Ophthalmology 2016 (1) (2016) 5126560.
[159] Q. Chen, N. Jiang, Y. Zhang, S. Ye, X. Liang, X. Wang, X. Lin, R. Zong, H. Chen, Z. Liu, Fenofibrate inhibits subretinal fibrosis through suppressing TGF-β—Smad2/3 signaling and wnt signaling in neovascular age-related macular degeneration, Front. Pharmacol. 11 (2020) 2020.
[160] R. Kumar, A. Singh, K. Sharma, D. Dhasmana, N. Garg, P.F. Siril, Preparation, characterization and in vitro cytotoxicity of fenofibrate and nabumetone loaded solid lipid nanoparticles, Mater. Sci. Eng. C 106 (2020) 110184.
[161] K. Lai, C. Luo, X. Zhang, P. Ye, Y. Zhang, J. He, K. Yao, Regulation of angiogenin expression and epithelial-mesenchymal transition by HIF-1α signaling in hypoxic retinal pigment epithelial cells, Biochim. Biophys. Acta Mol. Basis Dis. 1862 (9) (2016) 1594–1607.
[162] T. Li, X. Li, Y. Hao, J. Liu, B. Bao, Z. Yang, M. Zhou, H. Wei, R. Zhang, J. Hao, W. Jiang, H. Bi, D. Guo, Inhibitory effect of miR-138-5p on choroidal fibrosis in lens-induced Myopia Guinea pigs via suppressing the HIF-1α signaling pathway, Biochem. Pharmacol. 211 (2023) 115517.
[163] C. Shoda, D. Lee, Y. Miwa, S. Yamagami, H. Nakashizuka, K. Nimura, K. Okamoto, H. Kawagishi, K. Negishi, T. Kurihara, Inhibition of hypoxia-inducible factors suppresses subretinal fibrosis, FASEB J. 38 (13) (2024) e23792.
[164] S. Li, K. Pang, S. Zhu, K. Pate, J. Yin, Perfluorodecalin-based oxygenated emulsion as a topical treatment for chemical burn to the eye, Nat. Commun. 13 (1) (2022) 7371.
[165] S. Zhu, H. Shan, J. Li, L. Pan, S. Wang, J. Zhu, H. Guo, F. Mi, X. Wu, J. Yin, K. Pang, Therapeutic potential of topical administration of acriflavine against hypoxia-inducible factors for corneal fibrosis, Front. Pharmacol. ume (2022) 13–2022.
[166] R.K. Vadlapatla, A.D. Vadlapudi, D. Pal, M. Mukherji, A.K. Mitra, Ritonavir inhibits HIF-1α-mediated VEGF expression in retinal pigment epithelial cells in vitro, Eye 28 (1) (2014) 93–101.
[167] J. Zhang, D. Sharma, A. Dinabandhu, J. Sanchez, B. Applewhite, K. Jee, M. Deshpande, M. Flores-Bellver, M.W. Hu, C. Guo, S. Salman, Y. Hwang, N. M. Anders, M.A. Rudek, J. Qian, M.V. Canto-Soler, G.L. Semenza, S. Montaner, A. Sodhi, Targeting hypoxia-inducible factors with 32-134D safely and effectively treats diabetic eye disease in mice, J. Clin. Investig. 133 (13) (2023).

[168] V. Wang, A. Heffer, E. Roztocil, S.E. Feldon, R.T. Libby, C.F. Woeller, A. E. Kuriyan, TNF-α and NF-κB signaling play a critical role in cigarette smoke-induced epithelial-mesenchymal transition of retinal pigment epithelial cells in proliferative vitreoretinopathy, PLoS One 17 (9) (2022) e0271950.
[169] L. Chen, M. Mongan, Q. Meng, Q. Wang, W. Kao, Y. Xia, Corneal wound healing requires IKB kinase β signaling in keratocytes, PLoS One 11 (3) (2016) e0151869.
[170] K. Huang, R. Guo, H. Luo, H. Liu, D. Chen, T. Deng, J. Li, J. He, Z. Xu, M. Li, Q. He, Mucoadhesive liposomal delivery system synergizing anti-inflammation and anti-oxidation for enhanced treatment against dry eye disease, J. Contr. Release 368 (2024) 318–328.
[171] X. Cai, S. Seal, J.F. McGinnis, Sustained inhibition of neovascularization in vldlr−/− mice following intravitreal injection of cerium oxide nanoparticles and the role of the ASK1-P38/JNK-NF-κB pathway, Biomaterials 35 (1) (2014) 249–258.
[172] C. Yu-Wai-Man, R. Treisman, M. Bailly, P.T. Khaw, The role of the MRTF-A/SRF pathway in ocular fibrosis, Investig. Ophthalmol. Vis. Sci. 55 (7) (2014) 4560–4567.
[173] J. Luo, G. Tan, K.X. Thong, K.N. Kafetzis, N. Vallabh, C.M. Sheridan, Y. Sato, H. Harashima, A.D. Tagalakis, C. Yu-Wai-Man, Non-viral gene therapy in trabecular meshwork cells to prevent fibrosis in minimally invasive glaucoma surgery, Pharmaceutics (2022).
[174] A.D. Tagalakis, S. Madaan, S.D. Larsen, R.R. Neubig, P.T. Khaw, I. Rodrigues, S. Goyal, K.S. Lim, C. Yu-Wai-Man, In vitro and in vivo delivery of a sustained release nanocarrier-based formulation of an MRTF/SRF inhibitor in conjunctival fibrosis, J. Nanobiotechnol. 16 (1) (2018) 97.
[175] Z. Shi, M. Ren, D.C. Rockey, Myocardin and myocardin-related transcription factor-A synergistically mediate actin cytoskeletal-dependent inhibition of liver fibrogenesis, Am. J. Physiol. Gastrointest. Liver Physiol. 318 (3) (2020) G504–G517.
[176] R.S. Knipe, M. Nurunnabi, C.K. Probst, J.J. Spinney, E. Abe, R.J.C. Bose, K. Ha, A. Logue, T. Nguyen, R. Servis, M. Drummond, A. Haring, P.L. Brazee, B. D. Medoff, J.R. McCarthy, Myofibroblast-specific inhibition of the rho kinase-MRTF-SRF pathway using nanotechnology for the prevention of pulmonary fibrosis, Am. J. Physiol. Lung Cell. Mol. Physiol. 324 (2) (2023) L190–l198.
[177] M.A. Crespo, C.J. Rapuano, Z.A. Syed, Applications of mitomycin C in cornea and external disease, Turk J Ophthalmol 53 (3) (2023) 175–182.
[178] N. Zhang, Y. Yin, S.J. Xu, W.S. Chen, 5-Fluorouracil: mechanisms of resistance and reversal strategies, Molecules 13 (8) (2008) 1551–1569.
[179] S.B. Horwitz, Taxol (Paclitaxel): mechanisms of action, Ann. Oncol. 5 (Suppl 6) (1994) S3–S6.
[180] B.O. Balzamino, L. Dinice, A. Cacciamani, A. Re, F. Scarinci, L. Bruno, P. Cosimi, A. Micera, Short-term in vitro ROS detection and oxidative stress regulators in epiretinal membranes and vitreous from idiopathic vitreoretinal diseases, BioMed Res. Int. 2022 (1) (2022) 7497816.
[181] C. Verdejo, P. Marco, J. Renau-Piqueras, M.D. Pinazo-Duran, Lipid peroxidation in proliferative vitreoretinopathies, Eye 13 (2) (1999) 183–188.
[182] J.C. Fan Gaskin, R.C.K. Kong, M.H. Shah, A.J. Edgley, H.M. Peshavariya, E. C. Chan, Inhibitory effects of 3′,4′-Dihydroxyflavonol in a mouse model of glaucoma filtration surgery and TGFβ1-Induced responses in human tenon's fibroblasts, Transl. Vis. Sci. Technol. 11 (8) (2022), 18-18.
[183] L. Yang, M. Qu, Y. Wang, H. Duan, P. Chen, Y. Wang, W. Shi, P. Danielson, Q. Zhou, Trichostatin A inhibits transforming growth factor-β-induced reactive oxygen species accumulation and myofibroblast differentiation via enhanced NF-E2-related factor 2-antioxidant response element signaling, Mol. Pharmacol. 83 (3) (2013) 671–680.
[184] T. Wang, W. Cao, X. Wang, M. Dong, L. Yu, Y. Feng, N. Yang, H. Song, Composite synthetic protein hydrogel for inhibition of corneal fibrosis and treatment of corneal wounds, Int. J. Biol. Macromol. 307 (2025) 142013.
[185] J. Yang, J. Li, Q. Wang, Y. Xing, Z. Tan, Q. Kang, Novel NADPH oxidase inhibitor VAS2870 suppresses TGF-β-dependent epithelial-to-mesenchymal transition in retinal pigment epithelial cells, Int. J. Mol. Med. 42 (1) (2018) 123–130.
[186] X. Ma, W. Wu, M. Hara, J. Zhou, C. Panzarin, C.M. Schafer, C.T. Griffin, J. Cai, J.-X. Ma, Y. Takahashi, Deficient RPE mitochondrial energetics leads to subretinal fibrosis in age-related neovascular macular degeneration, Commun. Biol. 7 (1) (2024) 1075.
[187] D.Y. Shu, E.R. Butcher, M. Saint-Geniez, Suppression of PGC-1α drives metabolic dysfunction in TGFβ2-Induced EMT of retinal pigment epithelial cells, Int. J. Mol. Sci. (2021).
[188] L. Xiang, X. Wang, Q. Jiao, Y. Shao, R. Luo, J. Zhang, X. Zheng, S. Zhou, Y. Chen, Selective inhibition of glycolysis in hepatic stellate cells and suppression of liver fibrogenesis with vitamin A-derivative decorated camptothecin micelles, Acta Biomater. 168 (2023) 497–514.
[189] M. Wang, F. Zeng, F. Ning, Y. Wang, S. Zhou, J. He, C. Li, C. Wang, X. Sun, D. Zhang, J. Xiao, P. Hu, S. Reilly, H. Xin, X. Xu, X. Zhang, Ceria nanoparticles ameliorate renal fibrosis by modulating the balance between oxidative phosphorylation and aerobic glycolysis, J. Nanobiotechnol. 20 (1) (2022) 3.
[190] T. Fujisawa, H. Miyai, K. Hironaka, T. Tsukamoto, K. Tahara, Y. Tozuka, M. Ito, H. Takeuchi, Liposomal diclofenac eye drop formulations targeting the retina: formulation stability improvement using surface modification of liposomes, Int. J. Pharm. 436 (1) (2012) 564–567.
[191] Y. Inokuchi, K. Hironaka, T. Fujisawa, Y. Tozuka, K. Tsuruma, M. Shimazawa, H. Takeuchi, H. Hara, Physicochemical properties affecting retinal Drug/Coumarin-6 delivery from nanocarrier systems via eyedrop administration, Investig. Ophthalmol. Vis. Sci. 51 (6) (2010) 3162–3170.
[192] A. Janaszewska, J. Lazniewska, P. Trzepiński, M. Marcinkowska, B. Klajnert-Maculewicz, Cytotoxicity of dendrimers, Biomolecules 9 (8) (2019).
[193] M. Ghezzi, S. Pescina, C. Padula, P. Santi, E. Del Favero, L. Cantù, S. Nicoli, Polymeric micelles in drug delivery: an insight of the techniques for their characterization and assessment in biorelevant conditions, J. Contr. Release 332 (2021) 312–336.
[194] L. Fang, J. Liu, Z. Liu, H. Zhou, Immune modulating nanoparticles for the treatment of ocular diseases, J. Nanobiotechnol. 20 (1) (2022) 496.
[195] W. Greene, T. Burke, G. Bramblett, Ltc, H.-C. Wang, Detection of retinal fibrosis in a rabbit model of penetrating eye injury, Mil. Med. 185 (Supplement_1) (2020) 443–447.
[196] B. Mahaling, S.W.Y. Low, S. Ch, U.R. Addi, B. Ahmad, T.B. Connor, R.R. Mohan, S. Biswas, S.S. Chaurasia, Next-generation nanomedicine approaches for the management of retinal diseases, Pharmaceutics (2023).
[197] J.T. Cox, D. Eliott, L. Sobrin, Inflammatory complications of intravitreal Anti-VEGF injections, J. Clin. Med. 10 (5) (2021).
[198] L. Huang, W. Liang, K. Zhou, R.A. Wassel, Z.D. Ridge, J.X. Ma, B. Wang, Therapeutic effects of fenofibrate nano-emulsion eye drops on retinal vascular leakage and neovascularization, Biology 10 (12) (2021).
[199] K. Hironaka, Y. Inokuchi, Y. Tozuka, M. Shimazawa, H. Hara, H. Takeuchi, Design and evaluation of a liposomal delivery system targeting the posterior segment of the eye, J. Contr. Release 136 (3) (2009) 247–253.
[200] J. Zuo, Y. Pan, Y. Wang, W. Wang, H. Zhang, S. Zhang, Y. Wu, J. Chen, Q. Yao, ROS-Responsive drug delivery system with enhanced anti-angiogenic and anti-inflammatory properties for neovascular age-related macular degeneration therapy, Mater. Today Bio 32 (2025) 101757.
[201] K. Fan, L. Yu, Y. Wu, L. Zheng, X. Yang, J. Lin, M. Wang, Y. Ye, R. Lin, Q. Chen, Z. Liu, Y. Xue, J. Xie, C. Li, Clickable corneal neovascularization therapy with ROS-Responsive polydopamine silica nanoparticles loaded with fenofibrate, Mater. Des. 235 (2023) 112412.
[202] A.H. Ghassemi, M.J. van Steenbergen, H. Talsma, C.F. van Nostrum, D. J. Crommelin, W.E. Hennink, Hydrophilic polyester microspheres: effect of molecular weight and copolymer composition on release of BSA, Pharm. Res. 27 (9) (2010) 2008–2017.
[203] M.R. Mohammadi, A. Nojoomi, M. Mozafari, A. Dubnika, M. Inayathullah, J. Rajadas, Nanomaterials engineering for drug delivery: a hybridization approach, J. Mater. Chem. B 5 (22) (2017) 3995–4018.
[204] B. Mahaling, M. Verma, G. Mishra, S. Chaudhuri, D. Dutta, S. Sivakumar, Fate of GdF3 nanoparticles-loaded PEGylated carbon capsules inside mice model: a step toward clinical application, Nanotoxicology 14 (5) (2020) 577–594.
[205] T.M. Shiju, R. Carlos de Oliveira, S.E. Wilson, 3D in vitro corneal models: a review of current technologies, Exp. Eye Res. 200 (2020) 108213.
[206] M.J. Song, R. Quinn, E. Nguyen, C. Hampton, R. Sharma, T.S. Park, C. Koster, T. Voss, C. Tristan, C. Weber, A. Singh, R. Dejene, D. Bose, Y.C. Chen, P. Derr, K. Derr, S. Michael, F. Barone, G. Chen, M. Boehm, A. Maminishkis, I. Singec, M. Ferrer, K. Bharti, Bioprinted 3D outer retina barrier uncovers RPE-Dependent choroidal phenotype in advanced macular degeneration, Nat. Methods 20 (1) (2023) 149–161.
[207] K. Little, J.H. Ma, N. Yang, M. Chen, H. Xu, Myofibroblasts in macular fibrosis secondary to neovascular age-related macular degeneration - the potential sources and molecular cues for their recruitment and activation, EBioMedicine 38 (2018) 283–291.
[208] R. Gater, T. Ipek, S. Sadiq, D. Nguyen, L. Jones, A. El Haj, Y. Yang, Investigation of conjunctival fibrosis response using a 3D glaucoma tenon's capsule + conjunctival model, Investig. Ophthalmol. Vis. Sci. 60 (2) (2019) 605–614.
[209] G.W. Lee, A. Chandrasekharan, S. Roy, A. Thamarappalli, B. Mahaling, H. Lee, K.-Y. Seong, S. Ghosh, S.Y. Yang, 3D bioprinting of stromal cells-laden artificial cornea based on visible light-crosslinkable bioinks forming multilength networks, Biofabrication 16 (3) (2024) 035002.
[210] S. Roy, S. Yadav, T. Dasgupta, S. Chawla, R. Tandon, S. Ghosh, Interplay between hereditary and environmental factors to establish an in vitro disease model of keratoconus, Drug Discov. Today 24 (2) (2019) 403–416.