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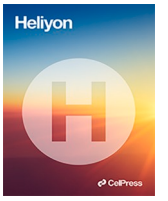

Review article

Tissue engineering strategies for ocular regeneration; from bench to the bedside

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ABSTRACT

Millions globally suffer from visual impairment, complicating the management of eye diseases due to various ocular barriers. The eye's complex structure and the limitations of existing treatments have spurred interest in tissue engineering (TE) as a solution. This approach offers new functionalities and improves therapeutic outcomes over traditional drug delivery methods, creating opportunities for treating various eye disorders, from corneal injuries to retinal degeneration. In our review of recent articles concerning the use of scaffolds for eye repair, we categorized scaffolds employed in eye TE from recent studies into four types based on tissue characteristics: natural, synthetic, biohybrid, and decellularized tissue. Additionally, we gathered data on the cell types and animal models associated with each scaffold. This allowed us to gather valuable insights into the benefits and drawbacks of each material. Our research elucidates that, in comparison to conventional treatment modalities, scaffolds in TE emulate the extracellular matrix (ECM) of the eye and facilitate cell proliferation and tissue regeneration. These scaffolds can be precisely tailored to incorporate growth factors that augment the healing process while also providing considerable advantages such as bacterial inhibition, biocompatibility, and enhanced durability. However, they also have drawbacks, such as potential immune responses, poor tissue integration, complex and costly manufacturing, and inconsistent degradation rates that can affect their effectiveness. In this review, we provide an overview of the present condition of eye regenerative treatments, assess notable preclinical and clinical research endeavors, contemplate the obstacles encountered, and speculate on potential advancements in the upcoming decade.

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1. Introduction

253 million individuals worldwide had vision impairment in 2017, of which 35 million were totally blind, according to the WHO. In fact, blindness and loss of vision rank among the most significant health issues that have an impact on patients' physical and mental well-being, particularly in older ages [1,2]. Unfortunately, damage to the eye often results in irreversible vision loss, with current treatments unable to fully restore lost vision [3]. At present, there is no established therapy for these degenerative conditions affecting the retina, cornea, and lens [4].

Ocular tissue engineering (TE) offers considerable benefits compared to existing standard treatments by emphasizing regenerative capabilities, customization, and sustainable solutions. It seeks to repair damaged ocular tissues, such as the cornea and retina, which may lead to the reversal of vision loss, while conventional treatments typically focus on alleviating symptoms without addressing the root causes [5]. By employing the patient's own cells, ocular TE minimizes the likelihood of rejection and complications associated with the use of foreign materials [6]. Moreover, it provides lasting solutions that enhance functional outcomes, improving visual acuity and overall quality of life, in contrast to standard treatments that often necessitate ongoing care [7]. Additionally, this approach offers innovative strategies for managing complex ocular diseases that are frequently inadequately treated by traditional methods [8]. In summary, TE in ophthalmology has shown great promise within the area of ocular regeneration [9].

Scientists have developed artificial corneas made from biocompatible materials that can be implanted in patients with corneal damage or disease [10,11]. One major aspect of TE in ophthalmology is the use of scaffolds, which play an essential role in supporting structural integrity and promoting cell growth and TE. Scaffolds are three-dimensional structures that imitate the extracellular matrix (ECM) of tissues and offer a structure for the attachment, growth, and differentiation of cells [12,13]. In ophthalmology, scaffolds can be used to repair damaged corneal tissue, restore vision, and treat various ocular diseases. Various scaffolds have been employed in ophthalmic TE, encompassing both natural materials like collagen, fibrin, and hyaluronic acid, and synthetic materials such as poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) [10,14]. The scaffolds can be tailored to possess distinct characteristics, such as biocompatibility, biodegradability, and mechanical strength, in order to meet the requirements of various ocular tissues [15].

Scientists have also investigated the utilization of stem cells in conjunction with scaffolds for the purpose of ocular regeneration. Stem cells possess the capacity to undergo differentiation into distinct cell types that are present in the eye. This characteristic makes them a highly promising and viable option for the regeneration of impaired tissues [16]. By seeding stem cells onto scaffolds, researchers can create complex tissue structures that closely resemble native eye tissues [17]. In recent years, advancements in biomaterials science and TE techniques have enabled researchers to develop innovative scaffold-based therapies for various ocular conditions. For example, corneal scaffolds have been used to treat corneal ulcers, while retinal scaffolds have been developed for the treatment of retinal degenerative disorders, such as age-related macular degeneration [18,19]. Current management options for these diseases have limitations: 1. Laser surgery and vitrectomy, while utilized, are frequently damaging and do not adequately tackle the fundamental crucial Basis of these disorders [4,20]. 2. Photodynamic therapy (PDT) may result in problems such as bleeding in the retina and vitreous, as well as the rupture of cells in the retinal pigment epithelium (RPE) [21]. 3. Angiostatic steroids necessitate repeated intravitreal injections and are associated accompanied by a multitude of adverse reactions when used for an extended period of time [22]. 4. Anti-vascular endothelial growth factor (Anti-VEGF) agents, while effective for some, fail to consider the function of inflammation in the development of diseases, and a substantial portion of patients continue to be unresponsive to this treatment [4,21]. 5. Gene therapies such as Luxturna, while revolutionary, encounter obstacles in manufacturing, research methodology, evaluation of long-term safety, and marketability, in addition to having potential negative effects [23]. 6. Tissue transplantation faces issues such as donor shortages, high rejection rates, and post-operative complications like infections [4,24–26]. TE strategies offer potential solutions to overcome these limitations. This interdisciplinary field combines biology with material science and employs two main approaches: Cell-based tactics involve the manipulation of cells to establish a customized microenvironment prior to transplantation. On the other hand, scaffold-based strategies utilize an artificial extracellular matrix (ECM) that imitates the natural structures of the body [27].

Scaffold-based methods stand out for their adaptability. In scaffold-based TE, scaffolds are designed with specific physical and chemical properties to promote cell adhesion, differentiation, and growth [28]. Ensuring scaffold biocompatibility is crucial for supporting cellular proliferation. Biodegradable and bioactive scaffolds have continued to develop over the last two decades with the goal of avoiding secondary surgeries to remove implants, stimulating cellular activities and functions, and eventually facilitating tissue regeneration in situ with leveraging the natural regenerative abilities of body tissues [4,24,27,29]. Moving forward, the translation of scaffold-based therapies from bench to bedside will require rigorous preclinical testing and clinical trials to ensure their safety and efficacy. Collaborations between researchers, clinicians, regulatory agencies, and industry partners will be vital for bringing these innovative therapies to patients in need. This study aims to review recent developments in eye TE and reconstruction, focusing on new strategies, challenges, and prospects. In this review article, we conducted a comprehensive search of databases including PubMed, ScienceDirect, and Google Scholar, selecting around 126 original and review research papers published between 2000 and 2024 for inclusion in our analysis.

1.1. Tissue engineering and common eye diseases

The first to third most common eye diseases that may be addressed through TE include corneal diseases (prevalence rate approximately 1 in 500), age-related macular degeneration (AMD) (affecting about 10 % of individuals over 65), and diabetic retinopathy (prevalence rate around 30 % among diabetics), all of which present opportunities for innovative therapeutic interventions [30–33].

TE presents significant potential for the treatment of various ophthalmopathies through the regeneration or repair of damaged ocular tissues. A key focus area is corneal diseases, where TE techniques can facilitate the regeneration of corneal stroma using biomaterials and stem cells to restore transparency and functionality [34]. In cases such as keratoconus, methods like collagen cross-linking and grafting are utilized to enhance corneal strength [35]. Furthermore, in the context of ocular surface disorders like limbal stem cell deficiency, the cultivation of limbal stem cells on appropriate scaffolds has been shown to restore the corneal epithelium and improve visual outcomes [36]. Engineered grafts also contribute to the healing of the corneal surface in instances of persistent epithelial defects [37].

In the field of retinal disorders, TE strategies are being investigated for conditions such as age-related macular degeneration (AMD). The development of retinal pigment epithelium (RPE) patches derived from stem cells offers a potential solution for replacing damaged cells [38]. Additionally, engineered retinal patches can aid in the reattachment and support of the retina in cases of retinal detachment [39]. These advancements are critical for restoring vision in patients with degenerative retinal diseases.

Moreover, TE is advancing in the treatment of glaucoma through the creation of implants designed to regulate intraocular pressure or regenerate damaged optic nerve fibers [40]. In the case of uveitis, the development of tissue-engineered drug-delivery systems allows for localized treatment aimed at reducing inflammation in the uvea [41]. Finally, TE approaches are also focused on regenerating the optic nerve using nerve grafts or scaffolds to support neuronal growth [42]. The field of eye TE has emerged as a significant area of clinical practice and research, offering innovative strategies that collectively promise to enhance the quality of life for patients with various ocular conditions [30,43].

1.2. Tissue engineering in regeneration

The main element for sustaining human life is the innate ability to repair itself naturally after physical damage [44]. Over the past three decades, there has been a notable development in the field of TE and regenerative medicine. This field primarily aims to regenerate impaired tissues, rather than resorting to their complete replacement. The approach involves the creation of biological substitutes that have the potential to restore and enhance tissue functionality [45]. The term 'tissue engineering' was initially introduced at a workshop organized by the National Science Foundation (NSF) at Granlibakken, California [22]. TE is classified into three categories, namely: 1. isolated cell implantation, which involves the transplantation of individual cells; 2. administration of growth agents to the cells to promote cellular proliferation; and 3. incorporation of cells onto or within various scaffolds designed to stimulate the production or secretion of ECM. The latter is the most frequently utilized TE technique, which involves the placement of viable cells onto synthetic or natural extracellular scaffolds to generate a substrate that can be implanted [46]. The surface of a scaffold serves as the primary locus for interaction with the surrounding milieu, thereby influencing the cell adhesion, cell proliferation, and cell differentiation [47]. The critical juncture lies in the chance to promote vascularization of the voluminous scaffolds, thereby facilitating the adequate supply of minerals, nutrients, oxygen, and growth factors necessary for tissue regeneration [48].

The scaffold has been created to specifically attract cells to the required volume for regeneration, enabling them to subsequently undergo cell division, and specialization, and finally form tissue within the scaffold. Over a period, the scaffold will deteriorate, resulting in the exclusive presence of the regenerated tissue [44,49]. Tissue-engineered nerve grafts (TENGs) have been identified as a viable alternative for autologous nerve grafts, which are considered as the most effective method for repairing peripheral nerves [50]. Henceforth, cell-based therapies are regarded as a preferred approach in tissue regeneration [51,52]. Restoring the functionality of impaired bodily tissues through the repair or reconstruction of faulty structures has long been a goal of medical science. TE has emerged as a field dedicated to tackling this very challenge [53].

1.3. Safety concerns for scaffold biomaterials

Safety considerations regarding scaffold biomaterials in TE and regenerative medicine encompass several critical dimensions. Primarily, the assurance of biocompatibility is fundamental to prevent adverse immune responses or toxicity [54]. Furthermore, the degradation products generated by scaffolds must be non-toxic and should not elicit inflammatory reactions [55]. The mechanical properties of scaffolds are also of paramount importance, as they must possess adequate strength to support tissue development without structural failure [56]. Ensuring sterility is critical to preventing post-implantation infections, while the maintenance of long-term stability is essential for mitigating the risk of chronic complications; furthermore, strict adherence to regulatory standards is imperative to guarantee safety and efficacy prior to clinical application [57–59]. Additionally, scaffolds should facilitate appropriate cellular interactions, including adhesion and differentiation, while avoiding any aberrant cellular behavior [60]. The origin of biomaterials presents substantial concerns regarding potential disease transmission and ethical implications, necessitates a comprehensive evaluation of their environmental impact to mitigate ecological risks, and underscores the importance of individualized assessments of scaffold safety due to variability in patient responses [61–63]. Addressing these safety considerations is imperative for the successful application of scaffold biomaterials in clinical practice, particularly in the realm of ocular diseases, where factors such as biocompatibility, sterility, and mechanical properties of scaffolds are critical for achieving favorable outcomes and minimizing complications associated with the regeneration and repair of ocular tissues.

1.4. Perspective for ocular tissue engineering

Ocular TE is increasingly recognized as a pivotal area within regenerative medicine, focusing on the restoration of vision and the repair of compromised ocular structures through the application of innovative biomimetic scaffolds and cellular therapies [64]. Recent

scholarly investigations underscore the development of advanced biomaterials that not only exhibit optimal biocompatibility and biodegradability but also possess mechanical properties specifically designed to accommodate the delicate environment of the eye [65]. Current research endeavors emphasize the utilization of stem cell technologies, particularly induced pluripotent stem cells (iPSCs), in conjunction with growth factors to enhance tissue regeneration and functionality in ocular applications [66]. Furthermore, the incorporation of 3D bioprinting and nanotechnology is gaining traction, enabling the fabrication of complex, structured tissues that closely replicate the architecture of natural ocular tissues, thereby enhancing the precision of TE methodologies [67,68].

Recent literature also highlights the critical importance of addressing safety concerns, including the risks of immune rejection and infection, which are essential for the successful translation of these technologies into clinical practice [69]. Compliance with regulatory standards and the ethical implications associated with the use of biological materials remain significant considerations that necessitate careful navigation [70,71]. The successful implementation of these advanced techniques in ocular TE holds considerable promise for improving therapeutic options for a spectrum of ocular diseases, such as corneal injuries, retinal degeneration, and glaucoma, ultimately enhancing patient outcomes and quality of life. Emerging studies suggest that personalized approaches, including the development of patient-specific scaffolds and targeted delivery systems, may further revolutionize treatment paradigms within this field [72] (Fig. 1).

2. Scaffolds used for eye tissue engineering

In this study, the scaffolds utilized for ocular TE have been classified into four categories according to tissue type: natural, synthetic, biohybrid, and decellularized tissue, with further details available in Table 1.

2.1. Natural biomaterials

2.1.1. Conjunctiva

Autologous fibrin has emerged as an effective conjunctival scaffold, particularly in studies utilizing the New Zealand white strain rabbit model. This approach involves harvesting fibrin from the patient, which is then utilized as a structural matrix for cultivating conjunctival tissue aimed at repairing conjunctival abnormalities. Research indicates that the efficacy of autologous fibrin in this

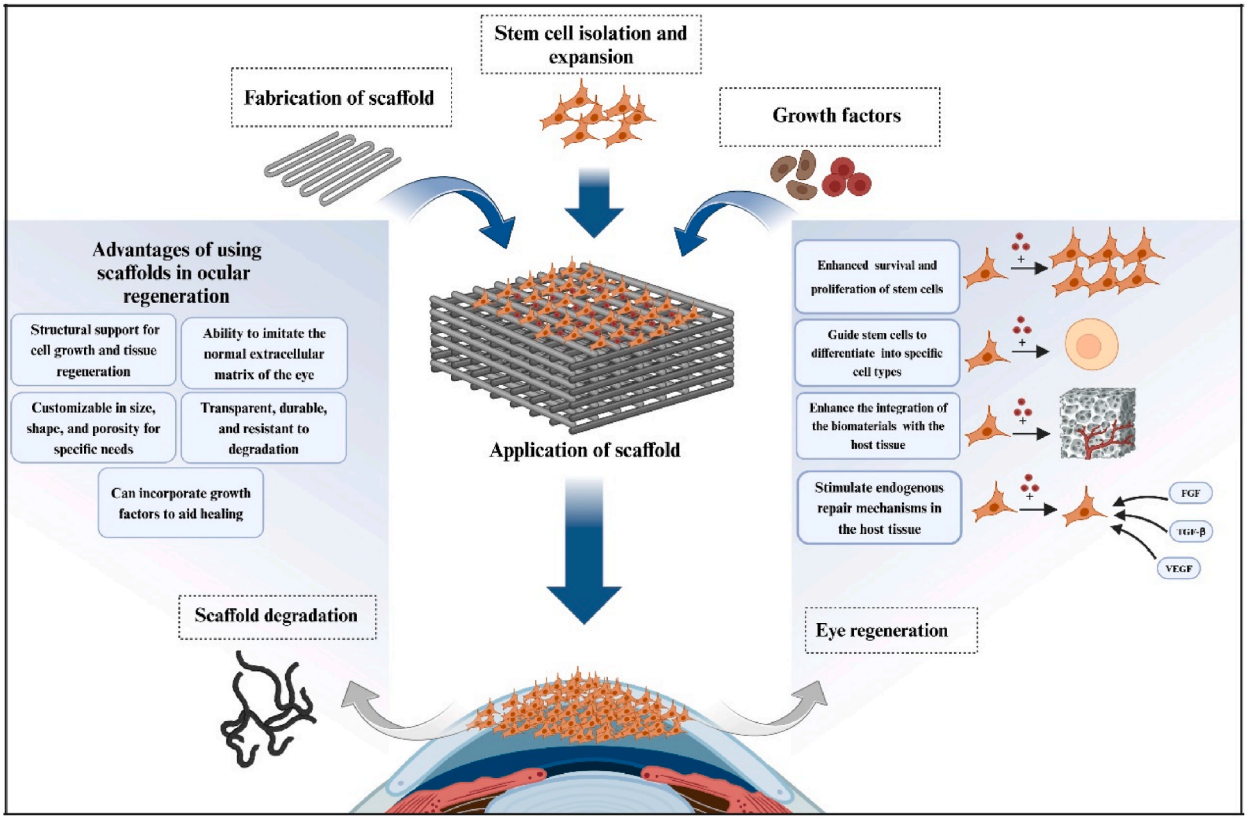

Fig. 1. This image shows the important role of scaffolds in eye tissue engineering. Scaffolds provide structural support and facilitate cell adhesion and growth, in addition to adding growth factors to enhance cell activity and differentiation and promote eye regeneration. Together, they create an optimal environment for eye tissue repair.

Table 1
Cell types, model studies, and advantages/disadvantages of biomaterials used in ocular tissue engineering.

Tissue	Material	Biomaterial	Cell types	Model study	Advantage	disadvantage	Ref.
Conjunctiva	Natural	autologous fibrin	CjECs	NZW strain rabbits	The availability, cost-effectiveness, and high tolerance to culture conditions, degrading swiftly without any detrimental impact on the survival of the cultivated limbal epithelial cells	not being contracted by stromal cells, in contrast to using collagen as substrate,	[73]
	Biohybrid	(SF/PLCL)	rCjECs	mice	having outstanding biocompatibility, demonstrating exceptional manifestation of CjEC genes and decreasing manifestation of inflammatory mediators, the capability to create a well-organized conjunctival epithelium, which includes the presence of goblet cells	Not applicable	[96]
		(PLA/EFMs) surface coated by CNF and/or SP loaded with LF	CjECs	NZW (New Zealand white) rabbits	Effective suppression of bacterial growth and reduction of antibiotic usage after surgery	Not applicable	[93]
		SF-rGo	CJMSCs	In vitro	offering advantageous mechanical and cytocompatibility characteristics, as well as a larger surface-to-area ratio compared to alternative manufacturing techniques by using SF, exhibiting exceptional electrical conductivity by use of rGO	Not applicable	[94]
		(collagen/PLCL)	CjECs	in vitro	displaying advantageous mechanical properties, wettability, and the ability to promote cell proliferation/mimicking the ECM and supporting the growth and differentiation of goblet cells/not induce an upregulation of IL-4, IL-5, and IL-6 expression, unlike what is observed in TCPS (tricalcium phosphate scaffold) culture	Not applicable	[95]
Cornea	Natural	microgrooved collagen films	CEC	In vitro	displaying comparable optical clarity, swelling and biodegradability Compared to the natural cornea, which promoted epithelial cell migration, wound healing, and keratocyte fibrosis retardation	Not applicable	[74]
		collagen-glycosaminoglycan	corneal keratocyte cell	In vitro	Characteristics include transparency, strength, elasticity, cell development, and resistance to collagenase destruction	Decreasing collagen synthesis	[75]
	Biohybrid	PCL microfibrous scaffold infused with rat tail collagen type I	LSSCs (in vitro)-keratocytes (in vivo)	Rat	Enhancing the organization of collagen and reducing the presence of fibroblasts and myofibroblasts in injured corneas, promoting	Not applicable	[10]

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Table 1 (*continued*)

Tissue	Material	Biomaterial	Cell types	Model study	Advantage	disadvantage	Ref.
					the ECM-related pathway and increasing the expression of various ECM-related genes in the injured group		
		biodegradable silk fibroin-based scaffolds containing GDNF	–	mice	promoting epithelialization, keratocyte and epithelial cell proliferation, stromal nerve plexus development, and anti-apoptotic activity	Not applicable	[12]
		(GelMA-HA)	Rabbit CS cell	In vitro	supplying CS cells with cues for spatial and directional organization and ECM remodeling	Not applicable	[101]
		(PVA-COL)	Human and rabbit CEC	In vitro/ rabbit	Making stratified epithelial histologically and functionally similar to healthy epithelial surface	Not expressing collagen type IV and VII even with soluble laminin and the protease inhibitor aprotinin, Failure to achieve stable epithelialization in vivo	[19]
		(AM)- (PVA-AM)	rabbit CEC	Japanese white rabbits	Being easy to handle and transplant to the cornea, Benefiting from AM tissue's inherent basement membrane and PVA's transparency and durability	Stabilizing the AM component of PVA-AM is still an issue remaining to be resolved	[97]
		(GP/PVA/SF/n-HA)	HCFs cells	In vitro	Regularizing PVA/SF/n-HA composite hydrogel, enhancing heat stability, and reducing moisture	Not applicable	[98]
		VH	–	rabbit	Biomechanical stability and optical transparency, preventing infections caused by S. aureus in implanted devices. in vivo and in vitro	Not applicable	[99]
		Aligned (PVA-COL)	HKs and HCECs	In vitro	Similar mechanical strength to real corneal tissue, enhancing electrospun scaffold mechanical characteristics	Not applicable	[100]
		sHAPN copolymers	rabbit cornea cells	In vitro/ rabbit	Being a thermo-responsive carrier, enhancing the ocular bioavailability of multiple ophthalmic medications, delivering crucial therapeutic benefits such as anti-inflammatory properties and corneal protection	Not applicable	[103]
		oHA	keratocytes	rabbit	enhancing gelatin microcarriers for greater oHA grafting by leveraging oxidation levels in aldehyde HA	Not applicable	[102]
	Decellular	LCs	primary corneal endothelial cells	In vitro	Increasing the surface area of focal adhesions in cells cultured on coated liquid crystals by at least twofold compared to other settings	completed digestion after 13 h for LC and amniotic membrane, whereas the DM was digested after 17 h	[109]
		decellularized (SMILE) lenticule (SL), (AM), and collagen-coated plates	hADSCs	New Zealand male rabbits	can culture Keratocytes better	Not applicable	[108]

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Table 1 (*continued*)

Tissue	Material	Biomaterial	Cell types	Model study	Advantage	disadvantage	Ref.
		carbodiimide crosslinked RHC	–	Human	Being stable for four years without rejection episodes and without immunosuppression, correcting visual acuity of 20/54 and gaining more than 5 Snellen lines on an eye chart	Not applicable	[110]
		Native porcine conjunctiva	CEC	rabbit	Better optical transmittance, tensile strength, stability, biocompatibility, and degradation resistance in vitro and in vivo, longer survive of donor cells	Not applicable	[111]
		Porcine	rabbit corneal limbal epithelial cells	In vitro	Not applicable	The necessity of Future research to assess the endurance of the treated cornea and study in vitro cell recellularization and penetration in the corneal matrix	[112]
		decellularized Human doner cornea	LEPC, LMSC and LM	In vitro	Using non-immunogenic tissue scaffolds for transplantation and having the ability to be repopulated by host cells either in situ or in vitro	Not applicable	[113]
		(FD-APCS)	CEC	In vitro/ NZW rabbits	Having no major differences from the APCS-transplanted or native cornea, providing a void area for cells and a collagen lamellae ultrastructure identical to native cornea stroma	Not applicable	[114]
		Decellularized murine corneas	(hESC-CEC)	In vitro	Not applicable	Not applicable	[119]
		decellularized human cornea	hCEC and hLEC	In vitro	Presenting characteristic indicators of (hCEC) and (hLEC) on their respective surfaces.	The vitality of Further research to evaluate if corneal structures are suitable for transplantation.	[120]
lacrimal gland	Synthetic	polyester membrane PES	pLGACs	In Vitro	Not applicable	Not applicable	[82]
			Lacrimal acinar epithelial cells of Sprague-Dawley rats	In Vitro	Excellent oxidative, thermal, and hydrolytic stability	Not being biodegradable	[81]
	Decellular	SIS-Muc	Porcine LG epithelial cells	In Vitro	Promoting normal lacrimal fluid production in epithelial cells grown on SIS-Muc, mimicking natural LG acini polarization	Failure to observe polarization or acini-like features in synthetic tissue	[116]
		NZW rabbit lacrimal glands ECM	adult rabbit lacrimal gland progenitor cells	In vitro	keeping cells alive and secreting for four weeks	Further research is needed to optimize decellularization	[13]
		DC-LG	LG epithelial cells	In vitro	A three-dimensional, supporting, and accessible matrix provides LG-specific ECM protein amounts, distribution, and composition	Requiring to Further evaluation of this LG construct by functional research in vivo	[115]
Lens	Biohybrid	biodegradable HA and nondegradable polymeric gel	–	Dutch Belt pigmented and NZW rabbits	Excellent cortical anatomy and lens clarity	Transparent regrowth in the lens and peripheral capsule bag, with opacified regrowth behind the polymeric scaffold	[104]

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Table 1 (*continued*)

Tissue	Material	Biomaterial	Cell types	Model study	Advantage	disadvantage	Ref.
Retina	Natural	GCH	Human embryonic stem cells	mouse	promoting retinal cell differentiation over other anterior forebrain cells and inducing a modest immune response, allowing the implant to survive 12 weeks	basic retinal lamination and cytoplasmic transfer instead of photoreceptor layer implantation	[77]
		Cask and Caskin1	–	In vitro	Having Global synaptic function	Not applicable	[76]
		RS1	–	In vitro	stabilizing retinal integrity	Not applicable	[79]
		Fibrin hydrogel	CJMSCs	In vitro	promoting cell growth and proliferation without harming cells Because of its flexibility and continual disintegration, fibrin hydrogel	Not applicable	[78]
	Synthetic	PCL	Mouse and Human RPCs	In vitro/ Adult Rho -/- or wildtype mice	the ability to engage with mRPCs and human RPCs and drive them toward a photoreceptor fate, allowing cell differentiation before transplantation	Not applicable	[17]
		PLLA and PLGA	RPCs	In vitro/rat	Being desired to simulate retinal polarization	Not applicable	[83]
		PLGA	RGCs	rabbits and monkeys	been discovered in rabbits' intraocular environments after 3 months	The necessity of Future studies to adjust the molecular weight of PLGA substance and extending the observation duration to determine the scaffold's biodegradability in vivo	[85]
		Laminin coated novel nanowire PCL	Mouse RPCs	Rho −/− mice	Showing Biocompatibility by cell attachment and sustained proliferation	Not applicable	[84]
		polyethylene terephthalate or poly (L-lactide-co-ε-caprolactone)	hfRPE	In vitro/ female Chinchilla Bastard rabbit	showing favorable subretinal biocompatibility	Not applicable	[86]
		microfabricated poly (glycerol-sebacate)	RPCs	In vitro	having a 10-fold higher maximum elongation at failure than earlier RPC scaffolds, significantly improving mechanical characteristics and reducing scaffold thickness	Not applicable	[87]
		PCL, PGS and POC	RPCs	In vitro	enhancing scaffold hydrophilicity and degradation, accelerating human retinal pigment epithelial cell proliferation, decreasing fiber diameter, and boosting tensile modulus	Not applicable	[18]
		3-D PCL cell encapsulation scaffold	Mouse RPC	In vitro	Enabling regulated, accurate, targeted administration of cells to the subretinal area, providing various benefits compared to earlier 2 and 2.5-D structures used for retinal progenitor cell transplantation/having the structure which is highly porous, facilitating diffusion and potential cell interactions from both the neural retina and the RPE	Not applicable	[88]

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Table 1 (*continued*)

Tissue	Material	Biomaterial	Cell types	Model study	Advantage	disadvantage	Ref.
		PLGA	hiPSC -derived retinal progenitor cells	In vitro	Modifications in the dimensions of the pores, the distance between the slices, the distance between the hatches, and the type of hatching.	Not applicable	[89]
		PLGA	hiPSC retinal organoid derived RGCs	rhesus monkey	allowing transplanted tissues to survive 1 year without tumorigenesis with enough graft–host contact	Not applicable	[14]
		PCL and PEG included taurine	CJMSCs	In vitro	assisting CJMSCs develop into photoreceptors by Taurine	Not applicable	[16]
	Biohybrid	(RWSF/PCL/Gt)	RPE	rabbits	Having good in vitro and in vivo cytocompatibility for RPE implantation as a prosthetic Bruch's membrane	Not applicable	[15]
		(SF/PLCL)	RPCs	in vitro	greatly increasing RPC proliferation, including photoreceptors with high porosity and ECM topography	Not applicable	[105]
		gelatin/chitosan	RPE	in vitro	imitating additional cellular matrix and Bruch's membrane nanofibrous structure, without cytotoxicity, and not modifying grown hRPE cells on gelatin/scaffold	needing further clinical trials to prove these scaffolds can treat retinal disorders	[106]
		HAMP/PCL	RPE cells	In vitro	Optimizing porosity, degradation, and biocompatibility	The necessity to use more realistic RPE cultures obtained from primary or stem cell cultures in Future investigations	[107]
Optic Nerve	Natural	Netrin-1 gradient	RGCs	In vitro	increasing the amount of transplanted RGCs whose axons reach the optic nerve head	not noticing polarized cell directionality	[80]
	Synthetic	PCL and PBG	RGCP	In vitro	successfully constructed, supporting cell survival and durable long neurite development along fibers	Not applicable	[91]
		PCL coated by tosylate + PEDOT	chick dorsal root ganglia and a mouse neuroblastoma cell line	In vitro	directing the nerve bundle	Not applicable	[90]
		PPy-G	RGCs	In vitro	Increasing RGC density and directing neurite outgrowth and nanofiber direction	Not applicable	[92]
	Decellular	porcine decellularized optic nerve	neurotrophin-3-overexpressing Schwann cells	In vitro/Rat	Increasing dorsal root ganglion neurite directional growth, myelin regeneration, neural stem cell adhesion, survival, and migration, and reducing inflammatory cells and chondroitin sulfate proteoglycan expression	The necessity of future studies to modify ECM proteins on the scaffold, assess animal behavior and electrophysiological function, and conduct large animal models for preclinical efficacy testing	[118]
		DON	DRG neurites	In vitro	causing lengthier extension, greater distances, and branching on the DON than the ON, selectively removing axon-inhibitory substances including myelin-associated glycoprotein	Not applicable	[117]

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Table 1 (*continued*)

Tissue	Material	Biomaterial	Cell types	Model study	Advantage	disadvantage	Ref.
					and chondroitin sulfate proteoglycans by Decellularization		

BrM = Bruch's membrane/ON = optic nerve/RGCs = Retinal Ganglion Cells/WHO = World Health Organization/TE = tissue engineering/NSF = National Science Foundation/AMD = Age-related Macular Degeneration/VEGF= Vascular Endothelial Growth Factor/TENGs = Tissue-engineered nerve grafts/HAM = human amniotic membrane/RS1= Retinoschisin/GCH=Gelatin/Chondroitin sulfate/Hyaluronic Acid/hESC = human embryonic stem cell/ONL= Outer Nuclear Layer/PES= Polyethersulfone/PCL= Polycaprolactone/PLLA= Poly L-lactic Acid/PLGA= Poly Lactic-co-Glycolic Acid/PGS= Poly Glycerol Sebacate/PPy-G = polypyrrole functionalized graphene/PLA= Poly Lactic Acid/EFMs = Electrospun nanofibrous membranes/CNF= Cellulose Nanofibrils/SP= Silk Peptide/LF = levofloxacin/SF= Silk Fibroin/rGo = reduced Graphene oxide/PLCL = poly (L-lactic acid-co-3- caprolactone)/SF/rGO= Silk Fibroin/reduced Graphene oxide/ ECM = extracellular matrix/ Collagen/PLCL = Collagen/poly (L-lactic acid-co-3- caprolactone)/CjECs = Conjunctival Epithelial Cells/SF/PLCL = Silk Fibroin/poly (L-lactic acid-co-3- caprolactone)/GelMA-HA = hyaluronic acid-modified gelatin-methacrylate/PVA-COL= Collagen-Immobilized Poly (Vinyl Alcohol)/AM = Amniotic Membrane/PVA-AM = polyvinyl alcohol hydrogel/GP/PVA/SF/n-HA= Genipin-crosslinked polyvinyl alcohol/silk fibroin/nanohydroxyapatite Hydrogel/PCL/collagen = Polycaprolactone/collagen/HA= Hyaluronic Acid/RWSF= Regenerated wild Antheraea pernyi Silk Fibroin/Gt = Gelatin/HAMP= Human amniotic membrane powder/LCs = Lens Capsules/FD-APCS= Freezing-Dry Acellular Porcine Cornea Stroma/SMILE= Small incision lenticule extraction/SL = lenticule/RHC= Recombinant Human Collagen/NZW= New Zealand White/(SIS-Muc) = Conversely decellularized porcine small intestine submucos/DC-LG = Decellularized porcine LG matrix/DON = Decellularized Optic Nerve/PLA=Poly Lactic Acid/SP= Silk Peptide/CJMSCs= Conjunctiva Mesenchymal Stem Cells/PLCL= Poly L-lactic acid-co-3- Caprolactone/rCjECs = rabbit Conjunctival Epithelial Cells/LCs = Lens Capsules/hADSCs = human Adipose Mesenchymal Stem Cells/PCL= Poly ε-Caprolactone/LSSCs= Limbal Stromal Stem Cells/GDNF = Glial Cell-Derived Neurotrophic Factor/LEPC= Limbal Epithelial Progenitor Cells/LMSC= Limbal Mesenchymal Stromal Cells/LM = Limbal Melanocytes/FD-APCS= Freezing Dry Acellular Porcine Cornea Stroma/GelMA-HA= Hyaluronic Acid-modified Gelatin-Methacrylate/CS= Corneal Stromal/hESC-CEC = human Embryonic Stem Cells- Corneal Epithelial Cells/PVA-COL= Colagen-Immobilized Poly Vinyl Alcohol/CEC= Corneal Epithelial Cells/GP= Genipin/n-HA = nanohydroxyapatite/HCFs = Human Corneal Fibroblasts/VH= Vancomycin-loaded collagen Hydrogels/hCEC = human Corneal Endothelial Cells/hLEC = human Limbal Epithelial Cells/PVA= Aligned Polyvinyl Acetate/HKs = Human Keratocytes/LG = Lacrimal Gland/PLGACs= Purified rabbit Lacrimal Gland Acinar Cells/RPCs= Retinal Progenitor Cells/RS= Retinoschisin/PCL= Polycaprolactone/mRPCs = mouse Retinal Progenitor Cells/hiPSC = human-induced Pluripotent Stem Cell/RPE = Retinal Pigment Epithelial/PEG= Polyethylene Glycol/DRG = Dorsal Root Ganglion/PBG= Poly-gamma-Benzyl-L-Glutamate/RGCP= Retinal Ganglion Cell Progenitors/PEDOT= PSS (polystyrene sulfonate) in water and isopropanol/TCPS = tricalcium phosphate scaffold/LCs = Lens Capsules/DM = Descemet's membrane/DHC = Decellularized Human Cornea/FD-APCS= Freezing Dry Acellular Porcine Cornea Stroma/GelMA-HA= Hyaluronic Acid-modified Gelatin-Methacrylate/PVA= Polyvinyl Alcoholhydrogel/POC= Poly (1,8-Octanediol-co-Citrate)/LSSCs= Limbal Stromal Stem Cells/hfRPE = Human fetal Retinal Pigment Epithelium cells/IL-4, IL-5, and IL-6 = interleukin-4, interleukin-5, Interleukin-6/sHAPN= Sulfated Hyaluronic acid with amine-terminated poly(N-isopropylacrylamide)/oHA = Oxidized hyaluronan.

context is comparable to that of human amniotic membrane (HAM), which has long been considered a gold standard in ocular surface reconstruction due to its anti-inflammatory properties and ability to promote epithelialization [73].

2.1.2. Cornea

In the field of corneal TE, innovative scaffold designs such as microgrooved collagen films and collagen glycosaminoglycan composites have been explored for their potential to mimic natural corneal properties. These scaffolds, tested in vitro, demonstrate several advantageous characteristics, including optical clarity, swelling behavior similar to that of natural cornea, and biodegradability. The microgrooved architecture of the collagen scaffolds is particularly beneficial, as it stimulates epithelial cell migration, accelerates wound healing processes, and reduces keratocyte fibrosis, thereby enhancing the overall regenerative capacity of the corneal tissue [74,75].

2.1.3. Retina

In the context of retinal scaffold development, a diverse array of biomaterials has been investigated, including Cask and Caskin1 proteins, the retinal protein retinoschisin (RS1), a Gelatin/Chondroitin sulfate/Hyaluronic Acid (GCH) composite, and fibrin hydrogel. Cask is essential for maintaining the integrity of all retinal synapses, facilitating synaptic signaling and structural stability. In contrast, Caskin1 appears to have specialized roles in particular retinal synapses, such as promoting neural pathway development and stabilizing synaptic connections during retinal maturation. The GCH scaffold has shown promise in delivering human embryonic stem cell-derived retinal progenitor cells (RPC) to the outer nuclear layer (ONL) of the retina in mouse models of retinal degeneration. Notably, some RPCs have been observed migrating into the inner retinal layers, indicating the scaffold's potential to not only support cell survival but also to facilitate integration within the retinal architecture. Furthermore, the fibrin hydrogel enhances the availability of oxygen and nutrients to transplanted cells, which is crucial for their viability and function post-transplantation [76–79].

2.1.4. Optic nerve

recent studies have explored the application of a Netrin-1 gradient in optic nerve regeneration, yielding encouraging outcomes. The strategic use of a protein gradient on a radially electrospun scaffold has been shown to significantly enhance retinal ganglion cell (RGC) axon growth, guiding axonal extensions in alignment with the developmental pathways of the optic nerve head. This innovative approach holds substantial promise for advancing cell transplantation therapies aimed at treating glaucoma and other optic neuropathies, as it may improve the survival and functional integration of transplanted cells within the damaged neural environment [80].

2.2. Synthetic biomaterials

2.2.1. Lacrimal gland

The fabrication of scaffolds for the lacrimal gland often utilizes polyester membranes and polyethersulfone (PES) due to their favorable mechanical properties. PES is particularly noted for its exceptional stability under in vitro conditions, exhibiting significant resistance to oxidation, thermal degradation, and hydrolysis. These characteristics make PES a promising candidate for a variety of biomedical applications. However, it is important to highlight that PES is non-biodegradable, which may limit its long-term applicability in biological systems, especially in scenarios where gradual degradation is beneficial for tissue integration and healing processes [81,82].

2.2.2. Retina

In the realm of retinal scaffolds, an extensive range of materials has been employed, including Laminin-coated novel nanowire polycaprolactone (PCL), poly(e-caprolactone) (PeCL), poly (L-lactic acid) (PLLA), poly(lactic-co-glycolic acid) (PLGA), polyethylene terephthalate (PET), and poly(L-lactide-co-ε-caprolactone). The synthetic strategies for these materials frequently involve electrospinning to produce nanofibrous structures that enhance surface area and porosity, thereby facilitating cellular infiltration and nutrient exchange. Additional techniques such as 3D bioprinting allow for precise control over scaffold architecture, while solvent casting combined with freeze-drying generates porous structures that closely mimic the ECM. Other materials, including microfabricated poly(glycerol-sebacate), poly(glycerol sebacate) (PGS), poly(1,8-octanediol-co-citrate) (POC), 3-D polycaprolactone (3DPCL), and PEG-modified taurine, have also been explored for their potential as scaffolding materials in retinal TE [16–18,83–89]. The use of Laminin-coated novel nanowire PCL in Rho−/− mice has shown promising biological compatibility, as evidenced by improved cell adhesion and sustained proliferation. These scaffolds have the potential to direct the differentiation of stem cells into photoreceptors, providing a viable platform for pre-transplantation cell differentiation. This capability is essential for preparing cells that are more likely to integrate successfully into host tissue following transplantation [84]. Furthermore, PLGA is particularly advantageous due to its ability to replicate the polarized characteristics of the retina, owing to its adjustable degradation rates and biocompatibility [83,85]. Studies indicate that PLGA scaffolds can support the survival and functionality of retinal cells, making them a promising option for retinal repair strategies. Additionally, PET has demonstrated favorable biocompatibility in studies involving female Chinchilla Bastard rabbits, particularly in the subretinal region, suggesting its viability for clinical applications in retinal surgery [86].

2.2.3. Optic nerve

In the context of optic nerve scaffolds, PCL, and poly-gamma-benzyl-L-glutamate (PBG) have been utilized, alongside PCL coated with tosylate and PEDOT (polystyrene sulfonate) in a water-isopropanol mixture, as well as polypyrrole functionalized graphene (PPy-G). The synthetic methodologies employed for these materials often include solvent casting, phase separation techniques, and layer-by-layer assembly, which facilitate the creation of porous structures that promote nerve regeneration. Additionally, chemical crosslinking methods can enhance the mechanical properties and stability of the scaffolds. These materials have been engineered to improve cell viability and encourage the growth of elongated neurites aligned with the fiber direction. Notably, PCL coated with tosylate and PEDOT has proven effective in guiding nerve bundles, highlighting its potential application in nerve regeneration. This guidance is crucial for restoring functional connectivity in damaged nerves, which could significantly enhance recovery outcomes for patients with optic nerve injuries [90–92].

2.3. Biohybrid scaffolds

2.3.1. Conjunctiva

The development of conjunctival biohybrid scaffolds has increasingly leveraged innovative biohybrid materials and methodologies to enhance biocompatibility, functionality, and overall efficacy in ocular applications. Central to this advancement are poly (lactic acid) (PLA) electrospun nanofibrous membranes (EFMs), often surface-coated with cellulose nanofibrils (CNF) and/or silk peptide (SP) loaded with levofloxacin (LF). This coating confers robust antibacterial properties, thereby significantly reducing the necessity for post-surgical antibiotic administration. These scaffolds have undergone rigorous testing in vivo, particularly in studies involving New Zealand white rabbits, which have demonstrated their effectiveness in promoting healing and preventing infections [93]. In addition to PLA-EFMs, scaffolds composed of silk fibroin (SF) and reduced graphene oxide (rGO) have emerged as promising alternatives. The incorporation of SF facilitates the formation of a larger surface area, effectively mimicking the natural ECM in multiple dimensions. This structural mimicry is crucial for enhancing cell adhesion, migration, and proliferation. Furthermore, rGO is characterized by its exceptional electrical conductivity, which can stimulate cellular responses and improve tissue integration [94]. Moreover, collagen combined with poly L-lactic acid-co-ε-caprolactone (PLCL) has been extensively studied for its favorable properties. Notably, in vitro analyses have shown that the presence of conjunctival epithelial cells on collagen/PLCL scaffolds does not induce an increase in the expression of pro-inflammatory cytokines such as IL-4, IL-5, and IL-6, indicating a supportive immunological profile [95]. Additionally, conjunctival epithelial cells cultivated on SF/PLCL hybrid scaffolds have demonstrated the ability to develop a stratified conjunctival epithelium, inclusive of goblet cells, when evaluated in murine models [96].

2.3.2. Cornea

Corneal biohybrid scaffolds are progressively incorporating innovative materials to improve tissue regeneration and functionality,

particularly PeCL microfibrous scaffolds infused with rat tail collagen type I, which have shown considerable promise in facilitating cellular infiltration and promoting ECM deposition. Additionally, biodegradable silk fibroin-based scaffolds that contain glial cell-derived neurotrophic factor (GDNF) have been recognized for their ability to facilitate epithelialization and enhance the proliferative activity of epithelial cells in murine models. Other noteworthy materials include hyaluronic acid-modified gelatin-methacrylate (GelMA-HA) and collagen-immobilized polyvinyl alcohol (PVA-COL), both of which have proven effective in creating scaffolds that closely mimic the natural corneal environment. Furthermore, amniotic membrane-immobilized polyvinyl alcohol hydrogel (PVA-AM) combines the advantageous properties of natural basement membrane components found in amniotic tissue with the transparency and durability of artificial PVA, rendering it a valuable option for corneal applications.

The genipin-crosslinked polyvinyl alcohol/silk fibroin/nanohydroxyapatite hydrogel (GP/PVA/SF/n-HA) has also been investigated for its potential to enhance mechanical properties and biocompatibility, thereby facilitating corneal tissue integration. Experimental studies have shown that corneas subjected to injury and treated with PCL/collagen scaffolds exhibit a more uniform distribution of collagen fibers and a reduced presence of fibroblasts and myofibroblasts, indicating improved healing outcomes. Moreover, scaffolds that incorporate vancomycin, such as vancomycin-loaded collagen hydrogels (VH), have proven effective in inhibiting Staphylococcus aureus infections associated with implanted devices, as demonstrated by both in vitro and in vivo studies conducted on rabbits [10,12,19,97–101]. sHAPN copolymers, composed of sulfated HA and amine-terminated poly(N-isopropylacrylamide), enhance ocular bioavailability and provide anti-inflammatory effects. Similarly, Oxidized hyaluronan (oHA) promotes keratocyte growth in rabbits by leveraging oxidation levels in aldehyde HA, improving gelatin microcarriers for effective scaffolding in ocular health [102,103].

2.3.3. Lens

Nondegradable polymeric gel and biodegradable hyaluronic acid (HA) were utilized in lens scaffolds. The combination of HA with nondegradable polymeric gels has shown superior outcomes in terms of lens clarity, tested on Dutch Belt pigmented and New Zealand white rabbits [104].

2.3.4. Retina

Regenerated wild Antheraea pernyi silk fibroin (RWSF), PCL, and gelatin (RWSF/PCL/Gt) exhibit excellent cytocompatibility in laboratory settings and biocompatibility in vivo, positioning them as promising candidates for prosthetic Bruch's membrane development. Gelatin/chitosan scaffolds successfully mimic the composition and nanofibrous architecture of the ECM without adverse effects, while human amniotic membrane powder combined with PCL (HAMP/PCL) scaffolds demonstrates optimal porosity and biocompatibility, although further investigation is warranted [15,105–107].

2.4. Decellularized tissue

2.4.1. Cornea

The field of corneal TE has seen the exploration of various materials, including human crystalline lens capsules (LCs), freeze-dried acellular porcine corneal stroma (FD-APCS), decellularized human small incision lenticule extraction (SMILE) lenticule (SL), amniotic membrane (AM), collagen-coated plates, carbodiimide crosslinked recombinant human collagen (RHC), native porcine conjunctiva, porcine cornea, decellularized human donor cornea, decellularized murine corneas, and vancomycin-loaded hydrogels (VH). In addition to these natural and decellularized materials, synthetic approaches have also been developed to enhance corneal scaffold performance. For instance, electrospinning techniques have been employed to create nanofibrous scaffolds that mimic the ECM, promoting cell adhesion and proliferation. Scaffolds made from biodegradable polymers such as polycaprolactone (PCL) and gelatin have been designed to provide mechanical support while maintaining biocompatibility. Furthermore, silk fibroin scaffolds enriched with growth factors, such as glial cell-derived neurotrophic factor (GDNF), have demonstrated improved epithelialization capabilities. Research findings indicate that cells cultured on coated LCs exhibit a focal adhesion surface area that is at least double that of cells in control conditions. The SMILE technique has facilitated the efficient culture of keratocytes, with successful trials conducted on New Zealand male rabbits. In clinical settings, RHC has been the sole material applied, resulting in an average corrected visual acuity of 20/54 among patients over four years, with many showing improvements of more than five Snellen lines on visual acuity charts. Additionally, the use of decellularized human cornea (DHC) offers patients the potential benefit of utilizing non-immunogenic tissue scaffolds for transplantation. Finally, studies involving FD-APCS in New Zealand white rabbits have demonstrated that the collagen lamellae present in FD-APCS closely resemble those found in native corneal stroma, highlighting its potential as an effective scaffold material. The combination of synthetic and natural approaches presents a promising avenue for advancing corneal TE [108–114].

2.4.2. lacrimal gland

Synthetic approaches involving the use of lacrimal gland scaffolds have gained attention in recent studies. Notably, the ECM derived from New Zealand White (NZW) rabbit lacrimal glands, decellularized porcine jejunum (SIS-Muc), and decellularized porcine lacrimal gland matrix (DC-LG) have all been explored in vitro. Among these, the SIS-Muc demonstrated a similar pattern of epithelial cell polarization on its upper surface, akin to that observed in the epithelial acini of the natural lacrimal gland. These scaffolds offer promising avenues for TE and regenerative medicine in the context of lacrimal gland function restoration [13,115,116].

2.4.3. Optic nerve

Advancements in synthetic approaches for nerve regeneration have facilitated the creation of optic nerve scaffolds derived from

decellularized optic nerve (DON) and porcine decellularized optic nerve. Both types of scaffolds have undergone in vitro evaluation, while the porcine variant has also been utilized in an in vivo study involving rats. Remarkably, the decellularized optic nerve from embryonic pigs exhibited longer axonal extensions, increased distances, and enhanced branching compared to the conventional optic nerve (ON). The benefits of these scaffolds stem from the targeted elimination of axon-inhibitory factors, including myelin-associated glycoprotein and chondroitin sulfate proteoglycans, achieved through the decellularization process. This underscores the significant potential of these decellularized scaffolds in promoting nerve regeneration and improving functional outcomes [117,118] (Fig. 2).

3. Cell types used for eye tissue engineering

As we see in Table 1, a variety of cell have been utilized for eye TE. Conjunctiva mesenchymal stem cells (CJMSCs) and rabbit conjunctival epithelial cells (rCjECs) were the major cell types used in conjunctival scaffolds and they were both successfully raised [93,94,96]. Human adipose mesenchymal stem cells (hADSCs), limbal stromal stem cells (LSSCs), keratocytes, rabbit corneal limbal epithelial cells, limbal epithelial progenitor cells (LEPC), limbal mesenchymal stromal cells (LMSC), and limbal melanocytes (LM), Rabbit Corneal stromal cell, human embryonic stem cells-corneal epithelial cells (hESC-CEC), rabbit corneal epithelial cells, corneal epithelial cells (CEC), human corneal fibroblasts (HCFs) cells, human corneal endothelial cells (hCEC), human limbal epithelial cells (hLEC), Human keratocytes (HKs), human corneal epithelial cells (HCECs), and corneal keratocyte cell were the main cellular components employed in the construction of cornea scaffolds and every one of them was grown successfully [10,98,100,108,113,119,120].

Adult rabbit lacrimal gland (LG) progenitor cells, Lacrimal acinar epithelial cells of Sprague-Dawley rats, Porcine LG epithelial cells, Purified rabbit lacrimal gland acinar cells (pLGACs) and LG epithelial cells were found as cells seeded in lacrimal glands scaffolds

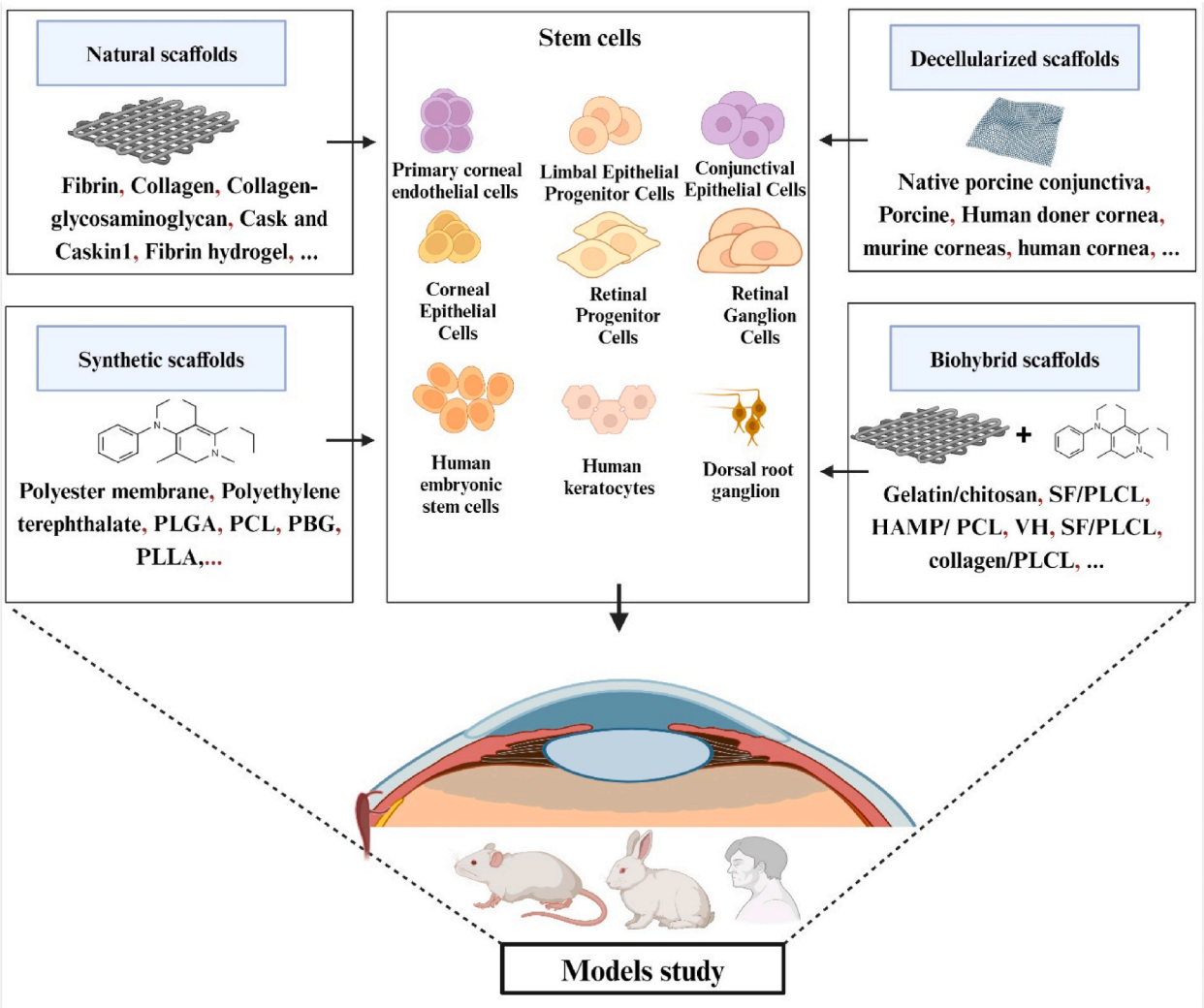

Fig. 2. Schematic illustration of depicts various scaffold types utilized in eye regeneration, including natural scaffolds, synthetic scaffolds, biohybrid scaffolds and decellularized scaffold Additionally, it highlights the different types of stem cells employed within these scaffolds.

[13,81,82,115,116].

Mouse retinal progenitor cells (mRPCs), retinal ganglion cells (RGCs), retinal pigment epithelium cells (RPE), human Fetal RPE (hfRPE), human embryonic stem cells, human-induced pluripotent stem cell (hiPSC), and CJMSCs are the main cells used effectively in retinal scaffolds [14,16,78,83,85,86]. In the construction of optic nerve scaffolds neurotrophin-3-overexpressing Schwann cells, dorsal root ganglion (DRG) neurites, RGCs, retinal ganglion cell progenitors (RGCP), chick dorsal root ganglia and a mouse neuroblastoma cell line are the main cellular components employed well [80,90–92,117].

4. Advantages and disadvantages of eye tissue engineering scaffolds

TE and regenerative medicine methodologies have demonstrated promising results in the context of eye tissue regeneration [121]. To address the issue of insufficient supply, numerous efforts have been undertaken to develop a functional implant through bioengineering. This implant serves as a substitute for donor tissues in eye grafting procedures [122]. The survival and functionality of cells after transplantation can be influenced by the environmental conditions in which they grow and mature. Ocular regeneration using scaffolds has shown promise in treating various eye conditions. Typically, an optimal scaffold should possess biocompatibility, non-immunogenicity, and mechanical strength to withstand manipulation during the process of implantation [123]. The variability in the outcomes of patients suffering from blindness who undergo stem cell grafts for the purpose of restoring eye health and improving vision can be attributed to the utilization of various biological and synthetic scaffolds employed in the delivery of these cells to the ocular tissue [124]. Here are some advantages, disadvantages, and limitations of using scaffolds in ocular regeneration.

Advantages.

1. Scaffolds serve as a framework that provide structural support for cells to proliferate and undergo differentiation, promoting tissue regeneration [15].
2. They have the ability to imitate the normal ECM of the eye, hence improving the adhesion and growth of cells [96].
3. Scaffolds can be tailored to specific requirements, such as size, shape, and porosity, to optimize tissue regeneration [120].
4. Growth factors or medicines can be incorporated into them to augment healing and mitigate inflammation [104].
5. Post-surgery bacterial inhibition, biocompatibility, stimulating the epithelialization process, Facilitating the movement of epithelial cells and expediting the process of wound healing [74].
6. Transparency and durability, being resistant to degradation by collagenase, outstanding oxidative, thermal, and hydrolytic stability [116].
7. Also mimicking the topographic features and the structure of the goal tissue and guiding specific cells in right direction are a part of prominent benefits of specific eye scaffolds [106].

Disadvantages.

1. Scaffolds may trigger an immune response or cause inflammation in some patients [109].
2. They may not integrate well with surrounding tissues, leading to complications such as scarring or rejection [19].
3. The fabrication of scaffolds can be complex and costly, limiting their widespread use [106].
4. Scaffolds may degrade too quickly or too slowly, affecting their effectiveness in promoting tissue regeneration [80].

In Table 1, we have compiled the advantages and disadvantages of noticeable recent studies in this field, based on their respective materials.

5. Clinical trials using tissue engineering scaffolds

Here are two clinical trials in the field of eye scaffolds. The first one (EudraCT no. 2006-006585-42) has used carbodiimide crosslinked RHC implants as corneal scaffold to tackle the global scarcity of available corneas for donation [110]. Over a span of four years, the revived neo-corneas exhibited stable integration within the ocular environment, devoid of any instances of rejection. Notably, the recipients of these neo-corneas were spared the requirement of enduring the protracted immunosuppressive regimen typically mandated for individuals receiving donor corneas. No recruitment of inflammatory dendritic cells into the implant region was detected [110]. However, in the case of recipients of donor corneas, even with the administration of immunosuppressive agents, migration of dendritic cells into the central cornea was detected, which coincided with the occurrence of a rejection episode. Regeneration, as demonstrated by the ongoing repopulation of nerve and stromal cells, transpired over the course of a four-year period, resulting in the approximation of the micro-architecture akin to that of normal, healthy corneas [110]. Patients who underwent implantation procedures exhibited an average corrected visual acuity of 20/54 over a span of 4 years. Furthermore, these individuals experienced a notable improvement in their visual capabilities, as evidenced by a gain of more than 5 Snellen lines on an eye chart. Enhancement of visual acuity may be achieved through the utilization of more resilient materials that exhibit superior capacity for shape preservation [110]. The subsequent clinical trial conducted in this particular domain pertained to the corneal scaffold (EudraCT number: 2010-024290-40) [125]. The trial employed a nano-structured fibrin agarose corneal substitute, which integrated allogeneic cells, effectively emulating the mechanical, optical, and biological characteristics of the anterior human native cornea. This ongoing clinical trial, conducted in ten hospitals in Spain, is a controlled, randomized, open-label study encompassing both phase I and phase II [125]. Its primary objective is to assess the safety and feasibility of a bioengineered human corneal substitute in adults afflicted with

severe trophic corneal ulcers that have proven resistant to conventional treatment, or those who have developed complications because of prior ulcers. Additionally, the trial aims to gather clinical evidence regarding the efficacy of this novel intervention [125]. The assessment of adverse events, implant condition, symptoms of infection, and induced formation of new blood vessels are important factors in determining the safety and practicality of the bioengineered graft. These factors are considered the main outcomes in this study. The measurement of study endpoints is conducted over a span of 24 months, encompassing a total of 27 post-implant assessment visits. These visits occur at decreasing intervals throughout the follow-up period [125]. Ultimately, the utilization of scaffolds in TE methods shows significant potential for the regeneration of ocular tissues. By harnessing the power of biomaterials science and stem cell technology, researchers are paving the way for new treatments that could revolutionize the field of ophthalmology and improve outcomes for patients with various eye conditions [120].

6. Limitation and challenges

Overall, the future of ocular regeneration looks promising, with ongoing research efforts aimed at developing new treatments for a wide range of eye conditions [81]. While much work still needs to be done before these therapies become widely available, advancements in regenerative medicine offer hope for improved outcomes for patients with vision loss and other ocular disorders [126]. In summary, although scaffold-based ocular regeneration shows promise in enhancing patient outcomes, additional study is required to overcome obstacles and maximize scaffold utilization in this domain [88,127]. Some limitations in the therapeutic use of scaffolds in ocular diseases are described below.

1. The ongoing research is focused on examining the durability and effectiveness of scaffold-based ocular regeneration therapies over an extended period of time [112].
2. Scaffolds may not be suitable for all types of ocular injuries or diseases [97].
3. The optimal design and composition of scaffolds for ocular regeneration have not been fully established [75].
4. Clinical trials are needed to evaluate the effectiveness of scaffold-based therapies in treating

various eye conditions [85].

7. Conclusion

In our analysis of recent publications on scaffolds for ocular TE, we categorized the scaffolds utilized in eye TE into four types—natural, synthetic, biohybrid, and decellularized tissue—based on their tissue characteristics, while also compiling data on the associated cell types and animal models to gain valuable insights into the advantages and disadvantages of each material. Our findings indicate that scaffolds in TE not only mimic the ECM of the eye but also promote cell proliferation and tissue regeneration, offering significant benefits such as bacterial inhibition, biocompatibility, and enhanced durability. However, these scaffolds present challenges, including potential immune responses, inadequate tissue integration, complex and costly manufacturing processes, and inconsistent degradation rates that may affect their efficacy. This review comprehensively examines the current landscape of eye regenerative therapies, evaluates key preclinical and clinical research initiatives, addresses the challenges faced, and considers potential advancements over the next decade.

CRediT authorship contribution statement

Zeinab Mousavi: Writing – original draft, Investigation, Conceptualization. **Masood Bagheri:** Writing – original draft, Validation, Investigation. **Gelavizh Rostaminasab:** Writing – original draft, Investigation. **Abdolhamid Mikaeili:** Writing – original draft, Software. **Ali R. Djalilian:** Writing – review & editing, Writing – original draft. **Leila Rezakhani:** Writing – review & editing, Supervision, Project administration.

Data availability statement

All data are fully available without restriction.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used QuillBot and Monica to improve the readability and language of the manuscript. After using these services, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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.

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Abbreviation

BrM	Bruch's membrane
ON	Optic nerve
RGCs	Retinal Ganglion Cells
WHO	World Health Organization
TE	Tissue engineering
NSF	National Science Foundation
AMD	Age-related Macular Degeneration
VEGF	Vascular Endothelial Growth Factor
TENGs	Tissue-engineered nerve grafts
HAM	Human amniotic membrane
RS1	Retinoschisin
GCH	Gelatin/ Chondroitin sulfate/ Hyaluronic Acid
hESC	Human embryonic stem cell
ONL	Outer Nuclear Layer
PES	Polyethersulfone
PCL	Polycaprolactone
PLLA	Poly L-lactic Acid
PLGA	Poly Lactic-co-Glycolic Acid
PGS	Poly Glycerol Sebacate
PPy-G	polypyrrole functionalized graphene
PLA	Poly Lactic Acid
EFMs	Electrospun nanofibrous membranes
CNF	Cellulose Nanofibrils
SP	Silk Peptide
LF	Levofloxacin
SF	Silk Fibroin
rGo	Reduced Graphene oxide
PLCL	Poly (L-lactic acid-co-3- caprolactone)
SF/rGO	Silk Fibroin/ reduced Graphene oxide
ECM	Extracellular matrix
Collagen/PLCL	Collagen/poly (L-lactic acid-co-3- caprolactone)
IL-4, IL-5, and IL-6	Interleukin-4, interleukin-5, Interleukin-6
CjECs	Conjunctival Epithelial Cells
SF/PLCL	Silk Fibroin /poly (L-lactic acid-co-3- caprolactone)
GelMA-HA	Hyaluronic acid-modified gelatin-methacrylate
PVA-COL	Collagen-Immobilized Poly (Vinyl Alcohol)
AM	Amniotic Membrane
PVA-AM	Polyvinyl alcohol hydrogel
GP/PVA/SF/n-HA	Genipin-crosslinked polyvinyl alcohol/silk fibroin/nanohydroxyapatite Hydrogel
PCL/collagen	Polycaprolactone/collagen
HA	Hyaluronic Acid
RWSF	Regenerated wild Antheraea pernyi Silk Fibroin
Gt	Gelatin
HAMP	Human amniotic membrane powder
LCs	Lens Capsules
FD-APCS	Freezing-Dry Acellular Porcine Cornea Stroma
SMILE	Small incision lenticule extraction
SL	lenticule
RHC	Recombinant Human Collagen
NZW	New Zealand White
(SIS-Muc)	Conversely decellularized porcine small intestine submucosa
DC-LG	Decellularized porcine LG matrix
DON	Decellularized Optic Nerve

PLA Poly Lactic Acid
SP Silk Peptide
CJMSCs Conjunctiva Mesenchymal Stem Cells
PLCL Poly L-lactic acid-co-3- Caprolactone
rCjECs Rabbit Conjunctival Epithelial Cells
LCs Lens Capsules
hADSCs Human Adipose Mesenchymal Stem Cells
PCL Poly ε-Caprolactone
LSSCs Limbal Stromal Stem Cells
GDNF Glial Cell-Derived Neurotrophic Factor
LEPC Limbal Epithelial Progenitor Cells
LMSC Limbal Mesenchymal Stromal Cells
LM Limbal Melanocytes
FD-APCS Freezing Dry Acellular Porcine Cornea Stroma
GelMA-HA Hyaluronic Acid-modified Gelatin-Methacrylate
CS Corneal Stromal
PVA-COL Colagen-Immobilized Poly Vinyl Alcohol
CEC Corneal Epithelial Cells
GP Genipin
n-HA Nanohydroxyapatite
HCFs Human Corneal Fibroblasts
VH Vancomycin-loaded collagen Hydrogels
hCEC Human Corneal Endothelial Cells
hLEC Human Limbal Epithelial Cells
PVA Aligned Polyvinyl Acetate
HKs Human Keratocytes
LG Lacrimal Gland
PLGACs Purified rabbit Lacrimal Gland Acinar Cells
RPCs Retinal Progenitor Cells
RS Retinoschisin
PCL Polycaprolactone
mRPCs Mouse Retinal Progenitor Cells
hiPSC Human-induced Pluripotent Stem Cell
RPE Retinal Pigment Epithelial
PEG Polyethylene Glycol
DRG Dorsal Root Ganglion
PBG Poly-gamma-Benzyl-L-Glutamate
RGCP Retinal Ganglion Cell Progenitors
PEDOT PSS (polystyrene sulfonate) in water and isopropanol
TCPS Tricalcium phosphate scaffold
LCs Lens Capsules
DM Descemet's membrane
DHC Decellularized Human Cornea
FD-APCS Freezing Dry Acellular Porcine Cornea Stroma
GelMA-HA Hyaluronic Acid-modified Gelatin-Methacrylate
PVA Polyvinyl Alcoholhydrogel
POC Poly (1,8-Octanediol-co-Citrate)
LSSCs Limbal Stromal Stem Cells
hESC-CEC human Embryonic Stem Cells- Corneal Epithelial Cells
hfRPE Human fetal Retinal Pigment Epithelium cells
sHAPN Sulfated Hyaluronic acid with amine-terminated poly(N-isopropylacrylamide)
oHA Oxidized hyaluronan

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