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Review

Plasma rich in growth factors as a treatment for ocular fundus diseases: Mapping current applications and future directions

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ABSTRACT

Posterior segment diseases are a leading cause of irreversible blindness and remain challenging to treat with current therapies. Blood-derived products have emerged as promising regenerative tools due to their anti-inflammatory, neuroprotective, and regenerative properties. This review synthesizes evidence from 46 clinical studies published between 2019 and 2025, covering 1253 patients and 1570 eyes treated with platelet-rich derivatives for ocular fundus diseases. The most frequent indications were structural defects (59 %), inherited retinal dystrophies (11 %), optic neuropathies (11 %), age-related macular degeneration (7 %), and vascular dysfunctions (5 %). These therapies were administered via various routes, including intravitreal, subtenon, suprachoroidal, and subretinal injections, as well as eye drops and fibrin membranes. Across pathologies, platelet-derived therapies demonstrated high anatomical success rates, functional improvements, and low incidence of adverse events, most of which were transient and mild. Among the different formulations, plasma rich in growth factors (PRGF-Endoret®) stood out for its standardized preparation, immunosafe profile, and versatility in application. Despite promising clinical outcomes, heterogeneity in study designs, small sample sizes, and lack of standardized protocols limit generalizability. Further randomized controlled trials and mechanistic studies are needed to validate efficacy, define optimal formulations, and identify the patient populations most likely to benefit. Blood-derived products represent a promising therapeutic avenue in regenerative ophthalmology and may serve as effective adjuncts or alternatives in managing complex retinal and optic nerve disorders.

1. Introduction

Posterior segment disorders are among the leading causes of visual impairment and irreversible blindness worldwide, often proving resistant to current therapeutic approaches [1]. The increasing prevalence of systemic comorbidities - such as diabetes, hypertension, and metabolic syndrome – alongside an aging population, has further intensified the need for innovative regenerative strategies [2].

The ocular fundus is a highly specialized structure responsible for capturing light and transmitting visual signals to the brain [3]. It comprises the neurosensory retina, retinal pigment epithelium (RPE), optic nerve head, and choroidal vasculature. Owing to its complex architecture and high metabolic demands, the posterior segment is particularly susceptible to a wide range of degenerative, vascular, and inflammatory injuries [4]. Disorders affecting this region – including retinal vein occlusions, structural defects, retinal degenerations, and optic neuropathies – present substantial therapeutic challenges, especially given the limited efficacy, invasiveness, or disease-modifying capacity of current treatments [1, 5–7].

Against this backdrop, platelet-derived formulations have emerged as promising tools in regenerative ophthalmology. These autologous [8] – and in some instances, allogeneic [9] – products are obtained through centrifugation of whole blood to concentrate thrombocytes (platelets), which serve as natural reservoirs of biologically active molecules [10, 11]. Upon activation, platelets release a rich cocktail of growth factors (GF) and cytokines – including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and nerve growth factor (NGF) – that collectively promote wound healing and tissue regeneration through the modulation of angiogenesis, inflammation, and remodelling of extracellular matrix [12–16]. These mechanisms support tissue homeostasis and highlight

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their potential in treating ocular conditions characterized by neurodegeneration, vascular instability, and structural disorganization [17–19].

Platelet-derived products have already been explored in a wide range of ophthalmic indications, including dry eye disease, corneal ulcers, optic neuropathies and retinal degenerations [19]. Nonetheless, their clinical adoption has been hindered by the lack of standardized preparation and activation protocols, different cellular composition and inter-product variability. These limitations complicate the interpretation of clinical outcomes and challenge broader clinical application [20–22].

In this context, plasma rich in growth factors offers a standardized blood processing to obtain platelet-rich formulations[19]. This autologous product, prepared through a single-step centrifugation process that concentrates platelets while excluding leukocytes, aims to minimise the risk of inflammation and fibrosis [23,24]. It provides multiple ophthalmic formulations - including injectable solutions, eye drops, fibrin membranes, and autologous clots - that adapt to the anatomical targets and clinical requirements [19]. Importantly, the immunosafe presentation of PRGF-Endoret®, undergoes an additional heat-treatment step that inactivates immunogenic components while preserving its bioactivity– an essential safety consideration for intraocular use [25].

Given their pleiotropic mechanisms and regenerative capacity, blood-derived products may serve as valuable adjuncts or alternative to conventional interventions to treat posterior segment diseases involving ischemia, neurodegeneration, and structural compromise. This review aims to synthesize the current evidence on the application of platelet-derived products in ocular fundus diseases, with a particular emphasis on the biological rationale, therapeutic applications, and emerging promise.

2. Material and methods

2.1. Literature search

For this narrative review, a systematic literature search was performed in PubMed, Web of Science (WOS) and Scopus databases in July 2025, using the following search strategy: “("Platelet Rich Plasma" OR "Plasma Rich in Growth Factors") AND ("retinal diseases" OR "retinopathy" OR "macular degeneration" OR "macular hole" OR "glaucoma" OR "retinitis pigmentosa" OR "retinal vein occlusion" OR "ocular ischemic syndrome" OR "optic neuropathy")”. Only studies published between 2019 and 2025 were considered (Fig. 1). This time frame was selected to

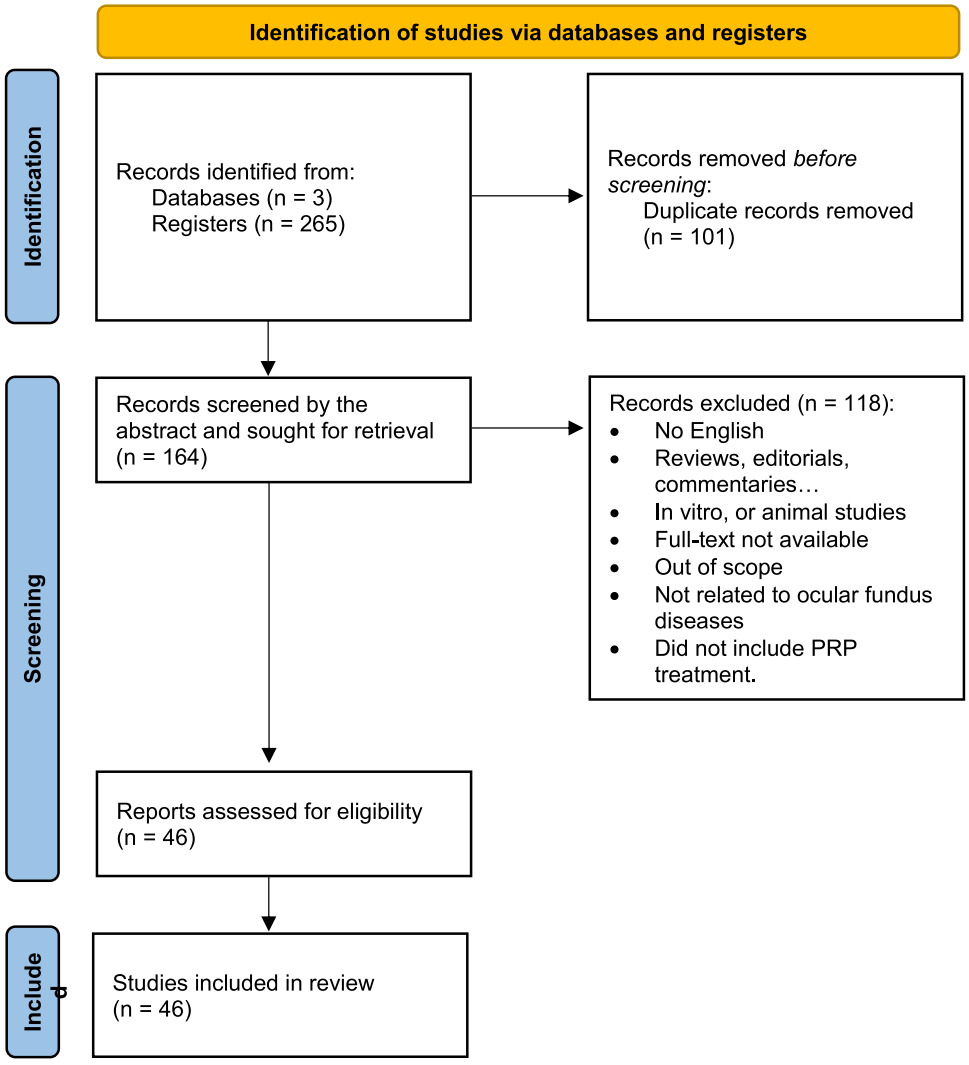

Fig. 1. Flow diagram of the literature selection process following PRISMA 2020 guidelines. While this narrative review does not adhere to a systematic review protocol, a structured and reproducible literature search strategy was employed across PubMed, Web of Science, and Scopus databases. The diagram shows the number of records identified, screened, excluded, and included based on predefined eligibility criteria. Source: Page MJ, et al# BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

reflect the most recent clinical advances and standardization efforts regarding blood-derived therapies for posterior segment diseases. Additionally, a comprehensive review on PRGF-Endoret® use across ophthalmology was published by our group in 2022 (*Progress in the use of plasma rich in growth factors in ophthalmology: from ocular surface to ocular fundus*, Anitua *et al.*) [19], covering broader applications up to that date. The present review focuses specifically on fundus pathologies, updating the evidence with clinical studies published after that milestone. Papers were excluded if they met any of the following criteria: 1) published in a language other than English; 2) duplicates; 3) reviews, editorials, commentaries, theses, book chapters, *in vitro* studies, or animal models; 4) full-text not available; 5) out of scope; 6) not related to ocular fundus diseases; 7) did not include PRP treatment or similar.

2.2. Data extraction

Studies that passed the initial title and abstract evaluation were retrieved for full-text review. For data extraction, an evidence table was created with Microsoft Excel. The following data were included: (a) publication details (year of publication, author, title, journal, institution, study design, indication); (b) blood derivatives' issues (type of anticoagulant, number of centrifugations, acquisition method, activator type, blood-derived product classification, final formulation, platelets content, leukocytes presence); (c) study characteristics (sample size, patient demographics (age and sex), interventions, treatment group(s), use of adjuvant therapies, administration volume, site of application, number of doses and frequency); (d) ocular fundus assessments (follow-up duration and ophthalmologic examination performed); (e) outcome measurements (primary, secondary and follow-up), (f) final results, and (g) adverse events.

3. Results

Due to the high heterogeneity of the clinical studies, in terms of pathologies, treatment, follow-up period and methodologic diversity, a meta-analysis and an overall quality of evidence using GRADE approach could not be conducted.

3.1. Study selection

The search strategy yielded a total of 265 articles from the three databases, published between 2019 and July 2025. A total of 101 articles were removed as duplicates. After a proper screening, 46 studies [26–71] were finally included for the analysis (Table 1).

3.2. Study characteristics

A total of 46 studies were included in this review, comprising 12 case reports (26 %), 9 case series (20 %), and 25 clinical studies (54 %). Among the case series, 4 were prospective and 5 retrospective, all of which were interventional. Of the clinical studies, 14 were prospective, 10 retrospective, including one that was partially retrospective.

Overall, the studies included over 1253 patients and 1570 eyes. The mean age of participants ranged from 14 to 84 years, with age data reported in 44 studies (96 %). Gender information was available in 42 studies (91 %), with an overall distribution of 41 % male and 59 % female participants.

When categorized by pathology, structural defects were the most frequently investigated conditions. Macular hole (MH) was addressed in 27 studies (59 %) including 694 patients and 702 treated eyes. Reported mean ages in these studies ranged from 14 to 78 years. Gender distribution was available in 26, encompassing 491 female and 197 male patients. One study reported gender distribution by treated eyes rather than by patient count, specifying 27 eyes from female patients and 15 from male patients. Retinal hole (RH) was evaluated in a single case report (2 %), involving one female patient aged 84 years.

Retinitis pigmentosa (RP) was the second most frequently studied condition, included in five studies (11 %) involving 251 patients and 492 treated eyes. Mean age ranged from 32 to 52 years. Four studies reported gender data, accounting for 84 female and 107 male patients.

Geographic atrophy (AG) secondary to age-related macular degeneration (AMD) was examined in three studies (7 %), compromising 47 patients and 94 eyes. The mean reported age was 75 years. Gender data were available in one study, including 5 female and 8 male patients.

Glaucoma was investigated in five studies (11 %), involving 139 patients and 149 treated eyes. The mean age was 65 years. All five studies reported gender distribution, with 62 female and 77 male participants. Nonarteritic anterior ischemic optic neuropathy (NAION) was the subject of one study (2 %), involving 25 patients and 25 eyes, with a reported mean age of 51 years. Gender distribution included 4 female and 21 male patients.

Less frequently studied conditions included central serous chorioretinopathy (CSCR), reported in one study (2 %) involving 22 patients and 22 eyes (mean age: 44 years; 4 female, 18 male); capillary ischemia reported in one study (2 %) with 17 patients and 28 eyes (mean age: 38 years; 8 female, 21 male); dense vitreous and retinal hemorrhages, investigated in one study (2 %) with 6 patients and 6 eyes (mean age: 65 years; 3 female and 3 male); and epiretinal membrane surgery was evaluated in one study (2 %) with 51 patients and 51 eyes (mean age: 73 years; 24 female, 28 male).

3.3. Preparation and composition of blood-derived products

Substantial heterogeneity was observed in the preparation methods and composition of blood-derived products across the 46 clinical studies reviewed (Table 2), highlighting the lack of standardized protocols and the frequent omission of critical technical details. This variability not only limits reproducibility but also hampers direct comparisons between studies [72,73].

Among the blood derivatives, PRP was the most frequently used, reported in 61 % of studies. This was followed by PRGF-Endoret® (22 %), umbilical cord blood-derived PRP (CB-PRP, 7 %), autologous platelet concentrate (APC, 7 %) and whole blood (4 %). Regarding preparation methods, 59 % of the studies employed commercial systems; the most frequently used kits were PRGF-Endoret® (37 %), Arthrex Angel System (15 %), Arthrex APC Kit (11 %), T-LAB PRP Kit (11 %), PRP Biomed (7 %), Regen Kit (7 %), Dr. PRP (4 %), and Ycellbio (4 %). The remaining 41 % either did not specify their preparation method or used non-commercial, custom-made protocols.

In terms of the use of anticoagulants, 72 % of the studies reported employing citrate-based solutions. Sodium citrate was the most used (37 %), followed by citrate dextrose (28 %). However, 7 % did not specify the exact citrate formulation. Of the remaining studies, 22 % did not disclose whether an anticoagulant was used, and 7 % explicitly stated that none was employed.

Centrifugation protocols varied among the included studies. A single centrifugation step was applied in 70 % of the studies, while 24 % employed a double centrifugation protocol. In 4 % of the studies, whole blood was not centrifuged, and one study did not provide details regarding the centrifugation process.

Platelet activation was frequently unreported. Sixty-seven percent of the studies did not specify whether activation was performed. Among the remaining studies, 22 % used calcium chloride to activate platelets, one employed a calcium ion solution, another used calcium gluconate, and three studies (7 %) explicitly stated that no activation was performed. Calcium chloride-mediated activation was consistently used in all studies employing the PRGF-Endoret® system. Additionally, three studies reported storing blood-derived products at −80 °C prior to use – a freeze-thaw process known to induce platelet lysis and subsequent growth factor release, as previously described by Doucet *et al.* [74].

In terms of final formulation, 78 % of studies administered the platelet-derived product in liquid form. Other formulations included

Table 1

Blood-derived products in ocular fundus-related studies. Search carried out in PubMed, Web of Science, and Scopus databases. Abbreviations: Acta Ophthalmol: Acta Ophthalmologica; Adv Ther: Advances in Therapy; AMD: Age-related macular degeneration; AJO: American Journal of Ophthalmology; Arch Soc Esp Oftalmol: Archivos de la Sociedad Española de Oftalmología; BMC Ophthalmol: BioMed Central Ophthalmology; Bulletin of RSMU: Bulletin of Russian State Medical University; JBSMFS: Bulletin of Stomatology and Maxillofacial Surgery; Case Rep Ophthalmol: Case Reports in Ophthalmology; CSCR: Central Serous Chorioretinopathy; Clin Pract: Clinics and Practice; C: Company; DRCI: Deep retinal capillary ischemia; ERM: Epiretinal membrane; Eur J Ophthalmol: European Journal of Ophthalmology; Eye (Lond): Eye (London, England); Front Med (Lausanne): Frontiers in Medicine; Graefes Arch Clin Exp Ophthalmol: Graefe's Archive for Clinical and Experimental Ophthalmology; I: Independent; Indian J Ophthalmol: Indian Journal of Ophthalmology; Int J Mol Sci: International Journal of Molecular Sciences; Int Med Case Rep J: International Medical Case Reports Journal; Int Ophthalmol: International Ophthalmology; Jpn J Ophthalmol: Japanese Journal of Ophthalmology; J Clin Med: Journal of Clinical Medicine; J Curr Ophthalmol: Journal of Current Ophthalmology; Klin Monbl Augenheilkd: Klinische Monatsblätter für Augenheilkunde; MH with RD: Macular hole with retinal detachment; MH with RP: Macular hole with retinitis pigmentosa; MH: Macular hole; NAION: Non-arteritic anterior ischemic optic neuropathy; Ocul Immunol Inflamm: Ocular Immunology and Inflammation; Ophthalmol Sci: Ophthalmology Science; Regen Med: Regenerative Medicine; Res Sq: Research Square; Retin Cases Brief Rep: Retinal Cases & Brief Reports; RD due to RH: Retinal detachment due to retinal hole; RP: Retinitis pigmentosa; Stem Cell Res Ther: Stem Cell Research & Therapy.

Year	Author	Title	Journal	Institution	Study Design	Indication
2019	Abdalrahman, O. *et al.* [26]	Treatment of chronic and extreme ocular hypotension following glaucoma surgery with intraocular platelet-rich plasma: A case report	Eur J Ophthalmol.	I	Case Report, interventional	Glaucoma
2019	Limoli, PG. *et al.* [27]	Stem Cell Surgery and Growth Factors in Retinitis Pigmentosa Patients: Pilot Study after Literature Review	Biomedicines	I	Clinical Study, prospective, interventional	RP
2019	Özmert, E. and Arslan, U. [28]	Management of Deep Retinal Capillary Ischemia by Electromagnetic Stimulation and Platelet-Rich Plasma: Preliminary Clinical Results	Adv Ther	I	Clinical Study, prospective, interventional, open-label	DRCI
2019	Sánchez-Ávila, RM. *et al.* [29]	Treatment of recurrent myopic macular hole using membrane of plasma rich in growth factors	Int Med Case Rep J.	I	Case Report, interventional	MH
2020	Arslan, U. and Özmert, E. [30]	Management of Retinitis Pigmentosa via Platelet Rich Plasma or Combination with Electromagnetic Stimulation: Retrospective Analysis of One-year Results	Res Sq	I	Clinical Study, retrospective, interventional	RP
2020	Arslan, U. and Özmert, E. [31]	Treatment of resistant chronic central serous chorioretinopathy via platelet-rich plasma with electromagnetic stimulation	Regen Med.	I	Clinical Study, prospective, interventional	CSCR
2020	Babu, N. *et al.* [32]	Comparison of platelet-rich plasma and inverted internal limiting membrane flap for the management of large macular holes: A pilot study	Indian J Ophthalmol	I	Clinical Study, prospective, interventional	MH
2020	Di Tizio, F. *et al.* [33]	Human amniotic membrane patch and platelet-rich plasma to promote retinal hole repair in a recurrent retinal detachment	Eur J Ophthalmol.	I	Case Report, interventional	RD due to RH
2020	Figueroa, M. S. *et al.* [34]	Long-term results of autologous plasma as adjuvant to pars plana vitrectomy in the treatment of high myopic full-thickness macular holes	Eur J Ophthalmol.	I	Clinical Study, retrospective, interventional	MH
2021	Schaub, F. *et al.* [35]	Outcome of autologous platelet concentrate and gas tamponade compared to heavy silicone oil tamponade in persistent macular hole surgery	Eur J Ophthalmol.	I	Clinical Study, retrospective, interventional	MH
2021	Finn, AP. *et al.* [36]	Combined Internal Limiting Membrane (ILM) Flap and Autologous Plasma Concentrate (APC) to Close a Large Traumatic Macular Hole in a Pediatric Patient	Retin Cases Brief Rep.	I	Case Report, interventional	MH
2021	Hagenau, F. *et al.* [37]	Highly Concentrated Autologous Platelet-Rich Plasma Restores Foveal Anatomy in Lamellar Macular Hole Surgery	Klin Monbl Augenheilkd.	I	Case Series, prospective, interventional	MH
2021	Giuseppe Limoli, P. *et al.* [38]	Mesenchymal stem and non-stem cell surgery, rescue, and regeneration in glaucomatous optic neuropathy	Stem Cell Res Ther.	I	Clinical Study, retrospective, interventional	Glaucoma
2021	Sahli, E. *et al.* [39]	Evaluation of the effect of subtenon autologous platelet-rich plasma injections on visual functions in patients with retinitis pigmentosa	Regen Med.	I	Clinical Study, retrospective, interventional	RP
2021	Shpak, A. A. *et al.* [40]	Surgical treatment of macular holes with and without the use of autologous platelet-rich plasma	Int Ophthalmol.	I	Clinical Study, partially retrospective, interventional	MH
2022	Arias, J. D. et al. [41]	Plasma rich in growth factors for persistent macular hole: A pilot study	Retin Cases Brief Rep.	I	Clinical Study, retrospective, observational	MH
2022	Hagenau, F. *et al.* [42]	Improving morphological outcome in lamellar macular hole surgery by using highly concentrated autologous platelet-rich plasma	Graefes Arch Clin Exp Ophthalmol.	I	Case Series, prospective, interventional	MH
2022	Rangel, C.M. *et al.* [43]	Plasma rich in growth factors as treatment for a full-thickness macular hole due to macular telangiectasia type 2	Arch Soc Esp Oftalmol.	I	Case Report, interventional	MH
2022	Sánchez-Ávila, RM. *et al.* [44]	Plasma Rich in Growth Factors in Macular Hole Surgery	Clin Pract.	C	Case Series, retrospective, interventional	MH
2023	Buzzi, M. *et al.* [45]	The Short-Term Results of Autologous Platelet-Rich Plasma as an Adjuvant to Re-Intervention in the Treatment of Refractory Full Thickness Macular Holes	J Clin Med.	I	Clinical Study, prospective, interventional	MH

(*continued on next page*)

Table 1 (*continued*)

Year	Author	Title	Journal	Institution	Study Design	Indication
2023	D'Alterio, F. M. *et al.* [46]	Platelet-rich plasma and macular hole surgery: A clue to their mode of action and the influence of anti-platelet agents	Eur J Ophthalmol.	I	Case Report, interventional	MH
2023	Giudice G, Lo. *et al.* [47]	Unilateral Macular hole in a patient with Retinitis Pigmentosa treated with cover flap technique with the use of platelet-rich plasma under air tamponade: case report	Retin Cases Brief Rep.	I	Case Report, interventional	MH with RP
2023	Hagenau, F. *et al.* [48]	Long-Term Results of Adjunct Autologous Platelet-Rich Plasma in Lamellar Macular Hole Surgery Showing Lasting Restoration of Foveal Anatomy	Int J Mol Sci.	I	Case Series, prospective, interventional	MH
2023	Parisi, G. *et al.* [49]	Macula-Off Retinal Detachment with Refractory Macular Hole Previously Closed with Autologous Platelet-Rich Plasma: A case Report	Case Rep Ophthalmol.	I	Case Report, interventional	MH with RD
2023	Rangel Gualdrón, C.M. *et al.* [50]	Plasma rich in growth factors membrane as a macular hole treatment in a vitrectomized patient due to rhegmatogenous retinal detachment	Arch Soc Esp Oftalmol.	I	Case Report, interventional	MH
2023	Rodríguez-Calvo, P. P. *et al.* [51]	Plasma Rich in Growth Factors as an Adjuvant Agent in Non-Penetrating Deep Sclerectomy	J Clin Med.	C	Clinical Study, prospective, interventional, randomized	Glaucoma
2023	Takhchidi, KhP. *et al.* [52]	Single-Stage Endovitreal Surgery of Retinal Detachment Complicated by Macular Hole Involving the Short-Term Perfluorocarbon Tamponade	Bulletin of RSMU	I	Case Report, interventional	MH with RD
2023	Takhchidi, KhP. [53]	Foveal Microsurgical Reconstruction Technique for Macular Hole	Bulletin of RSMU	I	Clinical Study, prospective, interventional	MH
2023	Voskanyan, L. and Aghabekyan, E. [54]	Macular Hole Recovery Surgery Using Autologous Platelet Rich Plasma	JBSMFS	I	Clinical Study, prospective, interventional	MH
2024	Bertonali, Y. *et al.* [55]	Successful use of PRGF-Endoret® and ILM peeling for full thickness macular hole in MacTel type 2: A case report and review of literature	Eur J Ophthalmol.	I	Case Report, interventional	MH
2024	Khan, P. *et al.* [56]	Electrophysiological and Visual Parameter Changes in Retinitis Pigmentosa Patients undergoing Autologous Platelet-Rich Plasma Therapy: A randomized Control Trial	J Curr Ophthalmol.	I	Clinical Study, prospective, interventional, randomized	RP
2024	Parisi, G. *et al.* [57]	Platelet rich plasma for primary macular hole: A case series	Eur J Ophthalmol.	I	Case Series, retrospective, interventional, non-randomized	MH
2024	Pereira, J. M. and Matos, A. C. [58]	Plasma rich in growth factors (PRGF) technology as adjuvant to *Ab Externo* trabeculectomy	Int Ophthalmol.	I	Clinical Study, retrospective, interventional, longitudinal	Glaucoma
2024	Ricardi, F. *et al.* [59]	The no-retina-touch technique: vitrectomy and platelet-rich plasma in the treatment of lamellar macular hole. New insights into pathogenesis	Eye (Lond).	I	Case Series, prospective, interventional	MH
2024	Rizzo, S. *et al.* [60]	Safety Results for Geographic Atrophy Associated with Age-Related Macular Degeneration Using Subretinal Cord Blood Platelet-Rich Plasma	Ophthalmol Sci.	I	Clinical Study, prospective, interventional, open-label, single-center, non-randomized, sequential-assigned	AMD
2024	Sahli, E. *et al.* [61]	Evaluation of the efficacy of subtenon autologous platelet-rich plasma therapy in patients with retinitis pigmentosa and factors affecting response to the treatment	Int Ophthalmol.	I	Clinical Study, prospective, interventional	RP
2024	Savastano, M.C. *et al.* [62]	Intravitreal cord-blood platelet-rich plasma for dry-AMD: Safety profile	AJO International	I	Clinical Study, prospective, randomized, interventional	AMD
2024	Jin, X. *et al.* [63]	Efficacy and safety of platelet-rich plasma for acute nonarteritic anterior ischemic optic neuropathy: a prospective cohort study	Front Med (Lausanne).	I	Clinical Study, prospective, interventional, non-randomized controlled trial	NAION
2025	Arslan, U.*et al.* [64]	Electromagnetic Iontophoresis: A Novel Nonsurgical Method for the Treatment of Dense Vitreous and Retinal Hemorrhages	Case Rep Ophthalmol.	I	Case Series, retrospective, interventional	Dense Vitreous and Retinal Hemorrhages
2025	Bertolani, Y. *et al.* [65]	First Case Report of Successful Use of ILM Peeling, Inverted Flap and PRGF-Endoret® in Bilateral Macular Hole in Behcet's Disease	Ocul Immunol Inflamm.	I	Case Report, interventional	MH
2025	Furashova, O. *et al.* [66]	Autologous platelet concentrate in epiretinal membrane surgery: A single-centre prospective comparative non-inferiority study	Acta Ophthalmol		Clinical Study, prospective, interventional, open-label, comparative non-inferiority series	ERM
2025	Hong, S. Y. *et al.* [67]	Long-term outcomes and prognosis in vitrectomy with autologous platelet concentrate injection for large, high myopic, or recurrent macular holes	Jpn J Ophthalmol.	I	Clinical Study, retrospective, interventional	MH
2025	Khouri, B. A. *et al.* [68]	Membrane Rich in Growth Factors for the Treatment of Refractory Macular Holes and its Effects on Retinal Vasculature and Anatomy	Retin Cases Brief Rep	I	Case Series, retrospective, interventional	MH
2025	Sacchi, M. *et al.* [69]	In Vivo Optical Coherence Tomography Outcomes of Hypotony After Trabeculectomy Management with Autologous Blood Injection: A Single-Center Retrospective Study	J Clin Med.	I	Case Series, retrospective, interventional	Glaucoma

(*continued on next page*)

Table 1 (*continued*)

Year	Author	Title	Journal	Institution	Study Design	Indication
2025	Savastano, M.C. *et al.* [70]	Intravitreal Injections of Cord Blood Platelet-Rich Plasma in Dry Age-Related Macular Degeneration: Regenerative Therapy	Ophthalmol Sci.	I	Clinical Study, prospective, interventional, randomized, controlled	AMD
2025	Xu, Z. *et al.* [71]	Effect of autologous whole blood in surgery for full-thickness macular hole: a propensity score matching analysis	BMC Ophthalmol.	I	Clinical Study, retrospective, interventional	MH

membrane (11 %), gel (4 %), and a combination of liquid and membrane forms (7 %).

To summarize, the most frequently reported preparation features were the use of PRGF-Endoret® kits, the use of sodium citrate as an anticoagulant, and a single-step centrifugation protocol.

Platelet concentrations varied substantially across studies and were often not reported. Furthermore, only 43 % of the articles included quantitative data on platelet counts. Among those that did, the reported concentrations varied greatly depending on the preparation method. For instance, a concentration of 1×10^6 platelets/μL ± 20 % was obtained in two studies using the PRP Biomed device with double centrifugation and resuspension in 1 mL of plasma (4 % of studies). CB-PRP, stored at −80 ºC, showed a markedly lower concentration of 1×10^3 platelets/μL (7 % of studies). Concentrations ranging from 1.5–4 $\times$ 10⁶ platelets/μL were reported in the lower plasma fraction (2 % of studies). One study using the APC, prepared by double centrifugation, reached 1×10^7 platelets/μL while another determined a concentration of 1.2×10^7 platelets/μl. Another protocol, reported in one study, used double centrifugation followed by platelet pellet resuspension in 1 mL of plasma, yielding a concentration of 654.75 $\times$ 10 ³ platelets/μL (3.33-fold higher than whole blood). Using the PRGF-Endoret® kit (with single centrifugation and calcium chloride activation) platelet concentrations were reported as two to three times higher than in whole blood when collecting the plasma column just above the buffy coat (F2 fraction) in 4 % of studies. Other studies using PRGF-Endoret® reported 2- to 3-fold or 3-fold increases (6 % of studies), while whole plasma formulations used for eye drop yielded 2.5-fold increase (2 % of studies). Additionally, one separate study using the same PRGF-Endoret® protocol to collect the F2 fraction did not report the platelet concentration, but it explicitly stated that the resulting preparation was classified as pure PRP (P-PRP). The Ycellbio system achieved concentrations 7- to 9-fold above the baseline (2 % of studies), while the Arthrex Angel System resulted in an 8.8-fold increase (7 %). In 2 % of studies using the RegenKit, platelets represented 79.2 ± 13.7 % of 10^5 total counted cells.

Despite the critical relevance of cellular composition to the bioactivity of blood-derived products, this parameter was reported inconsistently. In 70 % of the studies, no information was provided regarding the presence of red or white blood cells. P-PRP, defined as platelet- rich plasma with minimal leukocyte content, was clearly identified in 20 % of studies. Among these, one study did not specify the acquisition method while the rest employed the PRGF-Endoret® kit. A low red blood cell count was reported in 3 % of studies using the PRGF-Endoret®, while 8 % of studies using the Arthrex Angel System reported reduced leukocyte concentrations.

A subset of studies (7 %) described the simultaneous preparation of both P-PRP and pure platelet-poor plasma (P-PPP). In these protocols, the F2 fraction (two studies) or the F1 fraction (one study) was used for fibrin membrane formation, while the F1 (two studies) or the whole plasma column (one study) was employed to prepare liquid formulations.

All the blood-derived products were of human origin. The vast majority (91 %) were autologous, whereas 9 % were allogeneic, obtained from either pooled umbilical cord blood donations (15 donors per pool) or from healthy relatives with the same blood types, in the case of two patients from a reported case series.

3.4. Blood-derived products in ocular fundus

As the therapeutic relevance of blood-derived products in ophthalmology continues to expand, exploring their targeted application across distinct posterior segment pathologies becomes essential. Emerging evidence supports their use in vascular, structural, degenerative, neuropathic and hemorrhagic retinal disorders, as well as in disorders of the vitreoretinal interface, such as epiretinal membrane. These biologics have demonstrated neuroprotective, anti-inflammatory, and regenerative properties, making them promising candidates for multimodal retinal therapy. Fig. 2 summarizes the various delivery routes employed to enhance the bioavailability and clinical efficacy of platelet derivatives according to the anatomical and pathological context. This framework provides a basis for the subsequent discussion of disease-specific mechanisms and clinical approaches.

3.4.1. Vascular dysfunctions

Retinal vascular diseases disrupt perfusion and compromise tissue homeostasis, initiating a cascade of pathological events including edema, oxidative stress, glial activation, and progressive neurodegeneration [75]. Under such conditions, photoreceptors and retinal neurons lose access to adequate metabolic support, entering a dormant, non-functional state (OFF mode), characterized by reduced metabolic activity but preserved viability. If this dormant phase persists due to ongoing ischemia and a hostile microenvironment, cells undergo oncosis – a form of cell death characterized by swelling and fluid accumulation. Crucially, modulating local ischemia and inflammatory cytokine levels before the onset of oncosis can allow dormant (sleep mode) cells to revert to an active state (ON mode) [76–78].

A key determinant of this cellular dormancy is the availability of GFs within the retinal microenvironment. A decline in local growth factor levels initiates dormancy, with photoreceptors downregulating their metabolic activity. If this deficiency persists, the cells ultimately undergo irreversible apoptotic death. The duration between dormancy and apoptosis varies depending on individual genetic backgrounds, thus offering a crucial therapeutic window for neuroprotection [77,79,80].

The PRP, rich in neurotrophic and anti-apoptotic GF, has been proposed as a supportive therapy to preserve or restore photoreceptor function. When injected into subtenon space, PRP diffuses through tyrosine kinase (Trk) receptors, which are particularly abundant in entry sites such as the limbus, extraocular muscle insertions, and the optic nerve head [81]. This receptor-mediated mechanism facilitates the reactivation of dormant photoreceptors and supports their survival.

In parallel, the use of repetitive electromagnetic stimulation (rEMS) has shown promise in enhancing both the expression and sensitivity of Trk receptors on neural tissues [28, 82–84]. Additionally, rEMS exert an iontophoretic effect, improving the transscleral delivery of large peptides – including brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF) – which further contributes to neuroprotection [85–87]. rEMS boost both capillary blood flow and neurotransmission, providing complementary support for retinal tissue viability [88].

Patients with deep retinal capillary ischemia (DRCI), which may result from acute events or exacerbations of chronic systemic conditions such as severe anemia or chronic hypertension [89], frequently experience sudden vision loss. These events can lead to ischemia-reperfusion

Table 2
Overview of blood-derived products obtention method: Analysis of 46 published studies. Abbreviations: ACD: Acid Citrate Dextrose; ACD-A: Acid Citrate Dextrose Solution A; APC: Autologous Plasma Concentrate; CB-PRP: Cord-Blood Platelet Rich Plasma; CPD: Citrate–phosphate–dextrose; G: gel; L: liquid; Mb: Membrane; NM: not mentioned; P-PRP: pure-PRP; PRGF: Platelet Rich in Growth Factors; PRP: Platelet Rich Plasma; SC: Sodium Citrate; Fold change is expressed relative to platelet concentration in whole blood.

Year	Author (Year)	Type of Anticoagulant	Number of Centrifugations	Acquisition Method	Activation	Classification	Formulation	Platelets Content	Leukocytes Presence
2019	Abdalrahman, O. *et al.* [26]	NM	One	Whole plasma column	Calcium ion solution	PRP (Autologous)	L	NM	NM
2019	Giuseppe Limoli, P. *et al.* [27]	NM	One	RegenKit	NM	PRP (Autologous)	G	NM	NM
2019	Özmert, E. and Arslan, U. [28]	SC	One	T-LAB PRP KIT: Middle layer	NM	PRP (Autologous)	L	NM	NM
2019	Sánchez-Ávila, RM. *et al.* [29]	SC	One	PRGF-Endoret®: F2 (membrane) PRGF-Endoret®: F1 (liquid)	Calcium chloride	PRGF-Endoret® (Autologous)	Mb L	NM	P-PRP P-PPP
2020	Arslan, U. and Özmert, E. [30]	Citrate based	One	T-LAB PRP KIT: Bottom 1/3 of the upper plasma	NM	PRP (Autologous)	L	NM	NM
2020	Arslan, U. and Özmert, E. [31]	SC	One	T-LAB PRP KIT: Lower one-third of the upper plasma	NM	PRP (Autologous)	L	NM	NM
2020	Babu, N. *et al.* [32]	ACD-A	Double	Dr PRP Kit: Bottom of the upper compartment	NM	PRP (Autologous)	L	NM	NM
2020	Di Tizio, F. *et al.* [33]	ACD-A	Double	Platelet pellet supplemented with 0.6 mL of isotonic saline	NM	PRP (Autologous)	L	NM	NM
2020	Figueroa, M. S. *et al.* [34]	SC	One	PRGF-Endoret®: F2	Calcium chloride	PRGF-Endoret® (Autologous)	L	P-PRP	P-PRP
2021	Schaub, F. *et al.* [35]	NM	Double	Not mentioned	NM	APC (Autologous)	L	1×10^7 platelets/μL	NM
2021	Finn, AP. *et al.* [36]	Citrate based	One	Arthrex APC Kit	NM	PRP (Autologous)	L	NM	NM
2021	Hagenau, F. *et al.* [37]	ACD-A	One	Arthrex Angel System	NM	PRP (Autologous)	L	8.8-fold higher	Low concentration of white blood cells
2021	Giuseppe Limoli, P. *et al.* [38]	NM	One	RegenKit	NM	PRP (Autologous)	G	79.2 ± 13.7 % of platelets on a total of 10^5 cells	NM
2021	Sahli, E. *et al.* [39]	SC	One	Bottom layer of plasma	NM	PRP (Autologous)	L	1.5 to 4×10^6 platelets/μL	NM
2021	Shpak, A. A. *et al.* [40]	ACD	One	Ycellbio	Non-activated	PRP (Autologous)	L	7- to 9-fold higher	NM
2022	Arias, J. D. *et al.* [41]	SC	One	PRGF-Endoret®: F2	Calcium chloride	PRGF-Endoret® (Autologous)	Mb	2- to 3-fold higher	P-PRP
2022	Hagenau, F. *et al.* [42]	ACD-A	One	Arthrex Angel System	NM	PRP (Autologous)	L	8.8-fold higher	Low content of leukocytes
2022	Rangel, C.M. *et al.* [43]	SC	One	PRGF-Endoret®: F2	Calcium chloride	PRGF-Endoret® (Autologous)	Mb	3-fold higher	Low concentration of erythrocytes
2022	Sánchez-Ávila, RM. *et al.* [44]	SC	One	PRGF-Endoret®: F2 (membrane) PRGF-Endoret®: F1 (liquid)	Calcium chloride	PRGF-Endoret® (Autologous)	Mb L	NM	P-PRP P-PPP
2023	Buzzi, M. *et al.* [45]	SC	One	Bottom layer of plasma	NM	PRP (Autologous)	L	NM	NM
2023	D'Alterio, F. M. *et al.* [46]	SC	One	Not mentioned	NM	PRP (Autologous)	L	NM	NM
2023	Giudice G, Lo. *et al.* [47]	NM	One	Not mentioned	NM	PRP (Autologous)	L	NM	P-PRP
2023	Hagenau, F. *et al.* [48]	ACD-A	One	Arthrex Angel System	NM	PRP (Autologous)	L	8.8-fold higher	Low content of leukocytes
2023	Parisi, G. *et al.* [49]	ACD	Double	PRP Biomed Device: platelet pellet suspended in approximately 1 mL of plasma	NM	PRP (Autologous)	L	1×10^6 platelets/μL $\pm$ 20 %	NM

(*continued on next page*)

Table 2 (*continued*)

Year	Author (Year)	Type of Anticoagulant	Number of Centrifugations	Acquisition Method	Activation	Classification	Formulation	Platelets Content	Leukocytes Presence
2023	Rangel Gualdrón, C. M. *et al.* [50]	SC	One	PRGF-Endoret®: F2	Calcium chloride	PRGF-Endoret® (Autologous)	Mb	2- to 3-fold higher	P-PRP
2023	Rodríguez-Calvo, P. P. *et al.* [51]	SC	One	PRGF-Endoret®: Whole column of PRGF	Calcium chloride	PRGF-Endoret® (Autologous)	L	NM	P-PRP
2023	Takhchidi, KhP. *et al.* [52]	None	One	Arthrex ACP double syringe system	NM	PRP (Autologous)	L	NM	NM
2023	Takhchidi, KhP. [53]	NM	One	Arthrex ACP double syringe system	NM	PRP (Autologous)	L	NM	NM
2023	Voskanyan, L. and Aghabekyan, E. [54]	ACD-A	One	Arthrex Angel System	NM	PRP (Autologous)	L	NM	NM
2024	Bertonali, Y. *et al.* [55]	SC	One	PRGF-Endoret®: F2	Calcium chloride	PRGF-Endoret® (Autologous)	Mb	3-fold higher	NM
2024	Khan, P. *et al.* [56]	Citrate dextrose	One	Middle thin layer of PRP	NM	PRP (Autologous)	L	NM	NM
2024	Parisi, G. *et al.* [57]	ACD	Double	PRP Biomed Device: platelet pellet suspended in approximately 1 mL of plasma	NM	PRP (Autologous)	L	1×10^6 platelets/μL ± 20 %	NM
2024	Pereira, J. M. and Matos, A. C. [58]	SC	One	PRGF-Endoret®: F1 (membrane) PRGF-Endoret®: whole plasma column (eye drops)	Calcium chloride	PRGF-Endoret® (Autologous)	Mb L	1-fold 2.5-fold higher	P-PPP P-PRP
2024	Ricardi, F. *et al.* [59]	ACD	Double	Platelet pellet suspended in approximately 1 mL plasma	NM	PRP (Autologous)	L	654.75×10^3 platelets/μL (3.33-fold higher)	NM
2024	Rizzo, S. *et al.* [60]	NM	Double	Not mentioned	NM	CB-PRP (Allogenic)	L	1×10^3 platelets/μL	NM
2024	Sahli, E. *et al.* [61]	SC	One	Bottom layer of plasma	NM	PRP (Autologous)	L	NM	NM
2024	Savastano, M.C. *et al.* [62]	NM	Double	Not mentioned	NM	CB-PRP (Allogenic)	L	1×10^3 platelets/μL	NM
2024	Jin, X. *et al.* [63]	NM	NM	Not mentioned	NM	PRP	L	NM	NM
2025	Arslan, U.*et al.* [64]	Citrate based	One	Lower 1/3 of plasma column	NM	PRP (+Allogenic)	L	NM	NM
2025	Bertolani, Y. *et al.* [65]	SC	One	PRGF-Endoret®	Calcium chloride	PRGF-Endoret® (Autologous)	L	NM	P-PRP
2025	Furashova, O. *et al.* [66]	CPD (Citrate–phosphate–dextrose)	Double	Whole plasma column	NM	APC (Autologous)	L	1.2×10^7 platelets /μl	PPP
2025	Hong, S. Y. *et al.* [67]	ACD-A	One	Prosys PRS Bio Kit, Prodizen Inc.	NM	APC (Autologous)	L	NM	NM
2025	Khouri, B. A. *et al.* [68]	SC	Double	The outer fraction along with a portion of intermediate phase	Calcium gluconate	PRP (Autologous)	Mb	NM	NM
2025	Sacchi, M. *et al.* [69]	None	None	Whole blood	NM	Whole blood (Autologous)	L	NM	NM
2025	Savastano, M.C. *et al.* [70]	NM	Double	Not mentioned	NM	CB-PRP (Allogenic)	L	1×10^3 platelets/μL	NM
2025	Xu, Z. *et al.* [71]	None	None	Whole blood	NM	Whole blood (Autologous)	L	NM	NM

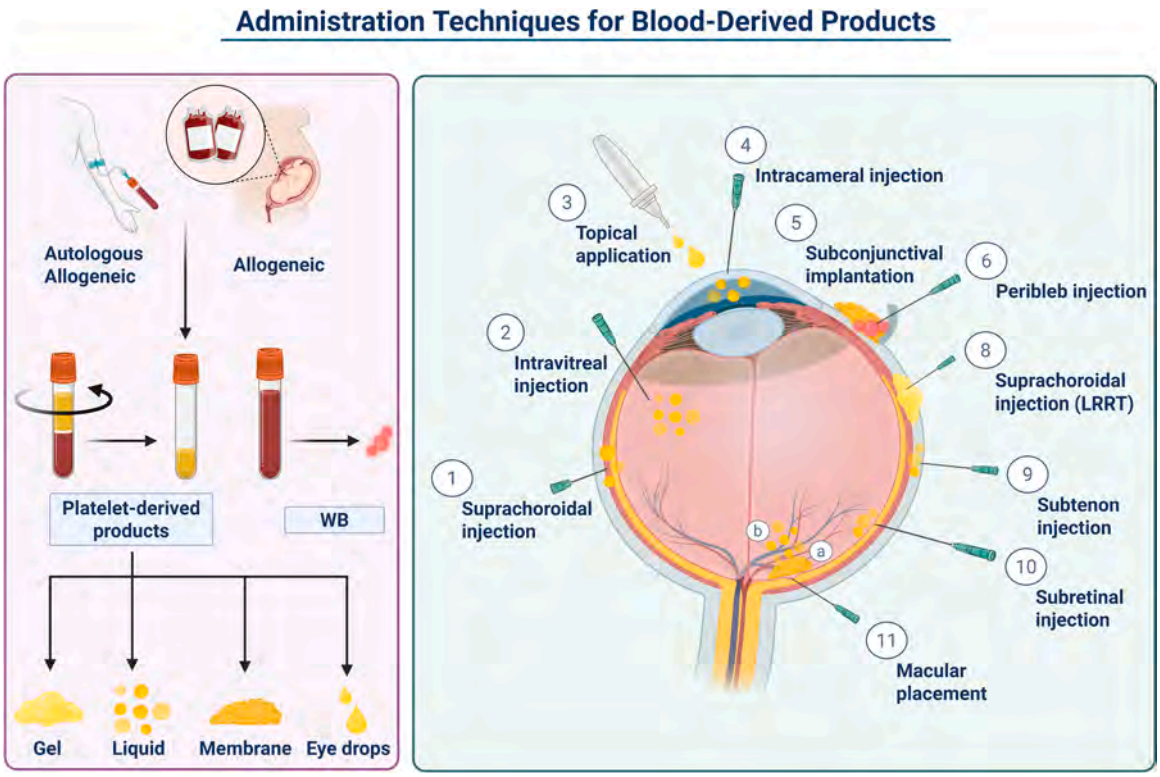

Fig. 2. Schematic representation of administration techniques for blood-derived products targeting posterior segment disorders. Blood-derived products – either autologous or allogeneic – can be formulated as liquid, gel, membrane, or eye drops. These can be delivered via multiple ocular routes, including: [1] suprachoroidal injection, [2] intravitreal injection, [3] topical application, [4] intracameral injection, [5] subconjunctival implantation, [7] macular placement, [8] suprachoroidal injection (Limoli retinal restoration technique, LRRT), [9] subtenon injection, and [10] subretinal injection. In addition, whole blood (WB) can be administered via [6] peribleb injection. These approaches are tailored to optimize therapeutic outcomes in vascular, structural, degenerative, and neuropathic retinal diseases. Created with BioRender.com.

injury, in which transient ischemia is followed by reperfusion and low-grade inflammation that further damages retinal structures [90]. A study by Özmert and Arslan [28] demonstrated that subtenon PRP injections and rEMS significantly improved deep retinal capillary density (DRCD) and best-corrected visual acuity (BCVA) in patients with DRCI. While rEMS alone significantly increased DRCD ($p = 0.01$), combination therapy yielded superior outcomes in both vascular and visual parameters ($p < 0.01$). No significant changes were observed in the control group ($p = 0.09$). These results suggest that a combination of rEMS and PRP therapy could effectively restore retinal function in DRCI patients who have not responded to conventional treatments.

Another retinal condition that may benefit from this combined approach is central serous chorioretinopathy (CSCR), a disorder characterized by subretinal fluid accumulation leading to serous retinal detachment and vision loss. CSCR can present acutely with spontaneous resolution or chronically, where persistent subretinal fluid results in photoreceptor damage and vision decline. It is often linked to retinal pigment epithelium (RPE) dysfunction, elevated cortisol levels, and choroidal congestion, all of which can be visualized through swept-source optical coherence tomography (SS-OCT) [91]. In chronic CSCR, patients often fail to respond to standard treatments. Özmert and Arslan [31] demonstrated that in patients with chronic CSCR resistant to conventional therapies, combined rEMS and PRP therapy significantly improved BCVA, submacular thickness (SMT), central macular thickness (CMT), and DRCD in such patients (all $p = 0.01$). These results suggest that rEMS and PRP could provide a promising treatment option for persistent visual impairment in CSCR.

Taken together, these findings suggest that combining PRP and rEMS in a therapeutic strategy may help restore retinal function in patients with vascular dysfunction and photoreceptor dormancy (Fig. 3).

In parallel, recent clinical experience further highlights the potential of this combined approach in ischemic and hemorrhagic retinal vascular diseases. In a prospective interventional case series [64], six patients (6 eyes) with intraocular hemorrhage due to vascular retinal disease were treated with subtenon PRGF-Endoret® and daily rEMS for 10 consecutive days. In selected cases, intravitreal anti-VEGF was also administered. All patients presented with acute visual loss due to dense sub-ILM, subretinal, or vitreous hemorrhage. The combination treatment led to complete resolution of hemorrhage in all eyes within 2–8 weeks, with BCVA improvements ranging from 2 to 5 Snellen lines. No adverse effects were observed. Notably, in the case of ischemic diabetic retinopathy, the therapy enabled adequate clearance of media opacity, allowing successful peripheral laser photocoagulation.

In this case series, subtenon PRGF-Endoret® combined with daily rEMS promoted rapid clearance of dense intraocular hemorrhages through multiple mechanisms. Citrated PRGF helped disaggregate clots and provided growth factors that stimulated RPE activity and phagocytosis. Meanwhile, rEMS enhanced drug penetration, mobilized erythrocytes trapped in retinal layers, and reactivated dormant retinal cells via neuromodulation. Together, these effects accelerated hemorrhage resorption, improved vision, and enabled early treatment of the underlying disease.

3.4.2. *Structural defects*

Macular hole (MH) surgery is one of the most successful interventions in vitreoretinal surgery, with anatomical closure rates ranging from 80 % to 95 %, particularly when employing pars plana vitrectomy (PPV) combined with internal limiting membrane (ILM) peeling and gas tamponade [92]. This standard approach efficiently relieves tangential traction at the foveal margins, promoting type 1 closure in most cases. However, surgical failure can still occur, particularly in large, chronic, high-myopic, or previously treated MHs, where

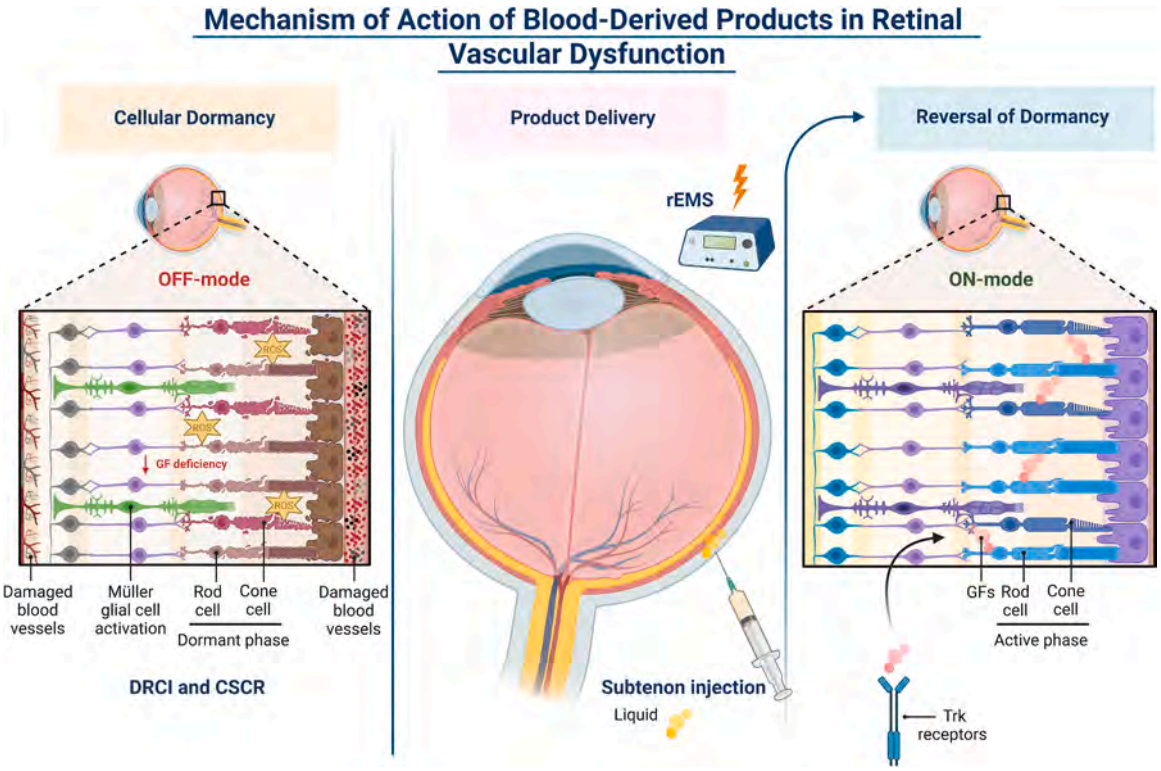

Fig. 3. Mechanism of action of blood-derived products in retinal vascular dysfunction. In retinal ischemic conditions such as deep retinal capillary ischemia (DRCI) and central serous chorioretinopathy (CSCR), damaged capillaries lead to a growth factor (GF) deficit, oxidative stress, glial activation, and photoreceptor dormancy. Subtenon injection of platelet-rich plasma (PRP), rich in neurotrophic GFs, combined with repetitive electromagnetic stimulation (rEMS), enhances GF delivery and tyrosine kinase (Trk) receptor activation. This promotes the transition of photoreceptors from a dormant to an active state, supporting retinal function restoration. Created with BioRender.com.

healing responses are often insufficient [93,94].

To address these challenging cases, several advanced techniques have been developed, including inverted ILM flap, retinal expansion procedures, macular hole hydrodissection, arcuate retinotomy, and anterior lens capsule transplantation [95–98]. Among these, the inverted ILM flap technique represents a major advance, enhancing both anatomical and functional outcomes in complex or refractory MHs [99].

Alongside these innovations, there has been an increasing focus on regenerative strategies that leverage the retina's innate neurobiological repair capacity. In this context, biological adjuvants such as the human amniotic membrane (hAM) and blood-derived products have demonstrated promising results in enhancing retinal repair and improving closure rates [100,101].

More recently, Xu *et al.* [71] conducted a retrospective propensity score-matched study comparing conventional MH surgery with and without the intraoperative use of autologous whole blood (WB). Despite significantly larger baseline hole diameters, the WB group achieved a 100 % closure rate, compared to 78.8 % in controls. Importantly, the authors attributed these improvements not only to the trophic factors present in WB but also to enhanced Müller cell activation, as evidenced by a significantly higher prevalence of gliosis and ellipsoid zone (EZ) restoration in the WB group. These findings suggest that WB may serve as a simple, effective biological adjuvant in primary MH repair – even in large or refractory cases.

A key mechanism underpinning these regenerative approaches involves the Müller glia, the principal supporting cells of the retina, known for their roles in structural integrity, neuroprotection, and wound healing. ILM peeling disrupts the basal lamina of Müller cells, inducing a gliotic response characterized by hypertrophy, proliferation, and migration to the lesion site [102]. This process facilitates the formation of a glial scaffold that spans the macular defect. When PRP is applied intraoperatively, platelet degranulation releases a cocktail of bioactive molecules – including PDGF, IGF-1, EGF, FGF, VEGF, and TGF-β1 – which activate intracellular signalling pathways (e.g., MAPK, PI3K/Akt) that enhance Müller cell activity and promote foveal repair [102–104]. This mechanistic model is detailed in Fig. 4.

The therapeutic benefit of blood-derived products appears most pronounced in the early-stages of MH, when the populations of Müller cell are intact and responsive. However, increasing evidence supports their use across a spectrum of clinical scenarios, including lamellar macular holes (LMH), persistent or recurrent MHs, atypical MH and secondary MH presentations [102,105].

Several studies report favorable outcomes when blood-derived products are used as an adjuvant in idiopathic MH surgery. Shpak *et al.* [40] conducted a large comparative study involving 214 eyes undergoing PPV and ILM peeling. Patients receiving a single intraoperative drop of PRP (n = 152) were compared with untreated controls (n = 62). Despite larger baseline MH diameters in the PRP group, the anatomical closure rate was significantly higher (100 % vs 93 %, p = 0.036), along with a statistically significant improvement in BCVA when adjusted for hole size. In a prospective clinical study, Babu *et al.* [32] compared PRP-assisted closure (n = 30) to the inverted ILM flap technique (n = 30). No statistically significant differences were observed in closure rates or BCVA at three months; however, PRP was associated with a simpler intraoperative course, suggesting potential procedural advantages. Takhchidi *et al.* [53] reported 100 % closure in a clinical study of ten eyes treated with 0.2 – 0.4 mL of PRP. Improvements were observed in uncorrected visual acuity (UCVA), BCVA, central retinal thickness, and retinal sensitivity, with benefits sustained up to 16 months. Voskanyan and Aghabekyan [54] expanded on these finding by applying PRP in both idiopathic and traumatic MHs. In their prospective study of 11 eyes treated with PRP and ILM peeling, all achieved anatomical closure, with an average gain of two Snellen lines and resolution of metamorphopsia. In a retrospective case series, Parisi *et al.*

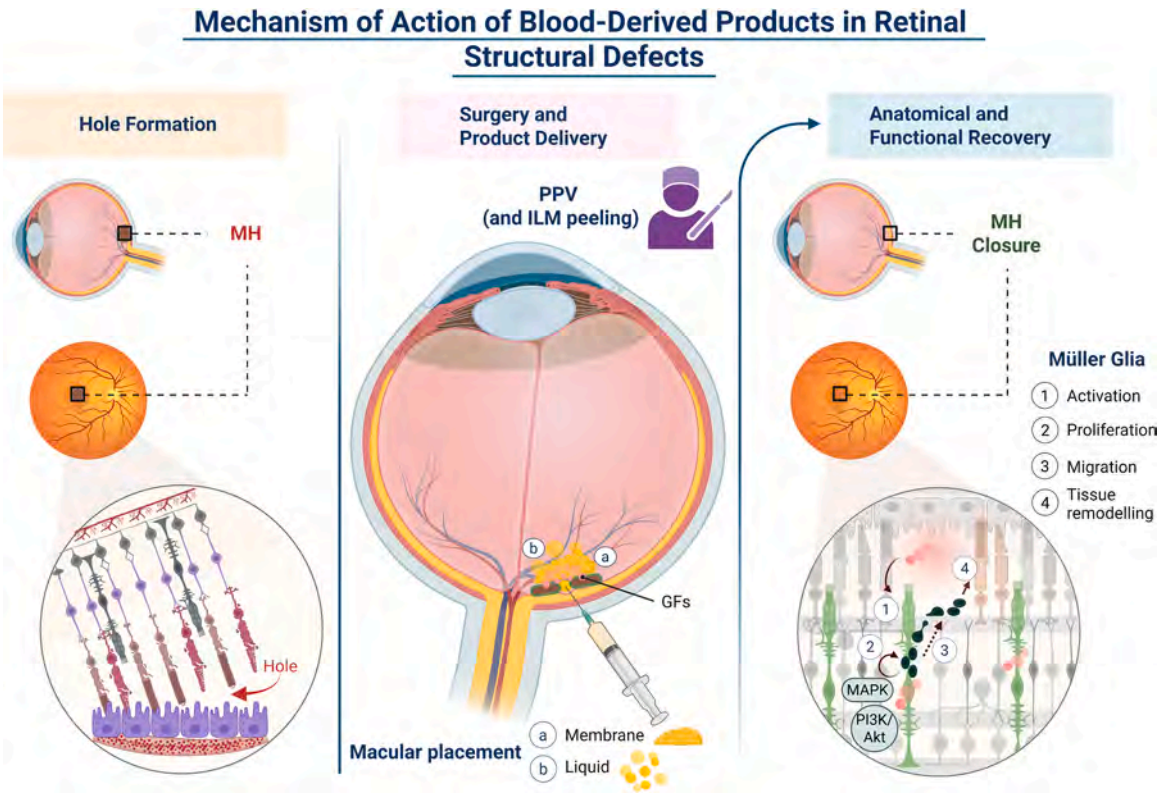

Fig. 4. Mechanism of action of blood-derived products in the treatment of retinal structural defects such as macular holes (MH). The scheme illustrates the therapeutic process from macular hole formation (left) to surgical intervention via pars plana vitrectomy (PPV) (and internal limiting membrane (ILM) peeling) with adjuvant application of blood-derived products – either as a platelet-rich plasma (PRP) liquid formulation or as a PRP-derived fibrin membrane (center) – and ultimately to anatomical and functional recovery (right). Upon application to the site of foveal injury, these products release a range of growth factors (GFs), which stimulate Müller glia activation, proliferation, migration, and tissue remodelling – critical steps in retinal repair. Intracellular signalling pathways such as MAPK and PI3K/Akt mediate these effects. This regenerative strategy may improve closure rates and visual outcomes, particularly in complex or refractory MHs. Created with BioRender.com.

[57] analyzed outcomes from ten eyes with idiopathic primary MH that had been treated with 0.1 mL of PRP following standard PPV and ILM peeling. All cases achieved successful closure, with progressive visual improvement from 20/160–20/80 over a six-month follow-up period.

The application of PRP in persistent or recurrent MH has also yielded favorable results, particularly in complex or refractory cases. Sánchez-Ávila *et al.* [29] treated a recurrent large myopic MH with a combination of a PRGF-Endoret® membrane and three drops of PRGF, achieving complete closure and improved BCVA (to 0.1) at six months. This finding was later corroborated by the same group [44] in a larger case series that treated eight eyes with recurrent MHs using PRGF-Endoret® membranes and/or intravitreal immunosafe PRGF-Endoret® formulation. The anatomical closure rate was 87.5 % closure in eight eyes, with functional improvement in six cases. Khouri *et al.* [68] retrospectively evaluated the outcomes of mPRGF in a case series of seven eyes with large, refractory, or traumatic MHs. All patients underwent PPV with gas tamponade and placement of a mPRGF. The anatomical closure rate was 71.4 % after one or more surgeries, with a single-surgery closure rate of 42.8 %. Among the three eyes requiring reintervention due to post-operative membrane dislocation, two achieved successful closure following repositioning. Final BCVA significantly improved from a mean of 1.46–0.71 logMAR (approximately from 20/570–20/100; $p = 0.036$), with an average gain of five lines. OCT analysis revealed restoration of inner retinal layers in 71.4 % of cases and outer layers in 14.3 %. Additionally, OCT-A showed a statistically significant reduction in foveal avascular zone (FAZ) area and increased foveal density post-operatively, both correlating with visual gains. Interestingly, one traumatic MH closed successfully without ILM peeling, suggesting that mPRGF may serve as an alternative scaffold that promotes retinal regeneration in select cases. Figueroa *et al.* [34] reported outcomes from 42 eyes with either naïve or persistent MHs treated with PRGF. The closure rates were 90 % and 91 % respectively, with significant BCVA improvements observed postoperatively.

In a retrospective single-center study, Hong *et al.* (2023) evaluated the long-term outcomes of vitrectomy with APC injection in 54 eyes presenting with large, highly myopic, or recurrent MHs. Patients were divided into three groups: PPV alone, PPV with flap techniques, and PPV with APC injection. Although anatomical closure rates were not statistically different among groups, the PPV + APC group achieved the highest closure rate (95 %), with no unclosed cases reported. Notably, glial proliferation – visible as a hyper-reflective lesion on OCT – was significantly more common in the APC group and was positively associated with successful MH closure, suggesting a regenerative role of blood-derived factors. While external limiting membrane (ELM) and EZ reconstruction rates were slightly lower in the APC and flap groups compared to PPV alone (possibly due to more advanced disease stages), all groups experienced significant BCVA improvement over a mean follow-up of over four years. Importantly, no significant complications were reported, and surgical time with APC was shorter than with flap techniques. The study underscores APC's safety and potential as a practical adjunctive tool in managing high-risk MHs, meriting further validation in complex surgical settings.

Schaub *et al.* [35] conducted a retrospective analysis comparing two reoperation strategies for persistent MH: APC with sulfur hexafluoride (SF6) gas (n = 13) versus APC with heavy silicone oil (HSO) tamponade (n = 35). While closure rates did not significantly differ (57.1 % and 45.7 %, p = 0.102), the SF6 group demonstrated superior functional outcomes when anatomical closure was unsuccessful, suggesting that

APC with SF6 may be a safer, more effective approach. Arias *et al.* [41] presented two successful cases of persistent MH managed with PRGF-Endoret® membranes. Both patients showed full anatomical closure and improvement in BCVA from 20/200 and 20/1500 to 20/100 in both patients at 12 months. Buzzi *et al.* [45] reported outcomes from 28 eyes with large, highly myopic, or optic disc pit-associated MHs undergoing revision surgery with three intraoperative PRP drops. The overall closure rate was 92.9 %, with significant BCVA gains across all subgroups. Lastly, Parisi *et al.* [49] described a challenging case of persistent MH following macula-off retinal detachment surgery. After initial surgical failure, a second intervention with PRP under SF6 tamponade led to complete closure within two weeks, with sustained visual improvement.

Beyond idiopathic and persistent full thickness macular hole (FTMH), blood-derived therapies have also been explored in LMHs and atypical or secondary MHs. Hagenau *et al.* were among the first to explore PRP for LMH. In a prospective case series [37], they treated eight eyes with 0.1 mL PRP, achieving complete anatomical closure in all cases and statistically significant improvement in BCVA ($p = 0.03$), despite stable microperimetry results. In a subsequent study [42], the same group observed an 83.3 % closure rate in 12 eyes, with two recurrences in cases without ILM peeling. Again, BCVA improved significantly ($p = 0.028$), though retinal sensitivity remained unchanged.

More recently, blood-based therapies have been explored in epiretinal membrane (ERM) surgery. In a prospective, open-label phase 4 study, Furashova *et al.* evaluated 51 eyes undergoing standard vitrectomy with or without intraoperative APC application. In the treated group, 0.4–0.5 mL was applied for 8 min following membrane removal. At six months, both groups showed improvements in central retinal thickness and reading acuity, but only the treated group achieved a statistically significant gain in BCVA, despite having more severe baseline pathology. These findings suggest a potential role for blood derivatives in enhancing recovery following ERM surgery, extending their application beyond full-thickness macular holes.

In a longer-term follow-up (14.2 ± 6,7 months), Hagenau *et al.* [48] treated 19 eyes with LMH using 0,1 mL of PRP. PRP dislocation occurred in one case due to poor positioning, and two cases without ILM peeling developed recurrent foveal defects. Overall, mean BCVA improved significantly from 0.33 to 0.18 logMAR ($p = 0.001$), and postoperative metamorphopsia decreased in all patients. More recently, Ricardi *et al.* [59] reported outcomes from eight eyes with LMH treated with PRP, achieving 88 % anatomical closure and restoration of EZ in 38 %. Improvements in BCVA ($p = 0.007$) and reading speed ($p = 0.029$) were also observed, underscoring the functional relevance of PRP in LMH surgery.

Building on these results, the use of blood-derived products has also been extended to atypical and secondary MH. In pediatric trauma, Finn *et al.* [36] reported anatomical and functional recovery in a large traumatic MH treated with ILM flap and PRP, with BCVA improving from 20/320–20/100. In the context of hereditary retinal disease, D'Alterio, F. M. *et al.* [46] described successful PRP-augmented closure of a persistent MH in a patient with Alport syndrome when using autologous blood-derived products.

Similarly, Bertolani *et al.* [65] presented the first documented case of bilateral full-thickness MH in Behçet's disease successfully treated with ILM peeling, inverted flap technique, and intraoperative PRGF-Endoret® drops. A 29-year-old patient with bilateral vitritis and chronic MH (705 μm and 638 μm) underwent sequential surgery after systemic immunosuppressive control. Both eyes achieved anatomical closure and improved BCVA (from 20/400 and 20/200–20/100), despite underlying macular ischemia and outer retinal layers (ORL) damage. The authors highlighted the regenerative and anti-inflammatory potential of PRGF in complex inflammatory MH, proposing its use as an adjunct in selected uveitic cases.

In macular telangiectasia type 2, Rangel, C.M. *et al.* [43] and Bertonali, Y. *et al.* [55] both reported favorable anatomical and functional outcomes using PRGF-Endoret® membranes; notably, the latter case achieved BCVA improvement from 20/400–20/25 without face-down positioning, though a transient herpetic keratitis episode resolved with topical acyclovir. In a patient with retinitis pigmentosa, Giudice G, Lo. *et al.* [47] combined PRP with ILM flap, leading to hole closure and modest visual gains.

Secondary MHs following retinal detachment have also been successfully treated: Rangel Gualdrón, C.M. *et al.* [50] applied a 100 μm PRGF-Endoret® membrane in a recurrent MH post-vitrectomy for rhegmatogenous detachment, achieving progressive BCVA recovery to 20/200 at 12 months. Similarly, Takhchidi et al. [52] treated a secondary MH associated with subtotal retinal detachment using PPV, ILM peeling, and 0.1 mL of APC, achieving restored foveal contour and sustained BCVA of 20/40 at six months. Finally, Di Tizio, F. *et al.* [33] reported successful integration of PRP with human amniotic membrane to seal a complex retinal detachment, highlighting the regenerative capacity of blood-derived therapies in highly challenging retinal scenarios.

Overall, complications were rare across all studies. Endophthalmitis was reported in three cases [35,47] and resolved with intravitreal antibiotics. Hagenau, F. *et al.* [48] documented cystoid macular edema in four cases post-PRP, managed with topical non-steroidal anti-inflammatory drugs (NSAIDs) or steroids. Dislocation of PRP was observed in at least one patient, requiring reapplication. The use of PRGF-Endoret® were shown to be safe even in high-risk or elderly populations, and no systemic complications were reported. Across diverse MH subtypes and clinical contexts, the adjunctive use of blood-derivatives has consistently demonstrated high anatomical closure rates – often ≥ 90 % – and meaningful visual recovery. These agents may be particularly valuable for recurrent, persistent, or atypical holes where conventional techniques have limited success. While ILM peeling remains a key component, some studies suggest that, in selected cases, PRGF-Endoret® membranes may be a suitable alternative. The biological rationale, ease of application, and low complication profile position blood-derivatives as effective tools in the evolving landscape of regenerative retinal surgery. Standardized protocols and prospective randomized trials are now warranted to define optimal formulations, dosages, and patient selection criteria.

3.4.3. Retinal degenerative disorders

Age-related macular degeneration (AMD) is a chronic and progressive disorder of the central retina (termed the macula), influenced by both genetic and environmental factors. Its complex pathophysiology involves oxidative stress, chronic inflammation, activation of the complement cascade, lipid dysregulation, angiogenesis, and remodelling of the extracellular matrix [106,107]. AMD is traditionally classified into two clinical forms: neovascular (wet) and non-neovascular (dry), with the latter accounting for approximately 90 % of the cases. Dry AMD is characterized by the accumulation of drusen, pigmentary changes, and geographic atrophy (GA) [108], which manifests as progressive and irreversible loss of photoreceptors, RPE and Bruchś membrane, and the underlying choriocapillaris [109].

Despite ongoing efforts to develop complement inhibitors and other emerging therapies, effective treatments that can halt or reverse GA progression remain allusive [110]. Blood-derived products have emerged as a potential disease-modifying therapy due to their rich content of trophic factors and antioxidants, which may provide sustained support to the outer retinal and mitigate atrophic expansion [60,111] (Fig. 5).

Cord blood-derived platelet-rich plasma (CB-PRP) has recently garnered attention as a regenerative agent due to its high concentration of neuroprotective GF, antioxidants, and proteins involved in phototransduction and retinoid metabolism. Proteomic profiling of CB-PRP has revealed over 200 bioactive proteins implicated in immune modulation, oxidative stress defense, and trophic support to the outer retinal layers and choriocapillaris – structures critically affected in GA [112,113].

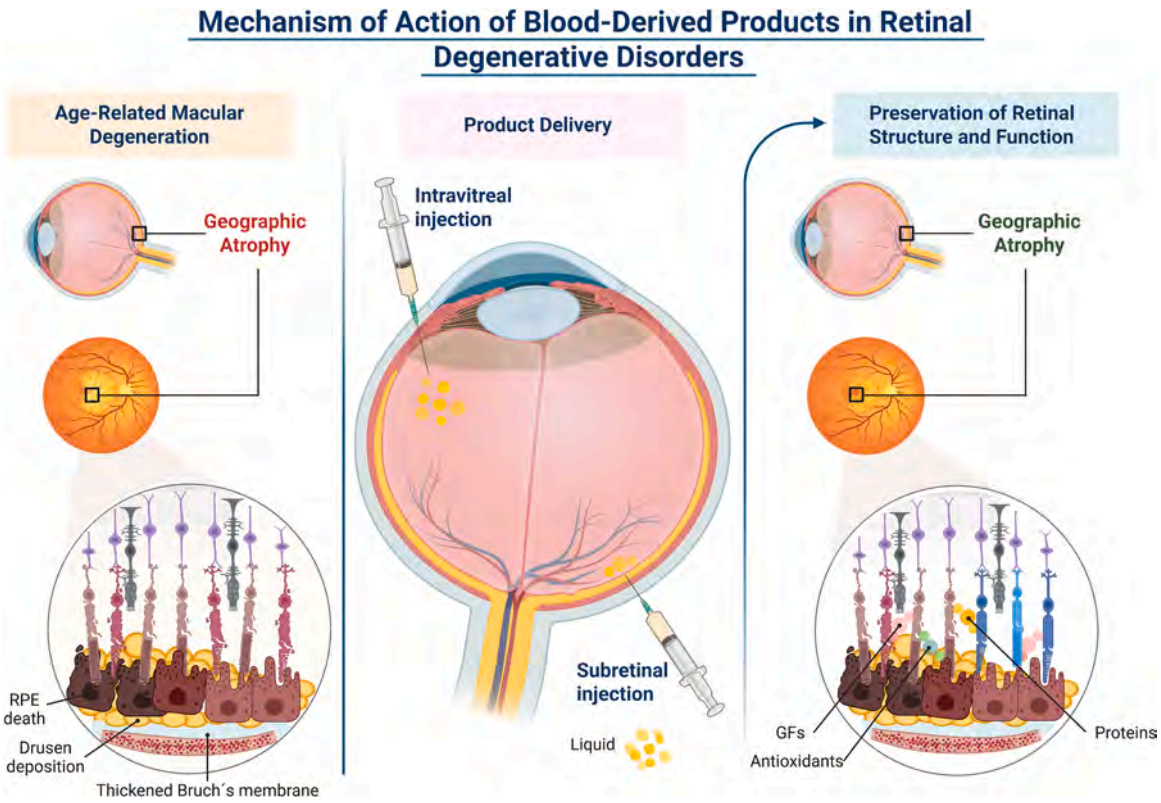

Fig. 5. Mechanism of action of blood-derived products in retinal degenerative disorders. In age-related macular degeneration (AMD), progressive atrophic changes lead to geographic atrophy (GA), characterized by drusen accumulation, retinal pigment epithelium (RPE) degeneration, photoreceptor loss, and thickening of Bruch's membrane (left). Blood-derived products such as cord blood-derived platelet-rich plasma (CB-PRP) can be administered via intravitreal or subretinal injection to deliver bioactive factors directly to the site of degeneration (center). The therapeutic components of CB-PRP – including growth factors (GFs), antioxidants, and structural proteins – support photoreceptors and the RPE by modulating inflammation, reducing oxidative damage, and promoting tissue maintenance. This intervention contributes to the preservation of retinal structure and function, rather than anatomical improvement, by slowing disease progression (right). Created with BioRender.com.

Building on these findings, Rizzo *et al.* [60] conducted a prospective pilot study assessing the safety and preliminary efficacy of subretinal CB-PRP in 26 eyes with GA secondary to dry AMD. Patients were divided into two groups to receive either pars plana vitrectomy followed by subretinal injection of 0.5 mL CB-PRP ($n = 13$), or no ocular treatment ($n = 13$). After 12 months, treated eyes demonstrated a trend toward improvement visual acuity, although the difference did not reach statistical significance ($p = 0.084$). Central macular thickness remained similar between groups ($p = 0.97$), and GA progression occurred in both arms ($p < 0.0001$). Importantly, no serious complications were reported, supporting the safety of the subretinal approach.

To explore less invasive therapeutic alternatives Savastano *et al.* [62] initiated a randomized clinical trial evaluating intravitreal CB-PRP injections, aiming to provide chronic neurotrophic support with a reduced procedural burden. In this study, 42 eyes with GA were randomized to receive intravitreal CB-PRP ($n = 21$) or no treatment ($n = 21$). Treated eyes were further stratified into three dosing schedules – monthly, bimonthly, or every three months – receiving between 4 and 12 injections over one year. Visual assessments included visual acuity, autofluorescence imaging, SD-OCT, optical coherence tomography angiography (OCTA), and IOP monitoring. Treated eyes exhibited greater anatomical stability and slower GA progression than their untreated counterparts, without any adverse events.

A subsequent prospective study by the same group included 26 eyes treated with intravitreal CB-PRP (0.05 mL) according to the same dosing regimens [70]. Visual acuity remained stable in both treated (from 48.92 ± 16.33–51.46 ± 12.27 letters; $p = 0.37$) and untreated eyes (from 67.69 ± 10.89–65.38 ± 10.34 letters; $p = 0.51$). Notably, the annualized growth rate of GA significantly lower in the treatment group (0.275 mm/year) compared to controls (0.321 mm/year), representing a 14.5 % reduction in atrophy progression ($p = 0.007$). No serious adverse events were recorded, with only transient conjunctival hyperemia, subconjunctival hemorrhage, and short-term floaters observed. However, due to the limited sample sizes of both studies, no definitive conclusions could be drawn regarding the relative efficacy of the three dosing regimens, highlighting the need for larger, multicenter trials with longer follow-up.

Together, these findings support CB-PRP as a promising, well-tolerated adjunctive therapy capable of stabilizing retinal structure and function in patients with geographic atrophy. Whether administered subretinally or intravitreally, CB-PRP may provide neurotrophic and antioxidative support to vulnerable retinal tissues and help delay disease progression in the absence of approved curative therapies.

3.4.4. Optic neuropathies

Optic neuropathies, including glaucomatous and ischemic subtypes, remain a significant clinical challenge due to the irreversible loss of retinal ganglion cells (RGCs) and the limited regenerative capacity of the optic nerve. Blood-derived products, enriched with autologous GF and bioactive mediators, have emerged as a candidate therapy with neuroprotective, antifibrotic, and pro-regenerative properties that support optic nerve repair [114] (Fig. 6).

Glaucoma, the most prevalent optic neuropathy, is primarily associated with elevated intraocular pressure (IOP). The defining feature of glaucomatous damage is glaucomatous optic neuropathy (GON), a chronic neurodegenerative condition characterized by progressive RGC loss, axonal degeneration, and excavation of the optic nerve head, including increased cupping and thinning of the retinal nerve fiber layer

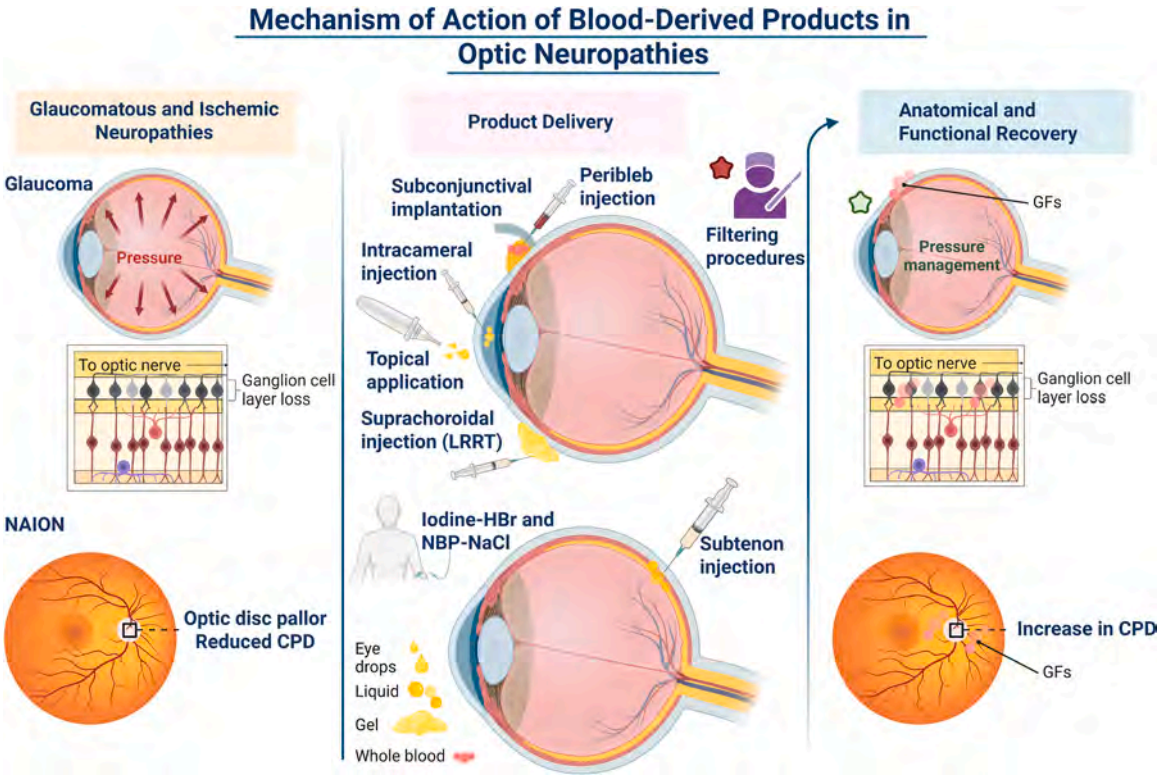

Fig. 6. Mechanism of action of blood-derived products in optic neuropathies. The figure illustrates the pathophysiological processes associated with glaucoma and non-arteritic anterior ischemic optic neuropathy (NAION), along with various delivery strategies for blood-derived products, including topical application, subtenon injection, and suprachoroidal injection through the Limoli Retinal Restoration Technique (LRRT). LRRT is a multimodal regenerative approach that combines suprachoroidal implantation of adipose-derived mesenchymal stem cells with intravitreal gel administration of platelet-rich plasma (PRP). In glaucoma, blood-derived products (e.g., PRGF-Endoret®) have been applied intraoperatively, postoperatively, and as membranes to improve filtering surgery outcomes by modulating the wound-healing cascade and reducing fibrosis. Additionally, in cases of postoperative hypotony and overfiltration, both intracameral PRP and perible autologous blood injections have been employed to restore intraocular pressure and promote bleb remodelling, as demonstrated in refractory cases after trabeculectomy or valve implantation. In NAION, PRP has also been used as an adjunct to standard treatment regimens including intravenous iodine hydrobromide and butylphthalide-sodium chloride (Iodine-HBr and NBP-NaCl), contributing to improved visual acuity and increased capillary perfusion density (CPD). Overall, therapeutic mechanisms of blood-derived products include neuroprotection, modulation of inflammation and fibrosis, enhancement of microvascular perfusion, and support of axonal regeneration, all of which contribute to the anatomical and functional recovery of the optic nerve. Created with BioRender.com

[115]. Despite the widespread use of IOP-lowering therapies, many patients – particularly in advanced disease stages – continue to experience functional decline, underscoring the unmet need for adjunctive neuroprotective strategies [116].

To address this need, the Limoli Retinal Restoration Technique (LRRT) has been proposed as a multimodal regenerative therapy, combining suprachoroidal implantation of adipose-derived mesenchymal stem cells (MSCs) with intraocular PRP administration. This approach is designed to provide trophic support, modulate inflammation and oxidative stress [38], and promote neuronal survival and axonal regeneration [117]. In a prospective study involving 35 eyes with GON, Limoli *et al.* [38] demonstrated that patients treated with LRRT and PRP ($n = 14$) exhibited significant improvements in BCVA, close-up vision, and microperimetric retinal sensitivity after six months (all $p < 0.05$), whereas untreated controls ($n = 21$) showed no statistically significant changes ($p > 0.5$). Importantly no adverse events were reported, supporting the safety and potential efficacy of this multimodal regenerative approach.

Beyond neuroprotection, blood-derived products have shown promise in optimizing surgical outcomes in glaucoma. Excessive subconjunctival fibrosis remains the primary cause of failure following filtering procedures such as non-penetrating deep sclerectomy (NPDS) [118,119] and trabeculectomy [120]. Standard antifibrotic strategies – including intraoperative mitomycin C (MMC) and postoperative corticosteroids – are commonly employed to mitigate scarring [119]. However, they often fail to achieve consistent outcomes, leading to a persistent need for additional interventions [118]. In this context, PRGF-Endoret® has been investigated for its role in modulating the postoperative wound-healing cascade, particularly by targeting the coagulative, inflammatory, proliferative, and remodelling phases [121]. PRGF-Endoret® may be applied at three different stages: pre-, intra- and postoperatively. In a prospective study Rodríguez-Calvo *et al.* [51] conducted a prospective study in patients with primary open-angle glaucoma (POAG) undergoing NPDS with intraoperative MMC. Patients were randomized to receive postoperative immunosafe PRGF-Endoret® eye drops ($n = 47$) or standard care ($n = 48$). Drops were administered four times daily for four months. At six months, both groups achieved significant IOP reductions; however, the PRGF-Endoret® group demonstrated a more pronounced decrease (-52.6 % vs. -27.2 %, $p < 0.01$). Moreover, filtering blebs with microcysts morphology were more prevalent in the PRGF-Endoret® group (76.7 % vs. 62.5 %), suggesting enhanced aqueous humor drainage and bleb viability. Although the incidence of postoperative complications was lower in the PRGF-Endoret® group (11 % vs. 25 %), this difference did not reach statistical significance ($p = 0.06$).

Complementary findings were reported by Pereira and Matos [58], who assessed PRGF-Endoret® application during trabeculectomy in a pilot study of nine eyes with POAG. A PRGF-Endoret®membrane was implanted subconjunctivally at the time of surgery, followed by postoperative PRGF-Enodret® eye drops. After 12 months, mean IOP decreased from 24.0 ± 8.8 mmHg to 12.9 ± 2.6 mmHg, and the mean number of hypotensive medications dropped from 4.3 ± 0.9–0.8 ± 1.1.

Complete surgical success (IOP ≤21 mmHg without medication) was achieved in 66.7 % of eyes. Notably, bleb morphology remained diffuse and low in height (1.6 ± 0.8 mm), suggesting a diffuse and well-tolerated filtration profile. Adverse events were minimal, including one case of iris incarceration and one transient hypotony; no cases of blebitis, leakage, or endophthalmitis were observed.

Additionally, autologous blood-derivatives have been explored for the management of severe hypotony secondary to overfiltration or scleral thinning after filtering procedures. Abdalrahman *et al.* [26] reported a case of a 49-year-old patient with Axenfeld–Rieger syndrome who developed chronic hypotony (IOP = 0 mmHg) and persistent corneal graft edema due to excessive transscleral filtration following Ex-Press valve implantation with MMC. After multiple failed interventions, a single intracameral injection of 0.3 mL of autologous PRP was performed. IOP normalized within 6 h, corneal transparency improved, and no further surgical interventions were required. Subsequent Descemet membrane endothelial keratoplasty (DMEK) achieved a final BCVA of 0.7 at 6 months, with a well-formed filtering bleb and no recurrence of hypotony.

In a retrospective series, Sacchi *et al.* [69] evaluated nine patients with hypotony maculopathy after trabeculectomy, treated with perible autologous blood injections. All patients had choroidal folds on OCT and IOP < 6 mmHg. A single injection (0.5–1 mL) was sufficient in most cases, leading to resolution of maculopathy in 7/9 patients within a mean of 5.3 ± 1.4 weeks. IOP increased significantly post-injection (mean +8.3 ± 2.4 mmHg, p = 0.008), and no IOP spikes or complications were observed. Two refractory cases required surgical bleb revision. These findings suggest that autologous biologics, including PRP and whole blood, may offer safe and effective adjuncts in managing challenging postoperative complications such as ocular hypotony and bleb failure.

PRP has also been evaluated in non-arteritic anterior ischemic optic neuropathy (NAION), a vision-threatening condition with a vascular origin [122] and limited therapeutic options [123]. In a controlled study by Jin, X. *et al.* [63], 25 patients with NAION received either standard care (intravenous iodine hydrobromide and butylphthalide-sodium chloride) in 13 patients or the same regimen supplemented with two subtenon injections of PRP (n = 12). In the PRP group, a significant improvement in BCVA was observed over 30 days (from 0.67 ± 0.59–0.43 ± 0.59; p = 0.005). Capillary perfusion density (CPD) also increased progressively (p < 0.001), with significantly higher values at day 7 compared to controls (p = 0.043). However, no intergroup differences were found in final BCVA or structural parameters such as the moth-eaten area index (p > 0.5).

In summary, these clinical findings support the potential of blood-derived products as a multifaceted therapeutic tool in optic neuropathies. Further large-scale, randomized studies are warranted to define the optimal dosing protocols and long-term efficacy for different optic neuropathy subtypes.

3.4.5. *Inherited retinal diseases*

Inherited retinal degenerations (IRDs) constitute a heterogeneous group of genetically mediated disorders characterized by progressive photoreceptor loss and vision impairment [124]. Among them, retinitis pigmentosa (RP) is one of the most prevalent and well-characterized forms, defined by the gradual dysfunction and degeneration of RPE, followed by photoreceptor apoptosis. Notably, while many photoreceptors degenerate as the disease progresses, a subset may enter a metabolically quiescent, dormant state, thereby offering a potential therapeutic window [79]. Blood-derived products, either alone or in combination with adjunctive techniques such as stem cell grafting or rEMS have shown early promise in targeting this dormant population

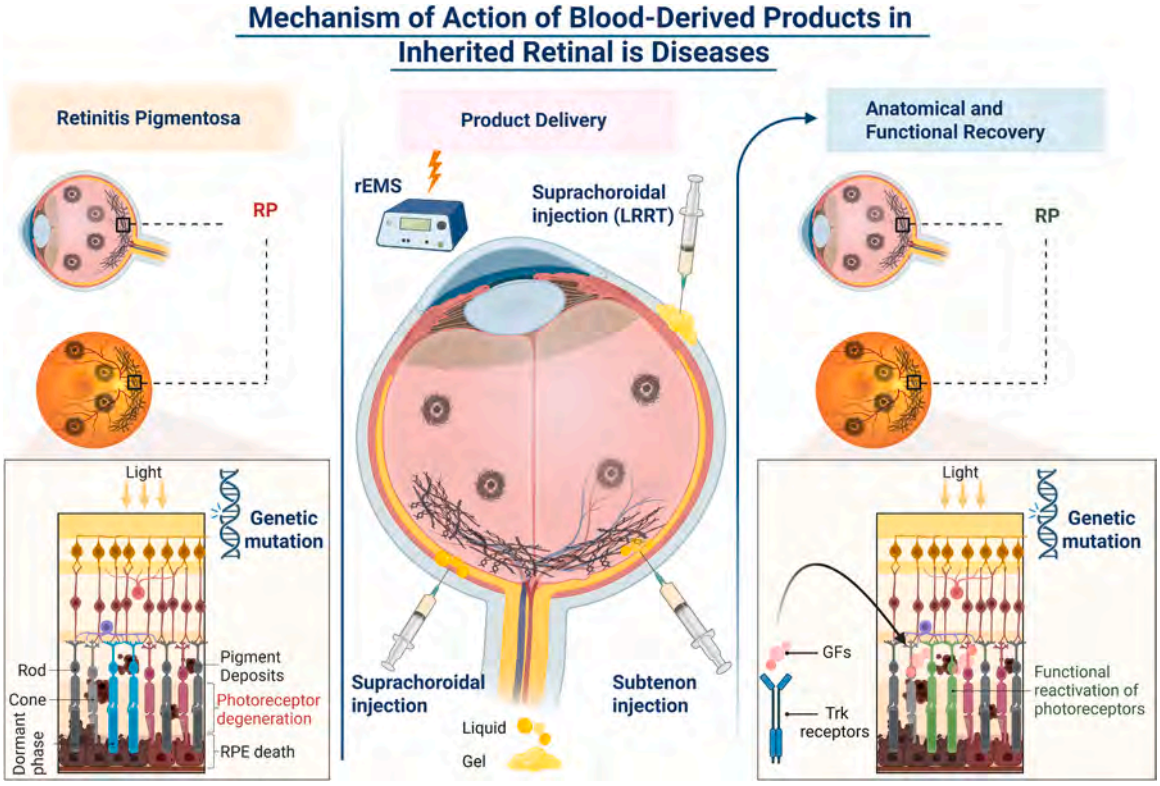

Fig. 7. Mechanism of action of blood-derived products in inherited retinal diseases (IRDs), exemplified by retinitis pigmentosa (RP). Genetic mutations induce retinal pigment epithelium (RPE) loss, photoreceptor degeneration, and pigment accumulation. A subset of photoreceptors may remain in a metabolically quiescent state. Platelet-rich plasma (PRP), administered via subtenon or suprachoroidal routes, delivers neurotrophic factors that engage tyrosine kinase (Trk) receptor pathways. Adjunctive techniques such as light-responsive retinal therapy (LRRT) or repetitive electrical muscle stimulation (rEMS) may enhance delivery and bioactivity. These interventions aim to restore photoreceptor function and improve retinal structure and vision. Created with BioRender.com

[27,30,39]. The proposed mechanism involves neurotrophic support via trans-scleral diffusion, activation of Trk receptor-rich pathways, and potential enhancement through adjunctive strategies (Fig. 7) [81].

Three clinical studies have explored the therapeutic potential of PRP monotherapy in RP [39,56,61], focusing on its ability to improve visual function through neurotrophic support. Sahli, E. *et al.* [39,61] administered PRP via subtenon injection, while Khan, P. *et al.* [56] applied a combination of subtenon and suprachoroidal administration. These studies, encompassing cohort of 188 [39], 85 [61], and 78 [56] eyes respectively, employed standardized outcome measures, including BCVA, microperimetry, OCT, and mfERG. Results consistently demonstrated statistically significant improvements in BCVA, contrast sensitivity, and fixation stability, alongside enhanced mfERG parameters – particularly amplitude density and waveform normalization – suggesting functional reactivation of photoreceptors. In the study by Khan, P. *et al.* [56] untreated eyes served as controls and showed no significant functional improvement, while two studies by Sahli, E. *et al.* [39,61] used patients´ own baseline values as internal comparators. No severe adverse events were reported across all studies, with only mild, transient ocular discomfort observed. Collectively, these findings support the hypothesis that PRP confers a neuroprotective effect in RP by promoting the recovery of metabolically inactive photoreceptors.

Beyond monotherapy, adjunctive strategies incorporating PRP have also been explored. Limoli *et al.* [27] implemented the previously described LRRT in a cohort of 21 RP eyes. Over six months, patients underwent SD-OCT, microperimetry, ERG, applanation tonometry, and slit-lamp biomicroscopy. While no significant changes in IOP or BCVA were observed across the cohort, stratified analysis revealed a trend toward improved near vision and retinal sensitivity in patients with preserved foveal thickness (>190 μm). Subjective visual improvement was reported in 71.4 % of eyes, with most responsive cases falling within this subgroup. Notably, no complications were encountered. These findings suggest that LRRT, when combined with adjuvant PRP, may provide functional benefits in carefully selected RP patients who retain central retinal structure.

Similarly, attention has turned toward rEMS as an adjunct to PRP therapy – also previously described - in RP. Arslan and Özmert [30] evaluated the combined use of rEMS and subtenon autologous PRP in a controlled study involving 120 eyes distributed across three groups: rEMS+PRP, PRP alone, and untreated controls. Patients received five treatment sessions and were followed for an average of 13 months. Compared to PRP alone, the combined therapy group showed better preservation of ellipsoid zone width and microperimetric sensitivity. In turn outperformed the control group. Although most changes did not reach statistical significance, the trend favored the combined intervention. No adverse events were reported, reinforcing the safety and potential utility of rEMS as a complementary approach to PRP in treating retinal degeneration.

In summary, emerging clinical evidence supports the use of PRP in inherited retinal diseases, particularly RP. By potentially reactivating dormant photoreceptors and stabilizing retinal function, PRP represents a promising therapeutic strategy. Furthermore, its combination with adjunctive therapies such as LRRT and rEMS may enhance outcomes in selected patients. Continued research is warranted to refine patient selection, optimize protocols, and validate long-term efficacy.

4. Discussion and future perspectives

The integration of blood-derived products into ophthalmic practice – particularly PRGF-Endoret® – represents a compelling advance in regenerative ophthalmology [19]. These biologic therapies have shown promising effects across a range of retinal and optic nerve disorders, including vascular dysfunction [28,31], structural defects [59], degenerative disorders [70], optic neuropathies [58,63] and IRDs [61]. Nevertheless, they are still in the early stages of clinical application, and several key challenges must be overcome to encourage wider use.

Although the reviewed studies consistently report a favorable safety profile – with no major adverse events linked to intravitreal or subretinal application – the therapeutic efficacy of blood-derived products is not yet fully established. Much of the existing evidence is derived from case reports, case series, or small non-randomized trials, which limits the generalizability and strength of the conclusions. Among the 46 included studies, only a few were randomized controlled trials, and many lacked control arms or comprehensive outcome assessments. These methodological limitations make it difficult to apply formal evidence-grading tools such as GRADE and restrict the capacity to form strong clinical recommendations.

Study design variability further complicates interpretation. Sample sizes are often small, follow-up durations inconsistent, and primary outcomes frequently limited to visual acuity or OCT-based anatomical measures. However, these metrics may not fully reflect therapeutic benefit, especially in conditions with slow progression or subtle functional changes. Functional assessments such as microperimetry and electrophysiology, as well as patient-reported outcomes, were seldom incorporated, despite their relevance for capturing the full therapeutic impact. Furthermore, few studies stratified patients by clinical subtypes or baseline characteristics, making it difficult to determine which populations may benefit most from these therapies. Future research should adopt standardized, multimodal outcome frameworks that combine structural imaging (e.g., OCT angiography, fundus autofluorescence), functional testing, and patient-centered metrics to provide a more comprehensive evaluation of clinical efficacy [125–129].

Among the various clinical indications explored, MH represent the most extensively studied and consistently responsive pathology to blood-derived therapies. Across idiopathic, recurrent, myopic, lamellar, and traumatic MHs, the use of PRP and PRGF-Endoret® – either as intraoperative drops or membrane formats – has demonstrated anatomical closure rates exceeding 90 %, even in challenging cases. These products appear to enhance Müller cell activation, reduce chronic gliosis, and promote tissue remodeling [102–104]. Moreover, their compatibility with *pars plana vitrectomy* and internal limiting membrane peeling techniques makes them particularly attractive as surgical adjuncts [101]. However, more studies are needed to assess these products in complex or persistent cases. Nonetheless, some reports have noted the intraoperative displacement of PRP drops, indicating that membrane-based formats may offer greater stability and retention in specific anatomical contexts [48].

Beyond macular holes, blood-derived therapies have also shown promise in optic neuropathies and inherited retinal degenerations. In glaucoma, PRGF-Endoret® has been applied postoperatively as eye drops or subconjunctival membranes to modulate fibrosis following filtering surgery. Several studies suggest improved IOP control and bleb morphology[51,58]. Additionally, its use as an adjunct to mitomycin C offers a potentially safer alternative for modulating wound healing [121]. In NAION, subtenon injections of PRP combined with systemic therapy have demonstrated gains in visual acuity and perfusion density [63]. Meanwhile, in RP, the neuroprotective potential of blood-derived products is particularly relevant given the presence of structurally preserved but functionally dormant photoreceptors. Clinical reports describe improvements in visual acuity, contrast sensitivity, and electrophysiological responses following subtenon or suprachoroidal PRP administration. Although these findings are encouraging, the limited sample sizes and short follow-up durations necessitate further investigation, particularly in early-stage RP or in combination with other supportive therapies.

One of the most pressing issues limiting the clinical translation of blood-derived products is the lack of standardization in their preparation. The reviewed studies exhibited marked variability in anticoagulant use (most frequently sodium citrate), centrifugation steps (single vs double spin), platelet activation methods (ranging from no pre-activation, allowing for *in situ* activation by tissue collagen and/or tissue factor, to exogenous activation using calcium chloride), and the final

physical formulation of the product (gel, liquid, membrane, or eye drops). This heterogeneity directly impacts the concentration, composition, and bioavailability of GFs, thereby influencing the reproducibility and comparability of biological and clinical outcomes [72,73]. Head-to-head comparisons of platelet rich plasma would shed light on the impact of leukocyte concentration, platelet count, or activation method on therapeutic outcomes. These questions warrant further mechanistic and clinical exploration.

In contrast, PRGF-Endoret® prepared using the PRGF-Endoret® kit has emerged as a more standardized and reproducible approach. This protocol uses a single centrifugation step and employs sodium citrate as an anticoagulant and calcium chloride as an exogenous activator [130]. This results in a higher concentration of platelet-derived GFs being released and a stronger biological response being elicited. It is important to note that most blood-derived product systems utilize citrate-based anticoagulants, which bind to and inhibit calcium ions, thereby blocking both coagulation and platelet activation. In this context, exogenous activation with calcium chloride restores the coagulation cascade and has been shown to induce a significantly greater release of GFs than collagen-based activation alone [131]. This results in a more robust biological response. Indeed, fibrin clot formation was observed only in the calcium chloride–activated group, highlighting its effectiveness. Calcium chloride-mediated activation was consistently used in all studies employing the PRGF-Endoret® system. This step allowed to obtain different ophthalmic formulations like eye drops, injectable liquid, membrane and clots that are tailored according to the clinical and anatomical needs. The therapeutic efficacy of plasma rich in growth factors products derive from their pleiotropic biological effects, which include neuroprotection, angiogenesis modulation, anti-apoptotic activity, immunoregulation, and extracellular matrix remodelling [11–13]. These functions make them well-suited for diseases with complex, multifactorial pathophysiology, and their impact varies depending on the disease target and delivery method [19]. Furthermore, immunosafe version of PRGF-Endoret® modifed the ophthalmic formulations by includeing a heat-treatment step intended to inactivate pro-inflammatory or immunogenic proteins. This approach may be particularly useful in patients with inflammatory or autoimmune diseases such as Behçet's disease, or in chronic degenerative conditions with an inflammatory component, such as atrophic AMD. However, comparative and mechanistic studies are needed to assess of the impact of immunosafe therapies in such applications.

Another long-standing concern among retinal specialists is the potential pro-angiogenic effect of blood-derived products, especially when used in diseases prone to neovascularization like AMD. However, the current evidence does not support this concern. None of the reviewed studies reported cases of pathological neovascularization attributable to these treatments [60,62,70]. Although these results refer specifically to CB-PRP, the findings are reassuring. Additionally, the application of leukocyte-free platelet rich plasma and immunosafe formulations would offer a favorable safety profile in inflammatory or degenerative settings.

Looking ahead, the future development of these therapies will require a concerted effort to address key scientific and clinical priorities. Robust, multicenter randomized controlled trials are essential to confirm their efficacy across different retinal pathologies. The detailed description of the preparation protocol, cellular composition and the activation method will be instrumental in identifying the most effective and safest approaches. In parallel, mechanistic studies are needed to determine which bioactive components are responsible for the regenerative and neuroprotective effects observed in clinical settings.

Finally, it is important to acknowledge the limitations of the present review. Although a systematic search strategy was followed, this is a narrative review that includes a wide variety of study designs – ranging from single case reports to small prospective trials – without formal grading of evidence quality. As such, the conclusions drawn should be interpreted with caution, and further high-quality clinical research is required before blood-derived products can be integrated into evidence-based treatment algorithms for ocular fundus diseases.

In summary, blood-derived products constitute a promising, albeit emerging class of regenerative therapeutics for posterior segment diseases. Their successful translation into clinical practice will depend on rigorous validation through translational and clinical research, the adoption of standardized protocols, and the establishment of sensitive outcome measures. If successfully implemented, these therapies may help redefine the treatment landscape for currently untreatable or refractory retinal and optic nerve disorders.

5. Conclusion

Blood-derived products, particularly PRGF-Endoret®, have gained attention as promising regenerative therapies for a broad range of posterior segment diseases. Their multifactorial mechanisms – encompassing anti-inflammatory, neuroprotective, anti-apoptotic, and pro-regenerative effects – position them as attractive candidates in both surgical and nonsurgical settings. Evidence from 46 clinical studies involving more than 1570 treated eyes highlights the safety profile and potential efficacy across conditions such as macular holes, ischemic retinopathies, optic neuropathies, and degenerative disorders. Blood-derived therapies represent an exciting frontier in regenerative ophthalmology, where addressing current evidence gaps with scientific rigor and methodological consistency will be instrumental in advancing their clinical use in the ocular fundus.

CRediT authorship contribution statement

Mohammad H. Alkhraisat: Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Iraia Reparaz:** Writing – review & editing, Writing – original draft, Data curation. **Eduardo Anitua:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Declaration of competing/conflicts of interest: The authors declare the following competing financial interest(s): E.A. is the Scientific Director and I.R. and M.H. are researchers at BTI Biotechnology Institute, a company that investigates in the fields of oral implantology and PRGF-Endoret technology.

Data availability

Data will be made available on request.

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