ST open

RESEARCH ARTICLE

Effect of prostaglandin F2 analog treatment on proliferation and MAPK/ERK signaling in conjunctival tissues of glaucoma patients

Filip Kelava[1], Marin Ogorevc[2]

[1]University of Split School of Medicine, Split, Croatia

[2]Department of Pathology, Forensic Medicine, and Cytology, University Hospital of Split, Split, Croatia

Correspondence to:
Marin Ogorevc
Department of Pathology, Forensic Medicine, and Cytology
University Hospital of Split
21000 Split, Croatia
marin.ogorevc@kbsplit.hr

Cite as:
Kelava F, Ogorevc M. Effect of prostaglandin F2 analog treatment on proliferation and MAPK/ERK signaling in conjunctival tissues of glaucoma patients. ST-OPEN. 2026;7:e2025.2408.45

DOI:
https://doi.org/10.48188/so.7.3

Aim: To compare the proliferation and activation of the MAPK/ERK signaling pathway in conjunctival cells between glaucoma patients treated with prostaglandin F2 (PGF2) analogs and those who did not receive PGF2 analog treatment. We hypothesized that PGF2 analog treatment increases both processes.

Methods: We conducted a retrospective cross-sectional study at the University Hospital of Split on conjunctival samples collected from PGF2-treated (PGF2-T) glaucoma patients (n = 6) and non-treated (PGF2-NT) patients (n = 4). Samples were stained for Ki-67 and phospho-ERK1/2 using immunofluorescence methods. We analyzed data using independent samples *t*-tests, with the significance threshold set at $\alpha = 0.05$ ($P < 0.05$).

Results: The proliferation marker Ki-67 and P-ERK1/2, a marker of MAPK/ERK activation, were expressed in both epithelial and stromal cells of the conjunctival tissues in glaucoma patients. Ki-67 expression was significantly higher in the conjunctival tissues of the PGF2-T group (mean ($\bar{x}$) = 8.40%, standard deviation (SD) = 1.30%, $P = 0.001$) compared to the PGF2-NT group ($\bar{x}$ = 4.25%, SD = 1.04%). Similarly, P-ERK1/2 expression in conjunctival tissues was significantly higher in the PGF2-T group ($\bar{x}$ = 17.29%, SD = 2.39%, $P = 0.0094$) compared to the PGF2-NT group ($\bar{x}$ = 11.93%, SD = 2.53%).

Conclusions: Treatment with PGF2 analogs increases cellular proliferation and activates the MAPK/ERK signaling pathway in conjunctival tissues of glaucoma patients. This may help explain the adverse effects of these drugs. Future studies should investigate the role of MAPK/ERK signaling in conjunctival tissues and alternative pathways affected by PGF2 analogs, which may help improve glaucoma therapy and reduce adverse effects.

Keywords: cell proliferation, conjunctiva, glaucoma, MAP Kinase signaling pathway, prostaglandins F

Introduction

Glaucoma is a group of eye conditions characterized by irreversible, progressive optic nerve damage, cupping of the optic disc, reduced numbers of retinal ganglion cells, and decreased peripapillary retinal nerve fiber layer thickness. These degenerative processes cause permanent visual field loss, making glaucoma one of the leading causes of blindness worldwide and the second most common cause of irreversible blindness in Western Europe (*1*–*3*).

Treatment for glaucoma focuses on reducing intraocular pressure, which is the most important modifiable risk factor influencing disease progression (*4*, *5*). This is mainly done through medications or laser therapy, while severe cases that are unresponsive to these treatments undergo surgery as the gold standard for managing glaucoma (*6*–*9*). Prostaglandin F2 (PGF2) analogs, such as latanoprost, bimatoprost, and travoprost, are the most effective drug therapy for glaucoma, as they significantly improve aqueous humor outflow through the uveoscleral tract (*10*–*13*). Recent studies identified baseline intraocular pressure, uveoscleral outflow, and BMI as predictors of response to PGF2 analog therapy, while comparisons of the efficacy, safety, and patient outcomes of different PGF2 analog medications revealed that bimatoprost has the strongest effect on intraocular pressure and highest risk for adverse effects, while tafluprost and latanoprost are more suited for treating mild forms of glaucoma (*14*–*16*).

Besides their primary effect on uveoscleral outflow, PGF2 analogs have unwanted adverse effects on the ocular surface (*17*, *18*). Clinical trials have shown that this drug group causes structural changes in conjunctival and other ocular tissues, including increased cell proliferation and marked hyperemia. Increased proliferation within hair follicles can cause hypertrichosis (increased number, thickness, and length of eyelashes), which may be cosmetically undesirable when occurring unilaterally (*19*). Hyperemia appears as excessive reddening of the conjunctiva, which is often a cosmetic problem for the patient, but can also jeopardize glaucoma filtration surgery (*20*). These processes may be related to activation of the MAPK/ERK signaling pathway, which plays a central role in cell growth, differentiation, migration, and survival (*21*). Previous studies have shown that stimulation of the prostaglandin F receptor (FP) by PGF2 analogs can activate the MAPK/ERK signaling pathway, suggesting a possible connection between PGF2 treatment regimens and proliferative activity in the conjunctiva (*22*).

Despite these insights, it is not fully understood how PGF2 analogs affect the proliferation of conjunctival cells or whether these effects directly correlate with activation of the MAPK/ERK signaling pathway. Therefore, we aimed to investigate cell proliferation and MAPK/ERK signaling pathway activation in conjunctival tissues of glaucoma patients treated with PGF2 analogs and compare them with a patient group that did not receive PGF2 analogs as part of their therapy. Based on previous findings, we hypothesized that PGF2 analog treatment increases conjunctival epithelial cell proliferation and activation of the MAPK/ERK signaling pathway.

Methods

Tissue collection and sectioning

Conjunctival samples were collected during deep sclerotomy procedures for glaucoma treatment at the Department of Ophthalmology, University Hospital of Split, between January 2011 and December 2022. The procedure began with opening the conjunctiva and Tenon's capsule in the upper quadrant of the limbus. The exposed scleral surface was abraded, and bleeding episcleral veins were cauterized. A superficial scleral flap was created, followed by a deeper scleral flap to expose the trabeculo-Descemet membrane. The inner wall of Schlemm's canal was removed. Finally, the superficial scleral flap and conjunctiva were sutured, and a sample of conjunctiva over the limbus was excised, placed in 4% paraformaldehyde solution in phosphate-buffered saline (PBS) for fixation, and sent to the Department of Pathology, Forensic Medicine, and Cytology at the University Hospital in Split.

The samples were originally collected by Stanic *et al.* (*23*), with all procedures performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of General Hospital in Zadar (protocol code 02-1 29831 1 9-41 1 I). Informed consent was obtained from all patients for the use of their tissues. The samples were embedded in paraffin blocks using standard protocols, sectioned into 5 µm slices with a microtome, and mounted on glass slides. Every tenth slice was stained with hematoxylin and eosin to confirm proper tissue preservation and morphology. Some tissue slices were used for research, while the remaining slices were archived for future studies at the Department of Histology and Embryology, University of Split School of Medicine. We received approval to use these archived samples from the Ethics Committee of the University of Split School of Medicine (class: 029-01/24-02/0001, registry number: 2181-198-03-04-24-0040). Samples were taken from four glaucoma patients who had never used PGF2 analogs for treatment (PGF2-NT group) and six patients who included PGF2 analogs in their regular treatment regimen (PGF2-T group).

Immunofluorescence staining

We performed immunofluorescence staining as described previously (*24*, *25*). In brief, after deparaffinizing and rehydrating the sample slices, antigen retrieval was performed by submerging the sections in 0.01 M sodium citrate buffer (pH 6.0) and heating them in a steam cooker at 95°C for 30 minutes. The slices were then cooled to room temperature and rinsed in 0.1 M PBS for 5 minutes. To prevent nonspecific antibody binding, the slices were treated with a protein-blocking buffer (Protein Block, Abcam, Cambridge, UK) for 20 minutes in a humid chamber. Next, the slices were incubated overnight with either Ki-67 (dilution 1:200, AB9260, Sigma-Aldrich, St. Louis, USA) or phospho-p44/42 MAPK (P-ERK1/2, dilution 1:200, 4370S, Cell Signaling Technology, Danvers, USA) rabbit monoclonal primary antibody diluted in PBS in a humid chamber, followed by two five-minute washes in PBS. An Alexa Fluor® 488-conjugated anti-rabbit lgG secondary antibody (dilution 1:300, 711-545-152, Jackson Immuno Research Laboratories, Baltimore, USA) was then applied, and the slices were incubated in a humid chamber for one hour before undergoing three addi-

tional five-minute washes in PBS. A 4',6-diamidino-2-phenylindole solution was applied for two minutes to counterstain the nuclei. To confirm the specificity of staining, negative control slices were prepared by omitting either the primary or secondary antibody from the staining protocol, which resulted in no detectable specific fluorescence signal. The stained slices were examined using an Olympus BX51 microscope (Olympus, Tokyo, Japan), and images were captured with a Nikon DS-Ri2 digital camera (Nikon, Tokyo, Japan) using NIS-Elements F software (Nikon, Tokyo, Japan).

Proliferation and MAPK/ERK pathway activation analysis

We performed the staining in replicates to improve the accuracy of the analysis and allow better comparison between the two sample groups. For each patient sample, two or three technical replicates were obtained, depending on tissue availability, to reduce measurement variability. Immunofluorescence staining was quantified by calculating the percentage of cells showing positive staining in the captured images. Only nuclear staining was considered positive for analysis of the proliferation marker Ki-67, while nuclear and/or cytoplasmic staining was considered positive for P-ERK1/2 (*26*, *27*).

For each technical replicate, we captured five nonadjacent representative regions of interest (ROIs) at ×400 magnification. The images were analyzed using ImageJ software (National Institutes of Health, Bethesda, USA). In each image, the number of cells displaying positive staining and the total number of cells were manually counted. The sum of positively stained cells in all five images was divided by the sum of total cell counts in all five images to obtain a single value representing the percentage of positively stained cells in a technical replicate. For each patient sample, ROI-level measurements from all technical replicates were averaged to obtain a single value per marker, which was used in the statistical analysis. Thus, the patient sample was the statistical unit. We used Adobe Photoshop, version 21.0.2 (Adobe, San Jose, USA) to create the composite figures.

Statistical analysis

We summarized the percentages of positive cells for the analyzed markers as means and standard deviation (SDs), and compared the differences in the percentage of positive cells between the groups using independent samples *t*-tests. Statistical significance was set at $\alpha = 0.05$ ($P < 0.05$). We performed all analyses and generated all graphs in GraphPad Prism, version 9.0.0 (GraphPad Software, San Diego, USA).

Results

We first analyzed the cell proliferation rate in the samples. The proliferation marker Ki-67 was primarily expressed in the nuclei of basal and suprabasal cells in the conjunctival epithelium of patients in the PGF2-NT group. In the epithelium of the PGF2-T group, many Ki-67-positive cells were also observed in the more superficial layers. The conjunctival stroma of PGF2-NT patients contained a few Ki-67-positive endothelial cells and fibroblasts, while the stroma of PGF2-T patients had comparatively more Ki-67-expressing cells, especially

endothelial cells (**Figure 1**, Panel A). The proliferation rate of cells in the conjunctival tissues of the PGF2-T group (8.40%, SD = 1.30%) was significantly higher ($P = 0.0007$) than in the PGF2-NT group (4.25%, SD = 1.04%) (**Figure 1**, Panel B).

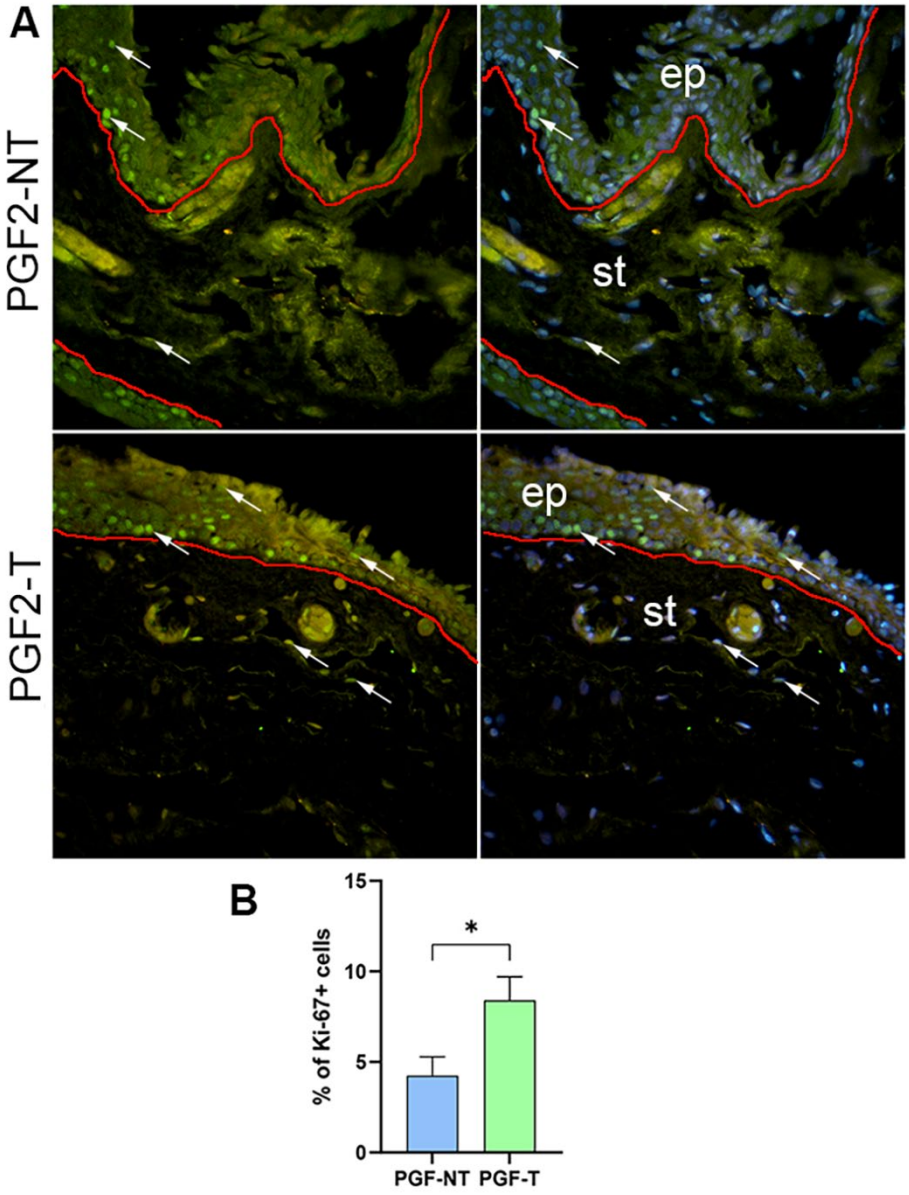

Figure 1. Ki-67 staining of conjunctival tissues from glaucoma patients. PGF2-NT refers to patients without prostaglandin F2α analog treatment, and PGF2-T refers to patients treated with prostaglandin F2α analogs. **Panel A.** The panels on the left show staining with Ki-67 (green signal). The panels on the right show merged images of Ki-67 and 4',6-diamidino-2-phenylindole (DAPI) nuclear staining (blue signal). Arrows indicate proliferating cells. The epithelium (ep) and stroma (st) are outlined in red. **Panel B.** The bar graph shows Ki-67 expression. Values are presented as the mean percentage of positive cells. Error bars indicate standard deviations. Statistical significance was determined by the independent samples *t*-test. *$P < 0.001$.

Activation of the MAPK/ERK pathway was assessed by analyzing the accumulation of phosphorylated ERK1/2 (P-ERK1/2) in the cells. In the conjunctival epithelium of the PGF2-NT group, cytoplasmic P-ERK1/2 staining was observed mainly in the basal layer, while in the PGF2-T group, staining was both nuclear and cytoplasmic and extended to the superficial layers. Strong P-ERK1/2 staining was present in the stroma of both patient groups; how-

ever, more cells showed P-ERK1/2 positivity in the PGF2-T group (**Figure 2**, Panel A). The percentage of P-ERK1/2-positive cells in the conjunctival tissues was significantly higher ($P = 0.0094$) in the PGF2-T group (17.29%, SD = 2.39%) than in the PGF2-NT group (11.93%, SD = 2.53%) (**Figure 2**, Panel B).

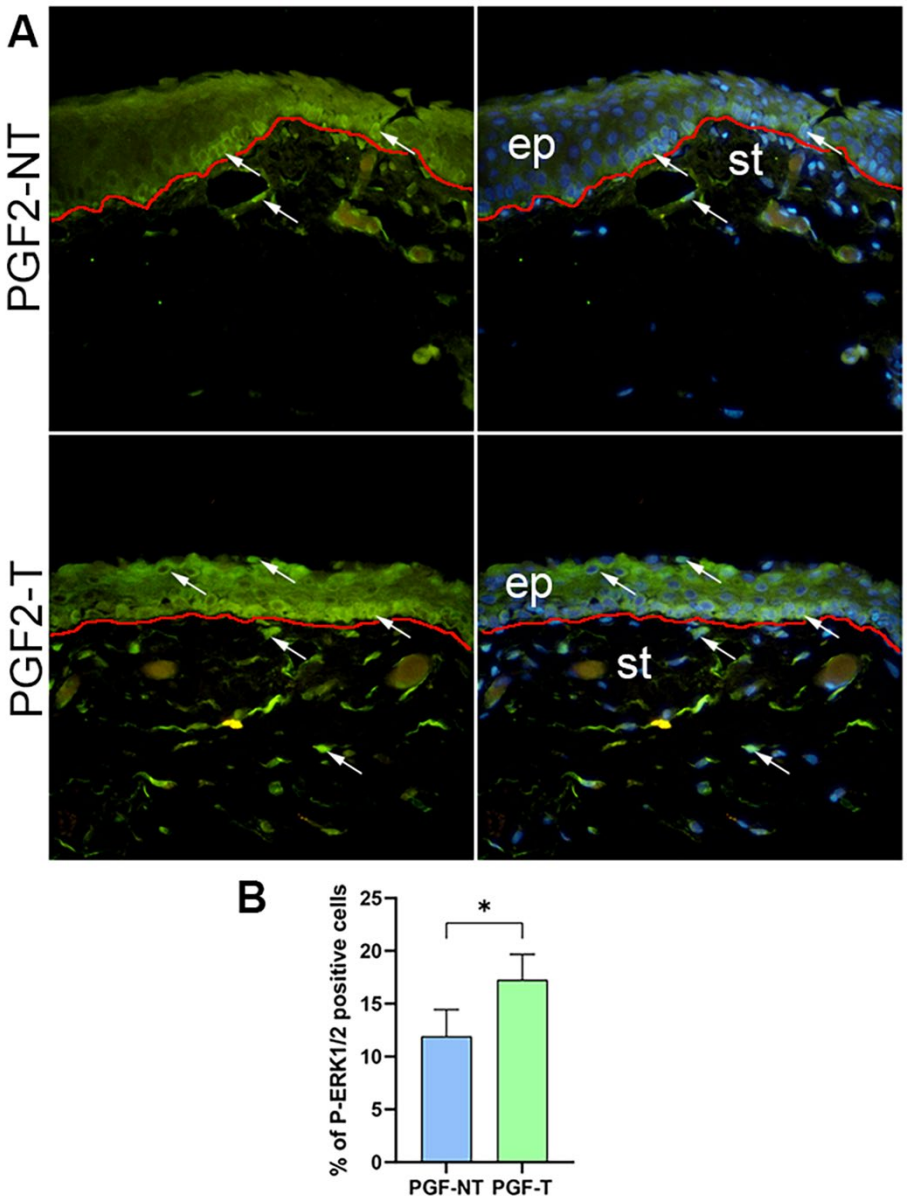

Figure 2. P-ERK1/2 staining of conjunctival tissues from glaucoma patients. PGF2-NT refers to patients not treated with prostaglandin F2α analogs, and PGF2-T refers to patients treated with prostaglandin F2α analogs. **Panel A.** The panels on the left show staining for P-ERK1/2 (green signal). The panels on the right show merged images of P-ERK1/2 and DAPI nuclear staining (blue signal). Arrows indicate cells with MAPK/ERK pathway activation. The epithelium (ep) and stroma (st) are outlined in red. **Panel B.** The bar graph shows P-ERK1/2 expression. Values are presented as the mean percentage of positive cells. Error bars indicate standard deviations. Statistical significance was determined by the independent samples *t*-test. *$P < 0.01$.

Discussion

We analyzed the proliferation and activation of the MAPK/ERK signaling pathway in the conjunctival tissues of glaucoma patients with and without PGF2 analog treatment. Immunofluorescence staining and quantitative analysis showed a significant increase in the proliferation rate (Ki-67 staining) and activation of the MAPK/ERK signaling pathway (P-ERK1/2 staining) in the conjunctival tissues of glaucoma patients treated with PGF2 analogs compared to those without PGF2 analogs.

A recent study investigated the effect of prostaglandin PGF2 on vascular endothelial growth factor (VEGF) secretion and mesenchymal stem cell proliferation and migration, showing that PGF2 significantly enhanced both processes and that specific concentrations potentiated VEGF secretion (*28*). Similarly, a study on endometrial samples demonstrated a dose-dependent increase in epithelial cell proliferation and a potential vasoconstrictive effect mediated by PGF2 acting on perivascular smooth muscle cells (*29*). Takada *et al.* showed that PGF2 derivatives, such as travoprost, significantly increase epidermal growth factor (EGF) mRNA expression in corneal epithelial cell lines, a key factor in epithelial proliferation and regeneration, highlighting the role of prostaglandins in corneal epithelial repair processes (*30*). In other ocular tissues, PGF2 mRNA and protein were found in conjunctival tissues, particularly in conjunctival epithelial cells, suggesting a role in modulating inflammation, regeneration, and tear production (*31*). In our study, microscopic examination of conjunctival tissues from patients treated with PGF2 analogs showed a marked increase in cellular proliferation in the conjunctival epithelium. Proliferation of stromal endothelial cells was also observed, possibly due to the increased VEGF secretion described previously. This mechanism may also contribute to conjunctival hyperemia, a common side effect of PGF2 analogs used in glaucoma therapy. Our findings regarding epithelial proliferation are consistent with the studies cited above.

PGF2 is known to activate the MAPK/ERK signaling pathway (*32*, *33*). This relationship has been confirmed in human adenocarcinoma models, where activation of PGF2 receptors increases ERK1/2 phosphorylation and promotes angiogenesis, tumor growth, and metastasis (*34*, *35*). Choi *et al.* also showed that FP-receptor stimulation by bimatoprost activates the MAPK/ERK pathway in retinal ganglion cells (*22*). In our study, increased P-ERK1/2 levels indicated significantly higher MAPK/ERK activity in conjunctival tissues of patients treated with PGF2 analogs compared to controls, with stronger activation in the epithelium than in the stroma. This is consistent with previous reports and may be explained by higher PGF2 receptor expression in epithelial cells.

Previous studies suggest that prostaglandins may activate the MAPK/ERK signaling pathway and interact with other signaling cascades (*21*); however, our study was not designed to investigate these mechanisms. Sales *et al.* reported that stimulation of the PGF2 receptor activates MAPK/ERK and increases proliferation in endometrial adenocarcinoma cells (*34*). In contrast, Milne *et al.* found that PGF2-induced proliferation of endometrial epithelial cells depends on phospholipase C signaling and is independent of ERK1/2, suggesting that MAPK/ERK primarily supports cell survival and inhibits apoptosis (*29*). Although we observed both increased proliferation and MAPK/ERK activity in conjunctival tissues

treated with PGF2 analogs, we cannot determine whether these two cellular processes are associated based on the analyses performed in our study.

The main limitations of our study are the small sample size and single-center design, which required the use of technical replicates and limited generalizability. In addition, only one marker of MAPK/ERK pathway activation was assessed, which limits mechanistic interpretation and the scope of biological inference. Therefore, no mechanistic conclusions about the cause of proliferation can be drawn. Despite these limitations, our results indicate that PGF2 analog treatment can have significant off-target effects on ocular tissues. Future studies should investigate other PGF2-mediated pathways involved in conjunctival proliferation and potential therapeutic targets for managing side effects such as conjunctival hyperemia.

In conclusion, treatment with PGF2 analogs was associated with increased cellular proliferation and activation of the MAPK/ERK signaling pathway in the conjunctival tissues of glaucoma patients. However, our study design did not allow us to determine whether these two processes were related. Qualitatively, staining appeared more prominent in the epithelium than in the stroma. Quantitative analysis was based on representative ROI-level measurements, with epithelial and stromal cells evaluated together, and no formal statistical comparison between tissue compartments was performed. Future studies should investigate the role of MAPK/ERK signaling in conjunctival tissues, alternative pathways affected by PGF2 analogs, and the long-term impact of these changes on ocular structures, which may help improve glaucoma therapy and reduce adverse effects.

Received: 19 May 2025 / **Accepted:** 14 February 2026 / **Published:** 12 March 2026

Provenance: Submitted. This article is based on the master's thesis by Filip Kelava, entitled "Effect of prostaglandin F2 analog treatment on proliferation and MAPK/ERK signaling in conjunctival tissues of glaucoma patients", defended at the University of Split School of Medicine under the supervision of Marin Ogorevc MD, PhD, and available at the Dabar repository (https://urn.nsk.hr/urn:nbn:hr:171:693049).

Peer review: Externally reviewed.

Acknowledgements: The authors would like to thank Prof. Katarina Vukojević MD, PhD, for providing the tissue samples used in the study.

Data availability statement: Raw data for this study are available upon request to the corresponding author.

Ethics statement: This study was approved by the Ethics committee from the University of Split School of Medicine (class: 029-01/24-02/0001, registry number: 2181-198-03-04-24-0040).

Funding: No funding was received for this study.

Authorship declaration: FK participated in the collection of raw data, data analysis and interpretation of the results, wrote the manuscript draft, and contributed to revisions of the manuscript. MO devised the concept and topic of the study, supervised data collection, performed data analysis and interpretation of the results, and contributed to revisions of the manuscript.

Disclosure of interest: The authors completed the ICMJE Disclosure of Interest Form (available upon request from the corresponding author) and disclose no relevant interests.

ORCID

Filip Kelava https://orcid.org/0009-0003-5773-3352

Marin Ogorevc https://orcid.org/0000-0002-3801-1026

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90(3):262–7. PubMed https://doi.org/10.1136/bjo.2005.081224
2. Schuster AK, Erb C, Hoffmann EM, Dietlein T, Pfeiffer N. The Diagnosis and Treatment of Glaucoma. Dtsch Arztebl Int. 2020;117(13):225–34. PubMed
3. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081–90. PubMed https://doi.org/10.1016/j.ophtha.2014.05.013
4. Salmon JF. Kanski's Clinical Ophthalmology: A Systematic Approach. 9th ed. Edinburgh (UK): Elsevier; 2020.
5. Shen TY, Hu WN, Cai WT, Jin HZ, Yu DH, Sun JH, et al. Effectiveness and Safety of Trabeculectomy along with Amniotic Membrane Transplantation on Glaucoma: A Systematic Review. J Ophthalmol. 2020;2020:3949735. PubMed https://doi.org/10.1155/2020/3949735
6. Kalala A, Gillmann K, Mermoud A. Prospective evaluation of penetrating deep sclerectomy in advanced open-angle glaucoma: Filtration surgery adapted to resource scarcity in developing countries. J Fr Ophtalmol. 2020;43(3):228–36. PubMed https://doi.org/10.1016/j.jfo.2019.07.024
7. Kozobolis V, Kalogianni E, Sideroudi H. Penetrating deep sclerectomy in primary open-angle and pseudoexfoliative glaucoma. Eur J Ophthalmol. 2020;30(2):264–8. PubMed https://doi.org/10.1177/1120672119827768
8. Mermoud A, Schnyder CC. Nonpenetrating filtering surgery in glaucoma. Curr Opin Ophthalmol. 2000;11(2):151–7. PubMed https://doi.org/10.1097/00055735-200004000-00015
9. Yamanaka O, Kitano-Izutani A, Tomoyose K, Reinach PS. Pathobiology of wound healing after glaucoma filtration surgery. BMC Ophthalmol. 2015;15(Suppl 1):157. PubMed https://doi.org/10.1186/s12886-015-0134-8
10. European Glaucoma Society Terminology and Guidelines for Glaucoma. 4th Edition - Chapter 3: Treatment principles and options Supported by the EGS Foundation: Part 1: Foreword; Introduction; Glossary; Chapter 3 Treatment principles and options. Br J Ophthalmol. 2017;101(6):130-95.
11. Kadri R, Shetty A, Parameshwar D, Kudva AA, Achar A, Shetty J. Effect of prostaglandin analogues on central corneal thickness in patients with glaucoma: A systematic review and meta-analysis with trial sequential analysis. Indian J Ophthalmol. 2022;70(5):1502–12. PubMed https://doi.org/10.4103/ijo.IJO_1971_21
12. Razeghinejad MR. The Effect of Latanaprost on Intraocular Inflammation and Macular Edema. Ocul Immunol Inflamm. 2019;27(2):181–8. PubMed https://doi.org/10.1080/09273948.2017.1372485
13. Zhou L, Zhan W, Wei X. Clinical pharmacology and pharmacogenetics of prostaglandin analogues in glaucoma. Front Pharmacol. 2022;13:1015338. PubMed https://doi.org/10.3389/fphar.2022.1015338
14. Kazemi A, Reitinger JC, Toris CB, Gulati V, Fan S, Reed DM, et al. Aqueous Humor Dynamics Changes and Predictors of IOP Response to Latanoprost in Healthy Subjects. J Glaucoma. 2025;34:1056–64. PubMed https://doi.org/10.1097/IJG.0000000000002585
15. Peng J, Huang W, Duan J. Efficacy and safety of prostaglandin drugs for elevated intraocular pressure: a Bayesian network meta-analysis. Front Med (Lausanne). 2025;12:1642986. PubMed https://doi.org/10.3389/fmed.2025.1642986
16. Mai AP, Ferguson TJ, Radcliffe N. New treatments for glaucoma. Curr Opin Ophthalmol. 2025;36:135–9. PubMed https://doi.org/10.1097/ICU.0000000000001110
17. Mukhtar M, Zafar F, Luqman F, Bibi H, Sarfaraz H. Effect of Topical Travoprost 0.004% Drops on Central Corneal Thickness in Patients With Primary Open-Angle Glaucoma. Cureus. 2025;17:e90802. PubMed https://doi.org/10.7759/cureus.90802

18. Subbulakshmi S, Kavitha S, Venkatesh R. Prostaglandin analogs in ophthalmology. Indian J Ophthalmol. 2023;71(5):1768–76. PubMed https://doi.org/10.4103/IJO.IJO_2706_22

19. Alm A. Latanoprost in the treatment of glaucoma. Clin Ophthalmol. 2014;8:1967–85. PubMed

20. Feldman RM. Conjunctival hyperemia and the use of topical prostaglandins in glaucoma and ocular hypertension. J Ocul Pharmacol Ther. 2003;19(1):23–35. PubMed https://doi.org/10.1089/108076803762718088

21. Wen X, Jiao L, Tan H. MAPK/ERK Pathway as a Central Regulator in Vertebrate Organ Regeneration. Int J Mol Sci. 2022;23(3):1464. PubMed https://doi.org/10.3390/ijms23031464

22. Choi CJ, Tao W, Doddapaneni R, Acosta-Torres Z, Blessing NW, Lee BW, et al. The Effect of Prostaglandin Analogue Bimatoprost on Thyroid-Associated Orbitopathy. Invest Ophthalmol Vis Sci. 2018;59(15):5912–23. PubMed https://doi.org/10.1167/iovs.18-25134

23. Stanić R, Vukojevic K, Filipovic N, Benzon B, Ogorevc M, Kunac N, et al. The Effect of Prostaglandin F2 Analog Treatment on the Immunoexpression of Fibrosis-Associated Factors in Patients with Glaucoma Undergoing Deep Sclerotomy. Int J Mol Sci. 2024;25(23):12618. PubMed https://doi.org/10.3390/ijms252312618

24. Mikulić P, Ogorevc M, Petricevic M, Kalicanin D, Tafra R, Saraga-Babic M, et al. SOX2, JAGGED1, beta-Catenin, and Vitamin D Receptor Expression Patterns during Early Development and Innervation of the Human Inner Ear. Int J Mol Sci. 2024;25(16):8719. PubMed https://doi.org/10.3390/ijms25168719

25. Ogorevc M, Kosovic I, Filipovic N, Bocina I, Juric M, Benzon B, et al. Differences in Immunohistochemical and Ultrastructural Features between Podocytes and Parietal Epithelial Cells (PECs) Are Observed in Developing, Healthy Postnatal, and Pathologically Changed Human Kidneys. Int J Mol Sci. 2022;23(14):7501. PubMed https://doi.org/10.3390/ijms23147501

26. Soliman NA, Yussif SM. Ki-67 as a prognostic marker according to breast cancer molecular subtype. Cancer Biol Med. 2016;13(4):496–504. PubMed https://doi.org/10.20892/j.issn.2095-3941.2016.0066

27. Vicent S, Lopez-Picazo JM, Toledo G, Lozano MD, Torre W, Garcia-Corchon C, et al. ERK1/2 is activated in non-small-cell lung cancer and associated with advanced tumours. Br J Cancer. 2004;90(5):1047–52. PubMed https://doi.org/10.1038/sj.bjc.6601644

28. Deezagi A, Shomali S. Prostaglandin F-2alpha Stimulates The Secretion of Vascular Endothelial Growth Factor and Induces Cell Proliferation and Migration of Adipose Tissue Derived Mesenchymal Stem Cells. Cell J. 2018;20(2):259–66. PubMed

29. Milne SA, Jabbour HN. Prostaglandin (PG) F(2alpha) receptor expression and signaling in human endometrium: role of PGF(2alpha) in epithelial cell proliferation. J Clin Endocrinol Metab. 2003;88(4):1825–32. PubMed https://doi.org/10.1210/jc.2002-021368

30. Takada Y, Yamanaka O, Okada Y, Sumioka T, Reinach PS, Saika S. Effects of a prostaglandin F2alpha derivative glaucoma drug on EGF expression and E-cadherin expression in a corneal epithelial cell line. Cutan Ocul Toxicol. 2020;39(2):75–82. PubMed https://doi.org/10.1080/15569527.2020.1722152

31. Ocklind A, Lake S, Wentzel P, Nister M, Stjernschantz J. Localization of the prostaglandin F2 alpha receptor messenger RNA and protein in the cynomolgus monkey eye. Invest Ophthalmol Vis Sci. 1996;37(5):716–26. PubMed

32. Goupil E, Wisehart V, Khoury E, Zimmerman B, Jaffal S, Hebert TE, et al. Biasing the prostaglandin F2alpha receptor responses toward EGFR-dependent transactivation of MAPK. Mol Endocrinol. 2012;26(7):1189–202. PubMed https://doi.org/10.1210/me.2011-1245

33. Zhu R, Wang XH, Wang BW, Ouyang X, You YY, Xie HT, et al. Prostaglandin F2alpha Regulates Adipogenesis by Modulating Extracellular Signal-Regulated Kinase Signaling in Graves' Ophthalmopathy. Int J Mol Sci. 2023;24(8):7012. PubMed https://doi.org/10.3390/ijms24087012

34. Sales KJ, Milne SA, Williams AR, Anderson RA, Jabbour HN. Expression, localization, and signaling of prostaglandin F2 alpha receptor in human endometrial adenocarcinoma: regulation of proliferation by activation of the epidermal growth factor receptor and mitogen-activated protein kinase signaling pathways. J Clin Endocrinol Metab. 2004;89(2):986–93. PubMed https://doi.org/10.1210/jc.2003-031434

35. Sales KJ, List T, Boddy SC, Williams AR, Anderson RA, Naor Z, et al. A novel angiogenic role for prostaglandin F2alpha-FP receptor interaction in human endometrial adenocarcinomas. Cancer Res. 2005;65(17):7707–16. PubMed https://doi.org/10.1158/0008-5472.CAN-05-0101