# SYSTEMATIC REVIEW OF LOSARTAN EYE DROPS IN MANAGING POST-SURGICAL CORNEAL HAZE


## ABSTRACT

This study aimed to analyze the effectiveness of losartan eye drops in the treatment of haze corneal secondary to surgical procedures such as Photorefractive Keratectomy (PRK), Laser in Situ Keratomileusis (LASIK), Phototherapeutic Keratectomy (PTK) and crosslinkingcorneal. For this purpose, this systematic review was carried out based on studies published between 2019 and 2024, selected from databases such as PubMed, Scopus and Web of Science. Inclusion criteria covered clinical trials, observational studies and experiments in animal models that investigated the use of topical losartan in the treatment of haze corneal. Data on haze density, visual acuity, side effects and tolerability were extracted and analyzed. In this way, 20 sources were included, consisting of patients and animal models. Most studies reported a significant reduction of up to 60% in haze density corneal in patients treated with losartan eye drops, with a robust decline in corneal opacity; as well as an efficacy of up to 55% in reducing fibrosis, and with signs of inhibition of myofibroblast generation between 25% and 60%. Regarding visual acuity, there was a reduction of up to 50% in corneal abrasion and a 30% improvement in visual acuity after treatment with losartan when compared to the control group. The most common side effects were mild, including eye irritation and hyperemia, occurring in very few cases. The tolerability of the treatment was considered high, with the majority of patients completing the therapeutic course. That said, topical losartan demonstrated significant efficacy in reducing haze corneal and improving visual acuity, with a favorable safety profile. These findings suggest that losartan eye drops may be a viable and safe alternative for the management of haze corneal secondary to surgical procedures for refractive correction and other corneal pathologies. However, additional studies, especially large-scale randomized clinical trials, are needed to consolidate these results and establish standardized clinical protocols, since one of the limitations found in this study was the scarcity of studies in this field of research, in addition to the low number of studies carried out exclusively on humans.



**Keywords:** Haze Corneal; Losartan; PRK; LASIK; PTK; Crosslinking Corneal; Visual Acuity; Therapeutic Efficacy.



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## 1. INTRODUCTION

Treatment of corneal haze secondary to surgical procedures such as PRK, LASIK, PTK and crosslinking corneal disease has always been a constant challenge in ophthalmology. In such a way that the haze corneal disease, characterized by opacification of the cornea, could result in significant visual impairment, causing a major impact on patients' quality of life. So, several approaches have been studied to

prevent and treat this condition, and one of the emerging therapies that attracted attention was the topical use of losartan, an angiotensin II receptor blocker, originally used in the treatment of arterial hypertension, but demonstrating potential in inhibiting the formation of myofibroblasts and the reduction of corneal fibrosis, the main mechanisms underlying the development of haze corneal. Thus, recent studies have explored the effects of this medication in experimental models and preliminary clinical trials, suggesting that topical application could offer a new therapeutic strategy for patients undergoing refractive and therapeutic procedures on the cornea (AMBRÓSIO JR; SOUZA, 2024). Therefore, the effectiveness of topical losartan in the prevention and treatment of haze corneal disease has been a rapidly growing field of investigation in recent years. So much so that Ambrosio Jr. and Souza (2024) discussed the potential application of losartan in ophthalmology, highlighting its ability to modulate fibrogenicprocesses, as did Pereira-Souza *et al.* (2022) who reported the first clinical results of the topical use of losartan in the treatment of corneal fibrosis, showing a significant reduction in corneal opacity in treated patients, similarly to Rodgers *et al.* (2024) also investigated the use of topical losartan after crosslinking corneal with riboflavin and UVA, observing a decrease in haze formation compared to control groups. Furthermore, Wilson (2023) provided practical guidelines for conducting clinical trials involving topical losartan, emphasizing the need for rigorous protocols to evaluate the efficacy and safety of this approach (PEREIRA-SOUZA *et al.*, 2022; RODGERS *et al.*, 2024; WILSON, 2023), while Sampaio *et al.* (2021) conducted experimental studies in animal models, demonstrating that losartan inhibited the deposition of type IV collagen and the formation of myofibroblasts after corneal injuries. These findings were corroborated by subsequent studies by Sampaio *et al.* (2022), who showed that losartan, in combination with corticosteroids, potentiated the inhibition of corneal fibrosis after alkaline injuries. Therefore, the current literature review suggested that topical losartan could be a valuable tool in the therapeutic arsenal for the management of haze corneal, however, the translation of these preclinical findings to clinical practice requires additional studies to confirm its efficacy and safety in a broader population of patients (SAMPAIO *et al.*, 2021; SAMPAIO *et al.*, 2022).

The rest, through the need for an analysis aimed at elucidating the peculiarities of the use of losartan eye drops for the treatment of haze secondary to

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surgical procedures on the cornea , addressing the mechanisms of action, clinical efficacy and future perspectives of this innovative therapy, recent literature was reviewed and the main studies that contributed to the current understanding of this therapeutic approach were discussed, as losartan, being a selective antagonist of the angiotensin II AT1 receptor and having antifibrotic properties that are already explored in ophthalmology, as well as angiotensin II, through its AT1 receptor, which plays a fundamental role in the regulation of fibrosis, promotes the modulation of the proliferation of myofibroblasts and the deposition of extracellular matrix. Above all, by blocking this receptor, losartan also interferes with the signaling cascade that leads to fibrosis, reducing the formation of myofibroblasts and the deposition of collagen in the cornea (WILSON, 2024).

Furthermore, experimental and clinical studies demonstrated that topical losartan could suppress the transformation of fibroblasts into myofibroblasts, cells responsible for excessive production of extracellular matrix and tissue contracture, hallmarks of corneal fibrosis. This is also corroborated by Sampaio *et al.* (2022) who observed that the application of losartan significantly reduced the presence of myofibroblasts in the cornea of rabbits undergoing PRK, a model commonly used to study postsurgical corneal fibrosis, as well as by Wilson *et al.* (2022) who reported that losartan negatively modulated the expression of type IV collagen, a key component of the basement membrane, and pro-fibrotic growth factors such as TGF-β, which are critical in promoting fibrosis. These findings suggested that losartan could interrupt the positive feedback loop that perpetuates corneal fibrosis (SAMPAIO *et al.*, 2022; WILSON *et al.*, 2022). The clinical efficacy of topical losartan in the management of haze corneal has been evaluated in several clinical studies. Like those undertaken by Pereira-Souza *et al.* (2022) who conducted a pioneering study that involved the application of losartan eye drops to patients with haze corneal post-PRK, observing a significant improvement in corneal transparency and visual acuity of treated patients, marking an important advance in the clinical validation of the use of topical losartan. While Rodgers *et al.* (2024) investigated the use of topical losartan in patients undergoing crosslinking corneal, reporting a reduction in haze density corneal and faster visual recovery compared to the control group. Furthermore, these findings were corroborated by experimental studies that demonstrated the ability of losartan to inhibit the formation of myofibroblasts and

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collagen deposition in animal models of corneal fibrosis (PEREIRA-SOUZA *et al.*, 2022; RODGERS *et al.*, 2024).

In parallel, Wilson's (2023) systematic analysis of existing clinical trials emphasized the need for standardization in treatment protocols, including the dosage and frequency of application of losartan. Therefore, additional studies were needed to determine the optimal treatment parameters and to evaluate the long-term effectiveness of topical losartan in preventing haze corneal, as the topical application of losartan for the treatment of haze corneal surgery represented a promising approach that could revolutionize the management of this condition, however the application of preclinical findings to clinical practice requires caution and continued investigation. Furthermore, better designed clinical trials, with larger samples and longer follow-up periods, are still essential to confirm the benefits and to establish standardized treatment protocols (WILSON, 2023). Furthermore, the combination of losartan with other antifibrotic therapies, such as corticosteroids, was able to potentiate the therapeutic effects and offer a more robust approach to preventing corneal fibrosis and future studies should explore these therapeutic combinations and investigate the mechanisms underlying the synergy between different antifibrotic agents(SAMPAIO *et al.*, 2022).

That said, topical losartan has emerged as an innovative therapy with significant potential to improve the visual outcomes of patients with haze corneal secondary to surgical procedures on the cornea. As well as the literature on the state of the art is current, but it provided a solid basis for continued research in this area, with the ultimate objective of incorporating this approach into clinical practice in a safe and effective way, and this research adds even more to this amalgamation, bringing a more dense perspective on the evaluation of the effectiveness of losartan eye drops in the treatment of haze secondary corneal, by reviewing its state of the art, and also measuring the reduction in haze density corneal ; evaluating the optimization of visual acuity of models treated with this technique; and recording possible side effects and tolerability of topical use of the drug (SAMPAIO *et al.*, 2022; MOSHIRFAR *et al.*, 2023).

## 2. METHODOLOGY

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The conduct of this review followed a rigorous methodological approach, seeking to compile and comprehensively analyze studies related to the effectiveness of losartan eye drops in the treatment of haze secondary corneal. The initial data search was carried out in several sources, such as virtual databases; specialized digital magazines, conference annals, dissertations and academic theses, covering studies in different locations.

## 2.1 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were strictly applied to ensure selection of relevant studies. Only studies that directly addressed the effectiveness of losartan eye drops in the treatment of haze were included. secondary corneal. The analysis of the included studies was carefully conducted, allowing the identification of patterns, trends and common points between the main findings and conclusions. Special emphasis was placed on the relationship of studies with research objectives, initially focusing on clinical application, and then on studies in animal models with losartan eye drops in the treatment of haze corneal.

## 2.2 Detailed Exclusion Criteria

Articles that did not directly address the effectiveness of losartan eye drops in the treatment of haze were excluded. secondary corneal. Other exclusion criteria included lack of relevance to the context of corneal haze treatment, the full inaccessibility of studies, lack of clear methodology, exclusive focus on technical aspects without considering impacts or correlations of clinical or experimental applications for treatment in practice, in addition to duplicate publications.

## 2.3 Critical Analysis and Data Synthesis

To guarantee the reliability and validity of the results obtained, methods of critical analysis and careful data synthesis were adopted. This approach allowed for

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the identification of knowledge gaps and areas for future investigation. The study sought to significantly contribute to the understanding of the effectiveness of losartan eye drops in the treatment of haze secondary corneal, providing information for professionals, researchers and decision makers in the public health and research sector.

## 3. RESULTS AND DISCUSSIONS

After checking the articles and other sources, the results and discussions were organized, analyzed and converted, didactically, into the following table. As well as the results obtained were divided into 4 discussion sessions with a view to better meeting the objectives that guided this research, a bibliography review session on the current state of the art on the use of losartan eye drops in the treatment of haze secondary corneal. In addition to a second session, in which the reduction in haze density was measured corneal in patients and animal models treated with losartan eye drops. And, also, in a third data analysis session, in which an evaluation of the optimization of the visual acuity of models treated with losartan eye drops was carried out. Also, in a last session, the possible side effects and tolerability of the topical use of losartan in patients undergoing treatment were analyzed. Furthermore, the results presented below were discussed in the light of comparison, with similar and contrary findings existing in the literature, as well as the theoretical data that elucidate the phenomena found here with that of other research were compared. In addition to, primarily, being compared to the findings of other researchers who exclusively researched losartan eye drops in the treatment of haze corneal, secondarily, they were also compared to the findings of studies with methodologies and objectives similar to those claimed in this research. Furthermore, the phenomena found in this research were discussed with studies that elucidated and/or related to them, in order to explain the data reported here from this research, but which had not been reported in articles in this field of study. Therefore, below, the most accessible and relevant published works that included the most prominent findings in the 4 categories covered in this research were displayed, as observed in the following sessions:

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### 3.1. CURRENT LITERATURE REVIEW OF THE USE OF LOSARTAN EYE DROPS IN THE TREATMENT OF SECONDARY CORNEAL HAZE

Efficacy of losartan eye drops for the treatment of haze" were identified secondary corneal " in several sources, including Google Scholar, ScieloBrasil, and Science Direct. This survey covered a period of analysis from 2019 to 2024. The distribution by source revealed that 12 studies were found on Google Scholar, 7 on ScieloBrasil and 1 in Science Direct. While the review, after applying the inclusion criteria, was carried out after fully reading published articles, focusing on the evaluation of the reduction in haze density. corneal in patients and animal models treated with losartan eye drops, as well as measuring the improvement in visual acuity of models treated with losartan eye drops, verifying the recovery of corneal transparency and visual functionality over time, and also analyzing the possible side effects and tolerability of topical use of losartan in patients undergoing treatment when possible. And after applying the exclusion criteria, 20 articles were selected for detailed analysis. Regarding the types of study, the majority of articles (10) adopted a theoretical approach in the form of a bibliographic review; followed by experimental studies (6), a minority of clinical studies (4), showing a gradual increase, however, there is still a small number of studies applied to patients in the state of the art on losartan eye drops for the treatment of haze corneal (See Table 1). As well as analyzing the geographic distribution, it was observed that there was a concentration of studies exclusively from the USA (12), exclusively from Brazil (6), and (2) in a joint partnership between Brazil and the USA, which reflected a modest national representation in the panorama of research on losartan eye drops for the treatment of haze secondary corneal. Furthermore, of the 20 sources selected, 19 were scientific articles and 1 was scientific dissemination, demonstrating equity in the contributions provided by scientific articles to understanding the effectiveness of losartan eye drops for the treatment of haze secondary corneal. All topics covered by the studies were consistent with the objectives of this research. As for temporal analysis, a partially progressive distribution of publications over the years was revealed: 2024 (8), 2023 (4), 2022 (5), 2021 (1), 2020(1), 2019 (1), as detailed in Table 1 below. This temporal distribution highlighted the constancy of interest in the topic over the last 6 years.

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**Table 1.**Presentation of scientific publications on the application of losartan eye drops for the treatment of haze secondary corneal, containing the names of the authors, years of publications, names of the journals, methodological approaches and main findings.

| AUTHOR | YEAR | SOURCE | TYPE OF PUBLICATION | STUDY LOCATION | RELATIONSHIP WITH RESEARCH OBJECTIVES | METHODOLOGICAL APPROACH | MAIN FINDINGS |
|---|---|---|---|---|---|---|---|
| Chandran *et al.* | 2024 | Biomedicines | Scientific Article | USA | Assessment of regenerative effects | Bibliographic review | "Losartan was effective in regenerating corneal transparency" |
| Ambrosio Jr & Souza | 2024 | Eye Pharma | Scientific Article | Brazil | Review of the use of losartan | Clinical study | "Losartan reduces the density of haze corneal and improves visual acuity." |
| Rodgers *et al.* | 2024 | Cornea | Scientific Article | USA | Post crosslinking haze treatment | Clinical study | "There was a significant reduction in haze with visual improvement, in the study where 30 treated patients were observed; as well as a reduction in haze in 75% of patients; and 65% showed improvement in visual acuity." |

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| Wilson | 2024 | Experimental Eye Research | Scientific Article | USA | Losartan use review | Bibliographic review | “This study confirmed the efficacy and safety of the use of topical losartan.” |
| Martinez *et al.* | 2024 | Cornea | Scientific Article | USA and Brazil | Comparative study of therapies | Experimental study | “Losartan was superior to other therapies in treating haze , and a study with rabbits; in which there was a 65% inhibition in the generation of myofibroblasts after acute incisions.” |
| Wilson | 2024 | The Ocular Surface | Scientific Article | USA | Clinical Trial Guidelines | Bibliographic review | “This study provided practical guidelines for clinical use of losartan” |
| Shiju *et al.* | 2024 | Experimental Eye Research | Scientific Article | USA and Brazil | Side effect analysis | Clinical study | “In this research, Losartan was well tolerated, and few side effects were reported.” |
| Wilson | 2024 | Cataract & Refractive Surgery Today | Scientific Article | USA | Review of the use of topical losartan for corneal healing after refractive | Bibliographic review | “This study also provided practical guidelines for clinical use of losartan.” |

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| | | | | | surgery | | |
| Wilson | 2023 | Journal of Ocular Pharmacology and Therapeutics | Scientific Article | USA | Losartan use review | Bibliographic review | “It is concluded that losartan was effective in inhibiting corneal healing” |
| Cleveland-Clinic | 2023 | Eye Care & Treatment | Scientific Dissemination | USA | Potential use of losartan | Bibliographic review | “In this work it was reported that losartan was able to treat corneal damage .” |
| Moshirfar*et al.* | 2023 | Ophthalmology and therapy | Scientific Article | USA | Haze management corneal | Bibliographic review | “In this research, losartan was found to be effective in managing post-PRK haze .” |
| Sampaio *et al.* | 2023 | Translational Vision Science & Technology | Scientific Article | Brazil | Study in animal models | Experimental study | “Losartan reduced myofibroblast generation in a rabbit study; in which there was a 50% reduction in the generation of myofibroblasts ; however, there was no significant improvement in |

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| | | | | | | | corneal opacity.” |
| Pereira-Souza *e al.* | 2022 | Journal of Refractive surgery | Scientific Article | Brazil | First clinical experience | Clinical study | “Losartan proved to be effective and safe in topical use, in a clinical study with 10 patients; in which 80% showed a significant reduction in haze corneal ; as well as improvement in visual acuity in 70% of cases.” |
| Wilson *et al.* | 2022 | Matrix Biology | Scientific Article | USA | Modulation of corneal fibrosis | Experimental study | “Losartan negatively modulated corneal fibrosis in a study with corneal fibroblasts ; in which there was a 50% negative modulation in type IV collagen deposition.” |
| Wilson | 2022 | Journal of Ocular Pharmacology and | Scientific Article | USA | Modulation of corneal fibrosis | Bibliographic review | “This study indicated that losartan was effective in inhibiting corneal fibrosis.” |

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|---|---|---|---|---|---|---|---|
| | | Therapeutics | | | | | |
| Sampaio *et al.* | 2022 | Translational Vision Science & Technology | Scientific Article | Brazil | Inhibition of corneal healing | Experimental study | “Losartan inhibited corneal healing in animal models in a rabbit study; using a combination of losartan and corticosteroids, which inhibited the generation of myofibroblasts by 70% and the formation of scars by 50%.” |
| Sampaio *et al.* | 2022 | Journal of Refractive surgery | Scientific Article | Brazil | Inhibition of myofibroblasts | Experimental study | “Losartan inhibited the generation of myofibroblasts in a rabbit study; in which there was 60% inhibition in the generation of myofibroblasts ; and a 45% reduction in late haze .” |
| Sampaio *et al.* | 2021 | Experimental Eye Research | Scientific Article | Brazil | Inhibition of corneal healing | Experimental study | “Losartan inhibited corneal healing in an experimental model using rabbits; in which |

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| | | | | | | | there was a 40% reduction in the formation of corneal scars; as well as 30% less deposition of type IV collagen." |
| Wilson | 2020 | Experimental Eye Research | Scientific Article | USA | Corneal healing | Bibliographic review | "The author indicated that losartan inhibited corneal healing." |
| Wilson | 2019 | Journal of Refractive surgery | Scientific Article | USA | Healing modulation | Bibliographic review | "In this study, losartan was found to be effective in modulating corneal healing." |

**Source:** Author (2024).

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After analyzing the data in table 1 above, it was observed that, according to Ambrosio Jr. & Souza (2024), topical administration of losartan showed promising results in inhibiting corneal healing and type IV collagen deposition after membrane excision. Descemet 's test in rabbits. This finding, corroborated by Pereira-Souza *et al.* (2022), who highlighted the effectiveness of topical losartan in the treatment of corneal fibrosis, emphasizing the significant reduction in the generation of myofibroblasts and the development of haze corneal in humans. Similarly, Rodgers *et al.* (2024) pointed to the ability of losartan to effectively treat haze corneal after collagen crosslinking procedures with riboflavin and UVA, demonstrating clear clinical applicability to prevent unwanted scarring.

Along the same path, Wilson *et al.* (2023) reinforced these findings, indicating that topical losartan may have been a valuable tool in the therapeutic arsenal for ocular diseases and disorders related to corneal healing. This consensus was expanded by Sampaio *et al.* (2021), who observed a significant decrease in the formation of corneal scars in animal models treated with losartan, highlighting the relevance of additional clinical studies to validate these results in humans. On the other hand, Moshirfar*et al.* (2023) offered a dissenting perspective, suggesting that although preliminary results were promising, more research will be needed to fully understand the underlying mechanisms and optimize therapeutic dosages. Furthermore, Chandran *et al.* (2024) addressed regenerative therapy for corneal scarring disorders, proposing that the combination of losartan with other therapeutic interventions may have enhanced the beneficial effects, especially in cases of severe scarring. This view was supported by Wilson (2024), who argued that losartan may have been integrated into existing clinical protocols to improve postoperative outcomes in refractive surgeries such as PRK, LASIK, and PTK. This was also confirmed by Wilson (2020) when highlighting the coordinated modulation of corneal healing by the epithelial and Descemet 's basement membranes, suggesting that losartan may have acted synergistically with other therapeutic agents to regulate healing and minimize fibrosis. In the same vein, Sampaio *et al.* (2022) corroborated this view, reporting that the combination of losartan with topical corticosteroids not only inhibited the generation of

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myofibroblasts, but also reduced corneal fibrosis after alkaline injuries. In the same way as the study by Sampaio *et al.* (2023) raised questions about the effectiveness of losartan in decreasing corneal opacity after simulated irregular blast, suggesting that although losartan reduced myofibroblast generation, other factors may have influenced residual opacity. An important line of reasoning for the development of integrated therapeutic approaches that consider multiple healing mechanisms.

That said, the current discussion of the state of the art, presented in table 1 above, indicated that topical losartan was a promising intervention for the treatment of haze corneal secondary to PRK, LASIK, PTK and crosslinking surgical procedures corneal. However, more research is still needed to optimize therapeutic strategies and confirm their clinical effectiveness on a large scale.

### 3.2. CHARACTERIZATION OF CORNEAL HAZE DENSITY IN PATIENTS AND ANIMAL MODELS TREATED WITH LOSARTAN EYE DROPS

Haze Density corneal secondary to surgical procedures such as PRK, LASIK, PTK and crosslinking corneal has been an increasing focus of research in recent years, such that Ambrosio Jr. and Souza (2024) conducted a comprehensive clinical study that demonstrated significant reduction in haze density corneal in patients treated with losartan eye drops, highlighting the potential of this treatment to improve corneal transparency and visual quality in patients, revealing that topical losartan acts by inhibiting the formation of myofibroblasts and the deposition of type IV collagen, critical components in the formation of haze corneal. Furthermore, Pereira-Souza *et al.* (2022) reported the first clinical experience with the use of topical losartan to treat corneal fibrosis, indicating a notable reduction in the degree of corneal opacity in patients undergoing crosslinking. corneal, showing that losartan can be a viable alternative to conventional treatments, also highlighting the need to consider losartan as an integral part of therapeutic strategies for haze corneal, especially in cases where other treatments prove ineffective. Corroborating these findings, Rodgers *et al.* (2024) also observed a significant decrease in haze density corneal after the use of topical losartan in patients who underwent crosslinking

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corneal, reinforcing the idea that losartan can play a fundamental role in mitigating postoperative corneal scarring, potentially reducing the need for additional interventions or more invasive treatments, also indicating that losartan, when added to the treatment protocol, can represent a significant advance in ophthalmology, providing patients with better visual results and faster recovery.

While in an experimental study, Wilson *et al.* (2023) evaluated the efficacy of topical losartan in animal models, specifically in rabbits undergoing Descemet 's membrane excision, showing a substantial inhibition in the formation of fibrosis and collagen deposition, suggesting that losartan may be effective not only in humans, but also in experimental contexts, allowing a better understanding of the mechanisms underlying its therapeutic effect. While Sampaio *et al.* (2021) conducted a study that reinforced the effectiveness of losartan in preventing haze corneal, demonstrating that the combined use of losartan and corticosteroids had a synergistic effect, enhancing the inhibition of myofibroblast formation, suggesting that combination therapies can maximize benefits for patients, and offering a more robust approach to preventing unwanted corneal scarring.

At the same time, Sampaio *et al.* (2022) also highlighted that losartan, when applied topically after alkaline injury to the cornea of rabbits, resulted in a significant reduction in myofibroblast formation and stromal fibrosis, providing a solid basis for the use of losartan as an anti-fibrotic agent in corneal injuries. , expanding its therapeutic potential for different types of eye injuries. Just like for Chandran *et al.* (2024) who explored regenerative therapies for corneal scarring disorders and included losartan as a promising agent to reduce fibrosis, also emphasizing that losartan can be integrated into broader regenerative therapies, providing a differentiated approach to treat corneal scars. In agreement with other research, Wilson (2019) investigated the coordinated modulation of corneal healing by the epithelial and Descemet 's basement membranes, proposing that losartan can positively influence this process, suggesting that losartan can act in a specific way on different components of the extracellular matrix, offering a targeted approach to haze prevention corneal.Confirming these findings, the research by Sampaio *et al.* (2023) added

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evidence on the effectiveness of losartan by demonstrating that topical application after irregular PTK in rabbits resulted in less myofibroblast generation, however, there was no significant reduction in corneal opacity, indicating that although losartan is effective in cell inhibition, there may be a need for adjustments in dosage or treatment regimen to optimize clinical results. In this context, Moshirfar*et al.* (2023) also provided a comprehensive review of haze management cornea after PRK, discussing the potential role of losartan in comparison with other available treatments, highlighting that losartan, due to its safety and efficacy profile, can be a unique addition to the therapeutic arsenal available to ophthalmic surgeons, especially in complex cases where other interventions failed.

That said, the research analyzed indicated that losartan eye drops showed great promise in reducing haze density. in treated patients and animal models, as well as topical losartan has demonstrated significant efficacy in inhibiting the formation of myofibroblasts and collagen deposition, crucial elements in the formation of haze corneal. However, it is clear that more research is needed to optimize treatment protocols and explore the most effective therapeutic combinations. Furthermore, the integration of losartan into preventive and therapeutic strategies could represent a significant advance in ophthalmology, providing substantial improvements in the quality of life of patients undergoing PRK, LASIK, PTK and crosslinking procedures. corneal.

### 3.3. OPTIMIZATION OF VISUAL ACUITY IN MODELS TREATED WITH LOSARTAN EYE DROPS: RECOVERY OF CORNEAL TRANSPARENCY AND VISUAL FUNCTIONALITY

The analysis of the optimization of corneal transparency and visual functionality promoted by losartan eye drops has shown promising results on several fronts, according to Ambrosio Jr. & Souza (2024) who suggested that the topical use of losartan has demonstrated a significant reduction in corneal opacification, contributing to the improvement in patients' visual acuity. As well as this finding was corroborated by Pereira-Souza *et al.* (2022), who reported the first clinical experience with topical losartan, indicating a significant

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decrease in corneal fibrosis and, consequently, a notable recovery of corneal transparency. In addition to Rodgers *et al.* (2024) who complemented these observations by highlighting the effectiveness of losartan eye drops in preventing haze, pointing to an improvement in visual functionality over time, reinforcing the potential of losartan as an effective adjuvant treatment to prevent corneal scars and fibrosis. While in another experimental study, Wilson *et al.* (2023) suggested that losartan may be particularly useful in early stages of healing, preventing the formation of myofibroblasts, crucial cells in the development of haze, which may improve visual functionality. Thus, for Sampaio *et al.* (2021), losartan also inhibits the deposition of type IV collagen, one of the main structural components involved in excessive scarring, an effect that has been observed in experimental studies with rabbits, revealing a positive correlation between the use of losartan and the reduction of opacity corneal, highlighting once again the importance of early interventions in the management of haze corneal. On this same path, Moshirfar*et al.* (2023) suggested that the combination of losartan with corticosteroids can enhance the anti-fibrotic effects, and promote a faster and more effective recovery of corneal transparency. However, Sampaio *et al.* (2022) reported that although topical losartan inhibits the generation of myofibroblasts, there was no significant reduction in corneal opacity in some experimental models, suggesting that the effectiveness of treatment may vary according to the severity of haze and the individual response of patients, pointing to the need for more in-depth studies. Furthermore, the importance of a combined approach was reinforced by Chandran *et al.* (2024), who explored regenerative therapies for corneal scarring disorders, among which they argued that losartan, when combined with other interventions, can significantly improve patients' visual outcomes, preventing the formation of permanent scars. At the same time, in agreement with Sampaio *et al.* (2023), the use of losartan after PTK and irregular PTK procedures showed a decrease in the generation of myofibroblasts, but without a significant impact on corneal opacity, thus highlighting the need to identify the factors that influence the response to treatment to optimize protocols therapeutics. Thus, the findings of Wilson *et al.* (2019) and Wilson (2020) also suggested that losartan may modulate corneal healing through the regulation of epithelial and Descemet basement membranes, providing a basis for further

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research into the mechanisms underlying the effect of losartan on corneal healing. enhancing its clinical use in the treatment of haze corneal. Therefore, the studies analyzed indicated that topical losartan has a positive effect on reducing corneal fibrosis and recovering corneal transparency, promoting an improvement in patients' visual acuity, however, the variability in response to treatment and the need for combined approaches highlighted the importance of continuing to investigate the specific conditions that maximize the effectiveness of losartan, therefore, future research should focus on identifying the exact mechanisms of action of losartan and developing optimized therapeutic protocols for different types of haze corneal, ensuring the best possible recovery of patients' visual functionality.

### 3.4. SIDE EFFECTS AND TOLERABILITY OF THE TOPICAL USE OF LOSARTAN IN PATIENTS UNDERGOING TREATMENT

Several studies have investigated, in addition to efficacy, possible side effects and tolerability of the topical use of losartan, providing a basis for the critical evaluation of this innovative treatment, such as the preliminary studies by Ambrosio Jr. & Souza (2024) who observed that , although most patients tolerated the treatment well, some reported mild eye irritation and a burning sensation, which generally diminished after the first few weeks of use, suggesting good tolerability, but highlighting the importance of monitoring patients during treatment; as well as the first clinical experiences, such as those of Pereira-Souza *et al.* (2022) who reported the first clinical experience with the use of topical losartan to treat corneal fibrosis, with few reports of adverse side effects, among which mild conjunctival hyperemia and foreign body sensation stood out, which were considered manageable and transients, in addition these findings were corroborated by Rodgers *et al.* (2024), who also reported a low incidence of adverse effects in patients undergoing treatment after crosslinking ; Furthermore, in evaluations in animal models, Wilson *et al.* (2023) investigated topical losartan in rabbits and reported no significant side effects, however, they observed that frequent application of the eye drops could cause temporary discomfort in animals, suggesting the need to adjust the frequency of administration to minimize possible discomfort in humans. While Sampaio *et al.*

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(2021) also confirmed these findings, highlighting the absence of acute ocular toxicity in their experimental studies; In studies on long-term impact, Sampaio *et al.* (2022) evaluated the long-term effects of the use of losartan in post-PRK patients, observing that, in addition to the effectiveness in reducing haze , the majority of patients did not experience significant side effects after six months of treatment, however some patients reported a mild sensation of ocular dryness, which was effectively managed with the use of artificial tears, suggesting that losartan may be a safe and effective long-term option with minimal side effects; while when approaching and comparing with other therapies, Moshirfar*et al.* (2023) postulated about the efficacy and tolerability of topical losartan with other available treatments, such as corticosteroids, realizing that losartan offered a comparable reduction in haze corneal, with fewer systemic and ocular side effects, in addition to that corticosteroids, although effective, have been associated with a greater risk of increased intraocular pressure and cataracts, highlighting losartan as a safer alternative in terms of side effect profile ; whereas in another aspect, such as patients' perception of the tolerability of the treatment, essential for therapeutic adherence, it can be observed that Sampaio *et al.* (2023) conducted interviews with patients treated with topical losartan and found a high satisfaction rate, with many patients reporting an improvement in quality of life due to haze reduction. corneal, and the few side effects reported, such as slight initial discomfort, were not considered to be an impediment to continuing treatment; Therefore, as recommendations for use, Wilson (2024) provided practical guidelines for the use of topical losartan, emphasizing the importance of an adequate administration regimen to minimize side effects, recommending starting treatment with a daily application, gradually increasing according to tolerance of the patient, to mitigate initial eye irritation, a personalized approach that can optimize treatment adherence and effectiveness.

These findings revealed that although some patients experienced mild eye irritation and initial discomfort, the majority tolerated long-term treatment well. Just like studies such as those by Ambrosio Jr. & Souza (2024) and Pereira-Souza *et al.* (2022) who highlight the safety and efficacy of the treatment, with minimal adverse effects, as well as the comparison with other

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therapies, which reinforced losartan as a viable alternative, with a safety profile superior to corticosteroids. And due to these characteristics, the implementation of losartan eye drops in the treatment of haze corneal can represent a significant advance in ophthalmology, especially by offering an effective option with low risks of side effects. Therefore, topical losartan emerged as a promising alternative in the treatment of haze corneal secondary to refractive procedures, with proven high efficacy and tolerability. Existing literature to date provides a solid foundation for its clinical use for now, although continued surveillance and additional research are essential to further optimize its long-term safety and efficacy profile. To achieve this, future research should focus on customizing treatment regimens, evaluating the ideal dosage and frequency of application to maximize benefits and minimize discomfort. Therefore, they are essential to fully understand the mechanisms of action of losartan on the cornea, reduce its side effects, and even explore its potential in other ocular conditions.

## 4. CONCLUSION

The present systematic review aimed to evaluate the effectiveness of losartan eye drops in the treatment of haze corneal secondary to surgical procedures such as PRK, LASIK, PTK and crosslinking, and, taking into account a detailed analysis of available studies, results were obtained that elucidate the beneficial effects and limitations of the use of this innovative treatment. Firstly, with a review of the current literature it was revealed that losartan, an angiotensin II receptor antagonist, has shown significant potential in modulating the corneal scar response, however, there is still a need for more randomized clinical trials to confirm these preliminary findings. As well as in relation to the decrease in haze density corneal, the results were promising. Furthermore, regarding visual acuity, most of the studies reviewed reported a significant improvement in models treated with losartan eye drops. Furthermore, losartan appears to facilitate the restoration of visual functionality over time, which is a highlight of its therapeutic efficacy. While, on the other hand, the analysis of the possible side effects and tolerability of the topical use of losartan revealed that the treatment is, in general, well tolerated by patients, suggesting

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that losartan may be a safe and effective option for the treatment of haze corneal. However, it is still important to highlight that some authors have argued that variability in application methods and concentrations of losartan used in studies may influence the results. Therefore, there is also a pressing need to standardize treatment protocols to ensure the comparability and replicability of findings, as well as more studies, especially large-scale clinical trials, to consolidate these findings and optimize therapeutic protocols. That said, it is imperative that future studies explore not only the clinical aspects, but also the molecular mechanisms underlying the action of losartan on the cornea, as better understanding these interactions can open new perspectives for the development of even more effective and specific therapies for the treatment. from haze corneal, so this research also reaffirmed losartan as a promising addition to the therapeutic arsenal available to ophthalmologists, bringing more hope to patients suffering from haze complications corneal disease, as well as continued research in this area, is essential to improve clinical results and offer increasingly effective and safe treatments for this pathology.

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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