

Montelukast in Ophthalmology: Molecular Mechanisms, Current Evidence, and Future Therapeutic Perspectives

Safieh Amiraslazadeh¹ , Hamid Mahmoudpour², Mojtaba Ziaee^{3,2*} 

¹Nikookari Eye Center, Tabriz University of Medical Sciences, Tabriz, Iran

²Research Center for Integrative Medicine in Aging, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran

³Medicinal Plants Research Center, Maragheh University of Medical Sciences, Maragheh, Iran

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*Corresponding Author:

Mojtaba Ziaee,

Email: m.ziaee@tbzmed.ac.ir

Abstract

Leukotrienes have traditionally been viewed as key mediators of allergic inflammation, but growing evidence indicates their involvement in immune responses, oxidative stress (OS), vascular dysfunction, and neuroinflammation, highlighting their therapeutic potential. Among available agents, montelukast, a selective cysteinyl leukotriene receptor 1 (CysLT₁) antagonist, represents a promising candidate for drug repurposing in ophthalmology.

Therefore, this review summarizes current knowledge of leukotriene biology in ocular tissues and critically evaluates the experimental and clinical evidence supporting montelukast across diverse ophthalmic diseases. According to preclinical studies, montelukast suppresses inflammatory signaling, reduces OS, attenuates leukocyte recruitment and microglial activation, and preserves vascular barrier integrity and retinal neuronal homeostasis. Moreover, clinical observations are most convincing in allergic conjunctivitis, while encouraging experimental data have been reported for dry eye disease, diabetic retinopathy, retinal ischemic injury, glaucoma, and uveitis. Contrarily, evidence for age-related macular degeneration remains preliminary and largely mechanistic. Despite these encouraging findings, clinical translation into remains limited by uncertain ocular pharmacokinetics following systemic administration, the absence of formulations optimized for posterior-segment delivery, and insufficient validated biomarkers and a lack of adequately powered randomized clinical trials.

Overall, current evidence supports leukotriene signaling as a convergent inflammatory pathway across multiple ocular diseases, identifying montelukast as an important proof-of-concept for leukotriene-directed therapy. Future advances in ocular drug delivery, biomarker-guided patient selection, and well-designed clinical studies will determine whether the modulation of this pathway can evolve into a disease-modifying therapeutic strategy in ophthalmology.

Keywords: Montelukast, Leukotrienes, CysLT₁ receptor, Ocular Inflammation, Drug Repurposing, Ophthalmology

Introduction

Inflammation and oxidative stress (OS) are central to the pathobiology of a broad spectrum of ocular disorders, ranging from common surface diseases (e.g., allergic conjunctivitis and dry eye disease) to posterior segment conditions (e.g., diabetic retinopathy [DR], age-related macular degeneration, and glaucoma).¹⁻³ Although major advances in ophthalmic therapy have improved symptom control and disease management, current treatments frequently remain directed toward downstream mediators or late clinical manifestations rather than the upstream pathways that sustain chronic inflammation and tissue injury.⁴ Accordingly, there is continued interest in identifying therapeutically relevant signaling cascades that may be amenable to drug repurposing, particularly in conditions where persistent inflammation, vascular dysfunction, and neurodegeneration converge.⁵

Among lipid-derived inflammatory mediators, leukotrienes occupy a biologically important position in

both innate and adaptive immune responses.⁶ Generated from arachidonic acid through the 5-lipoxygenase (5-LOX) pathway, cysteinyl leukotrienes (e.g., LTC₄, LTD₄, and LTE₄) signal predominantly through the cysteinyl leukotriene receptor 1 (CysLT₁) in order to promote vascular permeability, leukocyte recruitment, cytokine amplification, and sustained inflammatory activity.⁷ This pathway is well established in asthma and allergic disease, but experimental studies further suggest that leukotriene signaling may contribute to ocular surface inflammation, retinal vascular dysfunction, and neuronal injury.^{8,9} Importantly, however, the strength of evidence substantially varies across disease states, and mechanistic plausibility should not be conflated with proven clinical efficacy.

Montelukast is a selective oral CysLT₁ receptor antagonist that is widely used in asthma and allergic rhinitis.¹⁰ Beyond its approved respiratory indications, preclinical studies have shown that montelukast may exert anti-inflammatory,

antioxidant, anti-apoptotic, and possibly neuroprotective effects through the modulation of pathways such as nuclear factor-kappa β (NF- κ B) signaling and cytokine production.¹¹ These findings have made montelukast an attractive candidate for drug repurposing in chronic inflammatory disorders. However, such interest must be cautiously interpreted in ophthalmology: while the biologic rationale is compelling, the clinical evidence supporting benefit remains strongest in allergic eye disease and substantially weaker, or largely absent, in most posterior segment disorders.¹²

Leukotriene-related components have been identified in ocular tissues, including the conjunctiva, cornea, ciliary body, retinal pigment epithelium (RPE), retinal neurons, and optic nerve.¹³ Experimental work further indicates that leukotriene signaling may be upregulated in several ocular conditions characterized by inflammation or tissue stress.¹⁴ Nonetheless, the presence of a signaling pathway in diseased tissue does not, by itself, establish therapeutic relevance. In diseases such as allergic conjunctivitis and vernal keratoconjunctivitis, clinical studies provide at least limited support for leukotriene receptor antagonism as an adjunctive approach.¹⁵ By contrast, available data are predominantly preclinical or observational in disorders such as DR, glaucoma, dry eye disease, age-related macular degeneration, and retinal ischemic injury. Moreover, no robust body of human evidence currently supports routine clinical use.

Safety is another important consideration. Montelukast has drawn increased attention because of regulatory warnings regarding rare but clinically meaningful

neuropsychiatric adverse events.¹⁶ This issue is especially relevant when considering off-label use for chronic non-life-threatening ocular disease, where the threshold for acceptable risk is lower than in severe systemic illness. Therefore, any discussion of montelukast in ophthalmology requires a balanced appraisal of potential benefit, biological plausibility, translational limitations, and safety concerns.

In this review, the pharmacology of montelukast and the role of leukotriene signaling in ocular physiology and disease are critically examined, with emphasis on the distinction between mechanistic rationale and clinically validated efficacy. The current evidence across ocular surface disorders, retinal vascular disease, neurodegenerative eye disease, and inflammatory conditions of the eye is summarized, highlighting the major gaps that must be addressed before leukotriene receptor antagonism can be considered a truly evidence-based ophthalmic strategy.

Mechanisms of Action

Montelukast exerts its primary pharmacological effect through selective antagonism of the cysteinyl leukotriene type 1 (CysLT₁) receptor, a G protein-coupled receptor that mediates many of the pro-inflammatory actions of cysteinyl leukotrienes. Activation of this receptor amplifies inflammatory signaling by increasing vascular permeability, promoting eosinophil and leukocyte recruitment, stimulating mucus secretion, and enhancing cytokine production.¹⁷ Although these responses are traditionally associated with allergic airway disease, the same signaling network is increasingly recognized as contributing to chronic inflammation in several ocular disorders.⁸

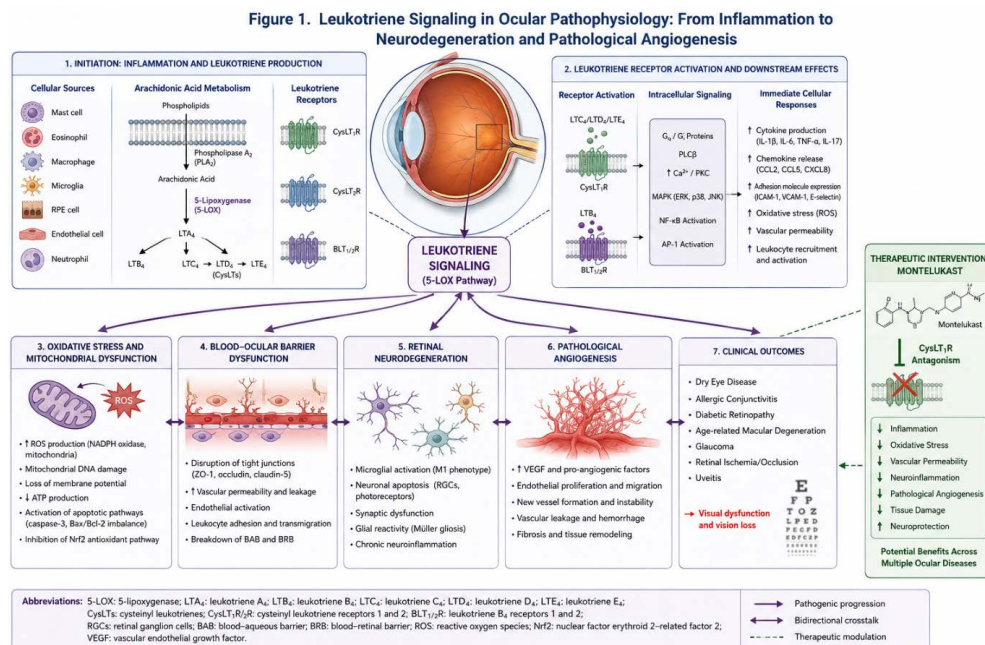


Figure 1. Leukotriene Signaling in Ocular Pathophysiology and the Therapeutic Rationale for CysLT₁ Receptor Antagonism

Note. CysLT₁: Cysteinyl leukotriene receptor 1; PLC/PKC: Phospholipase C/protein kinase C; MAPK: Mitogen-activated protein kinase; NF- κ B: Nuclear factor-kappa β . Leukotrienes generated through the 5-lipoxygenase pathway activate BLT and CysLT receptors on immune, vascular, and retinal cells, thus triggering inflammatory signaling cascades (PLC/PKC, MAPK, and NF- κ B) that promote cytokine production, oxidative stress, endothelial dysfunction, vascular leakage, and leukocyte recruitment. Moreover, sustained activation contributes to blood-ocular barrier disruption, mitochondrial dysfunction, microglial activation, retinal neurodegeneration, and pathological angiogenesis, culminating in vision loss across multiple ocular diseases. Montelukast, a selective CysLT₁ receptor antagonist, is proposed to interrupt these interconnected pathogenic mechanisms by reducing inflammation, oxidative stress, vascular permeability, and neuroinflammation, thereby providing a mechanistic framework for leukotriene-targeted therapy in both anterior and posterior segment disorders

By competitively occupying the ligand-binding pocket of the CysLT₁ receptor, montelukast prevents the interaction of endogenous leukotrienes with their principal signaling receptor, thereby interrupting one of the major downstream pathways activated by the 5-LOX cascade.¹⁸ This results in the attenuation of intracellular signaling pathways involved in inflammatory gene transcription, including NF- κ B and mitogen-activated protein kinase signaling, ultimately reducing the production of cytokines, chemokines, and other inflammatory mediators that sustain tissue injury.^{19,20} Importantly, this mechanism suppresses leukotriene signaling without interfering with upstream eicosanoid biosynthesis, distinguishing montelukast from 5-LOX inhibitors and contributing to its favorable safety profile.²¹

Over the past decade, however, it has become increasingly evident that the biological activity of montelukast cannot be attributed solely by CysLT₁ receptor blockade. Experimental studies performed across diverse models of inflammatory and neurodegenerative diseases have consistently demonstrated broader immunomodulatory effects that appear to extend beyond classical receptor antagonism.²² Although the precise molecular basis of these effects remains under investigation, accumulating evidence indicates that montelukast influences multiple interconnected inflammatory pathways that collectively regulate cellular survival, OS, and tissue remodeling.²³

One of the most consistently reported effects is the suppression of NF- κ B activation, a central transcriptional regulator of inflammatory responses. Inhibition of this pathway is accompanied by reduced expression of major pro-inflammatory mediators, including tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , IL-6, and monocyte chemoattractant protein-1, resulting in diminished recruitment and activation of inflammatory cells.²⁴ These anti-inflammatory effects have been confirmed across several experimental systems, suggesting that montelukast modulates the broader inflammatory microenvironment rather than targeting a single cytokine pathway.^{25,26}

OS represents another important target of montelukast. Excessive production of reactive oxygen species (ROS) contributes to mitochondrial dysfunction, lipid peroxidation, DNA damage, and activation of cell death pathways in many chronic ocular diseases.²⁷ According to experimental evidence, montelukast attenuates oxidative injury by reducing ROS generation while enhancing endogenous antioxidant defenses, partly through the activation of the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 signaling pathway.²⁸ Although these findings predominantly originate from preclinical studies, they provide a biologically plausible explanation for the protective effects observed in models of retinal ischemia, DR, and optic nerve injury.

Beyond regulating inflammation and OS, montelukast also appears to influence cell survival pathways. Several studies have demonstrated reduced activation of executioner caspases and preservation of mitochondrial integrity following montelukast treatment, implying

an anti-apoptotic effect under inflammatory or OS conditions.²⁹ These observations are particularly relevant to retinal neurons and retinal ganglion cells, whose progressive loss underlies irreversible visual impairment in disorders such as glaucoma and retinal ischemia.³⁰

Emerging evidence further suggests that montelukast modulates innate immune cell function. Experimental studies have documented shifts in macrophage and microglial activation toward less pro-inflammatory phenotypes, accompanied by reduced secretion of cytotoxic mediators and improved resolution of tissue inflammation.³¹ Given the increasingly recognized contribution of microglial activation to retinal neurodegeneration, this mechanism may represent an additional pathway through which montelukast exerts neuroprotective effects.³⁰ Nevertheless, the translational significance of these findings remains to be established through well-designed clinical studies.

Overall, current evidence indicates that montelukast should no longer be viewed solely as a leukotriene receptor antagonist used for allergic diseases but rather as a pleiotropic immunomodulatory agent capable of simultaneously targeting multiple biological processes (e.g., inflammation, OS, vascular dysfunction, and apoptosis) that are shared across numerous ocular disorders.⁸ This broad pharmacological profile provides a strong mechanistic basis for evaluating montelukast as a drug-repurposing candidate in ophthalmology. Nonetheless, confirmation of these experimental observations in human ocular disease remains a priority for future translational research (Figure 1).

Pharmacokinetics

An understanding of the pharmacokinetic profile of montelukast is essential when considering its potential repurposing for ocular diseases. Unlike conventional ophthalmic medications, which rely on topical administration to achieve local drug exposure, montelukast is orally administered and exerts its effects through systemic modulation of inflammatory pathways. Consequently, the therapeutic relevance of these pharmacokinetic characteristics extends beyond systemic exposure to include tissue accessibility, metabolic stability, and the potential to modulate inflammatory processes within immune-privileged ocular tissues.³²

Montelukast is well absorbed following oral administration and exhibits consistent bioavailability that supports once-daily dosing. Moreover, extensive plasma protein binding and predominant hepatic metabolism contribute to relatively stable systemic drug concentrations while minimizing large fluctuations during chronic treatment. These pharmacokinetic features have facilitated its long-term clinical use in asthma and allergic rhinitis, where the primary therapeutic objective is the sustained suppression of leukotriene signaling rather than rapid peak concentrations. A similar pharmacodynamic principle may be advantageous in chronic ocular diseases characterized by persistent low-grade inflammation.¹⁷

The drug undergoes extensive hepatic metabolism, predominantly through CYP2C8, with smaller contributions from CYP3A4 and CYP2C9.³³ Considering that elimination occurs primarily through biliary excretion, renal dysfunction has a negligible influence on systemic drug disposition. Clinically significant pharmacokinetic interactions are uncommon in routine practice, although caution is still warranted when montelukast is co-administered potent cytochrome P450 inducers that may reduce systemic drug exposure.³⁴ Overall, its predictable pharmacokinetic behavior has contributed to the favorable safety profile observed during long-term therapy.

One of the most relevant, and still actively investigated, aspects of montelukast pharmacology is its tissue distribution. According to experimental research, montelukast is capable of limited penetration into the central nervous system, particularly under conditions associated with the disruption of physiological barrier function.³⁵ Although the extent of blood-brain barrier (BBB) penetration in humans remains incompletely understood, these findings have raised interest in whether the drug may also access posterior segment ocular tissues, where inflammation, OS, and neurodegeneration play central roles in disease progression.³⁶ Direct pharmacokinetic evidence demonstrating therapeutically relevant concentrations in human retinal tissues remain limited, representing an important challenge in translating promising experimental findings into clinical practice.³⁷

Importantly, therapeutic efficacy in ocular disease may not necessarily depend on achieving intraocular drug concentrations.³⁸ Many inflammatory eye disorders, including allergic conjunctivitis, uveitis, DR, and age-related macular degeneration, are influenced by systemic immune activation and circulating inflammatory mediators. By attenuating leukotriene-dependent inflammatory signaling at the systemic level, montelukast may indirectly modulate the ocular inflammatory milieu without functioning as a conventional locally delivered ophthalmic drug.^{8,39} This concept distinguishes montelukast from topical corticosteroids or calcineurin inhibitors, supporting its potential role as an adjunctive systemic therapy in carefully selected patients rather than as a direct replacement for established ocular treatments.

Despite these encouraging pharmacological characteristics, several significant questions remain unresolved. The relationship between plasma exposure and ocular tissue concentrations has not been established, and the optimal dosage required for ocular indications is unknown. Furthermore, no pharmacokinetic studies have established a correlation between systemic drug levels with retinal or ocular surface biomarkers.⁴⁰ Addressing these knowledge gaps will be essential for determining whether the favorable experimental profile of montelukast can be translated into meaningful clinical benefits. Ultimately, future investigations combining ocular pharmacokinetics, pharmacodynamic biomarkers, and advanced drug-delivery strategies may help define the therapeutic window required for successful ophthalmic application.

Leukotrienes as Important Integrative Mediators and Regulators of Chronic Ocular Inflammation and Degeneration: From Molecular Amplification to Therapeutic Potential

Leukotrienes as Important Regulators of Ocular Inflammation

In the eye, inflammation must be tightly controlled to protect vision. Even minor disruptions can cloud the cornea, break down blood-ocular barriers (BOB), or harm retinal neurons that have little capacity to regenerate. Therefore, the ocular immune system depends on a delicate balance of lipid mediators, cytokines, chemokines, and resident cells to resolve inflammation before it becomes chronic.⁴¹

Leukotrienes, produced from arachidonic acid via the 5-LOX pathway under stress, injury, or immune activation, extend far beyond their classic role in asthma and allergies. Rather than initiating inflammation, they mainly sustain and amplify it by bridging innate and adaptive responses. Moreover, cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄) bind CysLT receptors, especially CysLT₁, on endothelial cells, epithelial cells, fibroblasts, mast cells, eosinophils, macrophages, microglia, and various resident ocular cells.¹³ This wide distribution allows them coordinate vascular permeability, adhesion molecule expression, leukocyte recruitment, and cytokine production (TNF- α , IL-1 β , IL-6, and chemokines) through cross-talk with NF- κ B and mitogen-activated protein kinase pathways.⁴²

What makes leukotrienes particularly potent in the eye is the convergence of multiple disease triggers on this pathway: hyperosmolar stress in dry eye, allergens in conjunctivitis, ischemia in DR, mechanical strain in glaucoma, and oxidative damage in retinal degeneration all activate phospholipase A₂ and boost 5-LOX activity.⁴³ This creates a self-reinforcing loop linking persistent lipid mediator signaling with cytokine storms, OS, and immune cell infiltration across both anterior and posterior segments.³⁰

This process closely intertwines with OS. ROS drive leukotriene production, while leukotrienes activate inflammatory cells that generate more ROS, thereby creating a vicious feed-forward cycle. In the retina, high-metabolic-demand cells such as photoreceptors, RPE, and ganglion cells are especially vulnerable, leading to mitochondrial damage, senescence, matrix remodeling, and eventual neuronal loss.⁴⁴

Likewise, leukotrienes shape the ocular immune microenvironment. They push retinal microglia toward a pro-inflammatory state, increasing cytotoxic cytokines, ROS, and complement. Similarly, infiltrating macrophages remain activated for longer, thus delaying repair. Leukotriene signaling acts as an upstream hub, since it integrates with prostaglandins, platelet-activating factor, complement, inflammasomes, vascular endothelial growth factor (VEGF), and other cytokines. Targeting this pathway, unlike single-cytokine blockade, can dampen multiple redundant inflammatory arms at once.⁴⁵

These mechanisms position montelukast, a CysLT₁

antagonist already used for asthma, as a promising repurposed agent. By interrupting leukotriene amplification, montelukast can potentially reduce vascular leakage, oxidative damage, immune recruitment, and neurodegeneration.^{12,46} Preclinical data from models of DR, the aging retina, and other conditions are encouraging, although most of the available evidence remains experimental. Whether leukotriene modulation can significantly alter disease progression in patients remains a key open question for future translational research.

Leukotrienes, Oxidative Stress, and Mitochondrial Dysfunction

OS represents a central driver across many ocular diseases, whether triggered by allergy, hyperglycemia, ischemia, mechanical pressure, aging, or environmental factors. Ocular tissues, constantly exposed to light and oxygen while sustaining intense metabolic activity, exist at a delicate balance between normal redox signaling and damaging ROS overload. Persistent ROS production actively contributes to cellular damage and disease progression rather than merely accompanying them.⁴⁷

Leukotrienes function at the crossroads of inflammation and OS, forming a bidirectional vicious cycle. Moreover, oxidative injury activates phospholipase A₂ and the 5-LOX pathway, thereby increasing cysteinyl leukotriene production. In turn, leukotriene signaling recruits and activates inflammatory cells that generate additional ROS through nicotinamide adenine dinucleotide phosphate oxidase and mitochondrial sources.⁴⁸ Hence, inflammation and oxidative damage become biologically interconnected, with leukotrienes helping to sustain this loop.⁴⁹

Nowhere is this more critical than in the retina, one of the body's most metabolically demanding tissues. Furthermore, photoreceptors, RPE cells, Müller glia, and ganglion cells rely on healthy mitochondria to maintain a continuous adenosine triphosphate (ATP) supply. Excessive ROS can damage mitochondrial DNA, disrupt the electron transport chain, reduce ATP production, open permeability transition pores, and trigger apoptosis. Mitochondrial dysfunction, in turn, further increase ROS production, thereby accelerating neuronal loss.^{50,51}

Leukotriene signaling further increases this vulnerability. Activation of the CysLT₁ receptor enhances inflammatory pathways that place additional stress on mitochondria through OS, cytokines, calcium dysregulation, fragmentation, and loss of membrane potential. Likewise, it promotes lipid peroxidation and weakens antioxidant defenses. In general, leukotrienes act upstream, contributing to the conditions that ultimately lead to mitochondrial dysfunction.⁵²

Montelukast shows several key protective effects that extend beyond simple CysLT₁ blockade. Across various experimental models, it lowers intracellular ROS, limits lipid peroxidation, preserves mitochondrial structure and function, and reduces oxidative DNA damage.⁵³ It can also activate the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 axis, thereby strengthening cellular

antioxidant responses while supporting mitochondrial quality control by limiting excessive fission, preserving membrane integrity, and reducing caspase-mediated apoptosis.⁵⁴ Overall, these effects may help restore cellular bioenergetics before the occurrence of irreversible damage.

This is particularly relevant to ophthalmology because mitochondrial dysfunction is a shared mechanism across several ocular conditions, including endothelial and capillary damage in DR, increased ganglion cell vulnerability in glaucoma, RPE and photoreceptor loss in age-related macular degeneration (AMD), and disruption of epithelial barriers in dry eye.⁵⁵⁻⁵⁷ Targeting an upstream regulator such as leukotriene signaling may therefore provide broader benefits than addressing isolated downstream effects.

However, several important limitations should be taken into consideration. Most available data come from cell and animal models, with limited direct evidence from human ocular tissues. It remains unclear to what extent the antioxidant effects of montelukast result from leukotriene blockade versus additional off-target effects. Accordingly, addressing these gaps will help determine whether modulation of OS represents a primary mechanism underlying its therapeutic effects or rather one component of a broader immunomodulatory profile.⁵⁸

Leukotrienes and Blood-Ocular Barrier Dysfunction

BOB plays an essential role in maintaining the immune-privileged status of the eye.⁵⁹ It consists of the blood-aqueous barrier in the anterior segment and the blood-retinal barrier (BRB), formed by tight junctions in retinal endothelial cells (inner) and the RPE (outer).^{60,61} It is noteworthy that these barriers tightly regulate the passage of cells, proteins, and mediators in order to preserve the precise microenvironment needed for clear vision.⁵⁹

Barrier breakdown is a common feature of many ocular diseases, regardless of the initial trigger, whether allergy, autoimmunity, diabetes, ischemia, aging, or trauma. When junctions loosen, plasma proteins leak into the tissue, inflammatory cells infiltrate, edema develops, and immune-privileged sites become exposed to systemic signals, turning localized inflammation into a self-sustaining process that drives chronic damage instead of repair.⁶²

Moreover, cysteinyl leukotrienes actively promote this dysfunction. Through CysLT₁ receptors on endothelial cells, these leukotrienes destabilize junctions, increase cytoskeletal contractility, boost permeability, and upregulate adhesion molecules and chemokines that facilitate leukocyte adhesion and transmigration. In the retina, increased 5-LOX pathway activity in DR, ischemia-reperfusion, and inflammatory models links leukotrienes to vascular leakage, leukostasis, and inner BRB breakdown, frequently in concert with cytokines and OS.⁶³

Additionally, leukotrienes intersect with VEGF, a major driver of pathological permeability in diabetic macular edema and neovascular AMD.⁵¹ They amplify VEGF effects by enhancing inflammation, OS, and endothelial activation, converging on shared pathways that weaken

tight junctions. This interaction suggests potential synergy between leukotriene modulation and anti-VEGF therapies, especially in cases with ongoing inflammation.¹⁴

Similar mechanisms operate at the ocular surface. Leukotriene-driven permeability in the BAB and conjunctival vessels promotes protein extravasation, mast cell and eosinophil activation, and edema, contributing to hyperemia and chemosis in allergic conjunctivitis and other surface disorders.⁶⁴ Thus, leukotrienes destabilize vascular homeostasis across both anterior and posterior segments.

Montelukast counters these effects by blocking CysLT₁, reducing permeability, limiting cell recruitment, and dampening cytokine networks. Preclinical models demonstrate decreased leakage, infiltration, and edema, though direct evidence of BRB restoration in human disease is still limited.^{65,66}

It should be noted that barrier failure is not merely a passive outcome of inflammation; instead, it actively perpetuates disease by allowing continuous crosstalk between systemic immunity and the eye. Therefore, strategies that protect barrier integrity can interrupt multiple downstream cascades, including infiltration, edema, oxidative injury, and neurodegeneration, at once.⁶⁷

Leukotrienes in Retinal Neurodegeneration

Retinal neurodegeneration is now recognized as a core process in many vision-threatening conditions, not just classic neurodegenerative diseases such as glaucoma and inherited dystrophies. Furthermore, neuronal dysfunction and loss occur early in DR, age-related macular degeneration, retinal ischemia, and chronic inflammatory disorders.⁶⁸ This shift redirects our focus from isolated vascular or inflammatory processes to the intricate cellular networks that determine whether retinal neurons survive.

The retina's extreme metabolic demands and minimal regenerative capacity make it highly vulnerable. Photoreceptors and ganglion cells require constant oxygen and ATP, leaving them exposed to mitochondrial failure, OS, and chronic inflammation. Dying neurons release damage-associated molecular patterns that activate glia and amplify inflammation, creating self-propagating cycle of damage driven by ongoing crosstalk among neurons, glia, vessels, and immune mediators.⁶⁹

Leukotrienes act as an important upstream regulator in this neuroinflammatory network. The 5-LOX pathway and CysLT receptors are expressed in ganglion cells, Müller glia, RPE, endothelial cells, and microglia. Under stress conditions such as ischemia, hyperglycemia, or oxidative injury, leukotriene production sharply increases, shifting the environment toward inflammation and neuronal loss.¹⁴

Microglial activation is a key mechanism. Normally, microglia survey and support the retina. After injury, leukotriene signaling promotes their shift to a pro-inflammatory state, boosting cytokines, ROS, nitric oxide, and complement. This sustained activation drives synaptic disruption, impairs neuronal signaling, and accelerates apoptosis in ganglion cells and other neurons.⁷⁰

As previously mentioned, leukotrienes also exacerbate

neuronal injury by intensifying OS and mitochondrial dysfunction. They impair antioxidant defenses, reduce ATP production, and trigger apoptotic pathways, devastating for neurons with little metabolic reserve.^{8,71}

Additionally, leukotrienes disrupt neurovascular coupling through endothelial activation, permeability increases, and leukocyte recruitment, thereby exposing neurons to secondary ischemia and inflammation, linking vascular and neurodegenerative processes.⁷²

These insights make montelukast an appealing neuroprotective candidate. Beyond CysLT₁ blockade, it reduces microglial activation, cytokine release, oxidative damage, and apoptosis in the central nervous system and retinal models of ischemia-reperfusion, optic nerve injury, and diabetic damage. Treated eyes show improved neuronal survival, reduced infiltration, and preserved tissue architecture.⁷³ However, the available evidence remains largely preclinical, and strong clinical data from human studies are still needed.

The broader appeal lies in neuroinflammation's shared role across glaucoma, DR, AMD, vascular occlusions, and dystrophies. Modulating leukotrienes could provide cross-disease benefits where current therapies frequently fall short on direct neuronal protection.⁷⁴

Open questions persist: the relative weight of leukotriene pathways versus others, optimal timing for intervention, and whether systemic montelukast achieves adequate retinal levels in humans. Hence, future work integrating imaging, biomarkers, pharmacokinetics, and trials will be essential.

Leukotrienes and Pathological Angiogenesis

Pathological angiogenesis remains a leading cause of irreversible vision loss in conditions such as neovascular AMD, proliferative DR, retinal vein occlusion, and retinopathy of prematurity. While VEGF is the primary therapeutic target, neovascularization arises from a broader inflammatory network involving lipid mediators, innate immunity, OS, and endothelial dysfunction that disrupts the organized retinal and choroidal architecture, causing leakage, fibrosis, hemorrhage, and neuronal damage.⁷⁵

Leukotrienes function as upstream amplifiers rather than direct initiators of new vessel growth. Via the 5-LOX pathway, they promote endothelial activation, increase vascular permeability, recruit leukocytes, and sustain cytokine production (e.g., TNF- α , and IL-1 β), creating a permissive microenvironment for aberrant angiogenesis.⁵¹

Strong crosstalk exists with VEGF pathways: leukotriene-induced cytokines boost VEGF expression, while VEGF enhances permeability and inflammation. This forms a self-reinforcing loop where inflammation fuels angiogenesis and immature vessels worsen hypoxia and OS, explaining persistent disease activity in some patients despite anti-VEGF therapy.¹⁴

Hypoxia further connects these processes. It stabilizes hypoxia-inducible factor 1 α to drive VEGF while simultaneously activating phospholipase A₂ and 5-LOX to increase leukotrienes.⁷⁶ It should be noted that the

resulting mix of hypoxia, ROS, and inflammation sustains endothelial activation and matrix remodeling.⁷⁷

Moreover, leukotrienes act indirectly by recruiting and activating macrophages and microglia, which release pro-angiogenic factors, matrix metalloproteinases, and growth factors that support vessel sprouting and remodeling.⁷⁸ Thus, immune regulation and angiogenesis are tightly intertwined.

Montelukast offers potential to disrupt this network by blocking CysLT₁, reducing cytokines, endothelial activation, leukocyte infiltration, and OS. In preclinical models of retinal ischemia and diabetic injury, this drug decreases leakage and helps preserve retinal structure, suggesting indirect benefits on angiogenic remodeling through upstream inflammatory control, even if it lacks the potent direct anti-angiogenic action of VEGF inhibitors.⁷⁹

This positions montelukast as a promising adjunct rather than replacement for anti-VEGF therapy. Many patients still show incomplete responses, require frequent injections, or have ongoing inflammation. Accordingly, combining approaches that target both VEGF and chronic inflammatory drivers could address these gaps.⁸⁰

Nonetheless, evidence is mostly preclinical, with no robust clinical trials demonstrating reduced neovascularization in humans. In addition, the relative role of leukotrienes versus other mediators (prostaglandins, complement, and inflammasomes) needs clarification. Future translational studies with biomarkers, imaging, and combined endpoints will be critical in this regard.

Why Target Leukotrienes in Ophthalmology?

Over the past two decades, ophthalmology has been transformed by anti-VEGF agents for neovascular diseases and advanced biologics or sustained-release steroids for inflammation. Nevertheless, many patients still face progressive vision loss, recurrent flares, or incomplete responses. These limitations highlight a key reality: most ocular diseases arise from complex, interconnected networks of inflammation, OS, vascular dysfunction, and neurodegeneration rather than a single pathway.⁸¹

This understanding has shifted the field away from the traditional “one target, one disease” model toward therapies that can modulate multiple pathogenic mechanisms at once.⁸² Leukotriene signaling is particularly attractive in this context because it sits at the crossroads of innate immunity, OS, vascular integrity, and neuroinflammation, acting as a powerful biological amplifier instead of a simple downstream mediator.⁸³

Although leukotrienes are best known for their role in asthma and allergic rhinitis, accumulating evidence from immunology and vascular biology shows that they orchestrate broader chronic inflammatory processes.⁸⁴ They promote leukocyte recruitment, endothelial activation, cytokine production, oxidative injury, and tissue remodeling. In the eye, these effects intersect with nearly all major drivers of chronic disease, including barrier breakdown, mitochondrial dysfunction, microglial activation, and pathological angiogenesis.¹

This positions leukotriene antagonism as a complementary approach to existing treatments. Although anti-VEGF therapies excel at controlling neovascularization, they have limited impact on chronic inflammation or oxidative damage. Further, corticosteroids suppress inflammation broadly but carry risks of cataract, glaucoma, and infection with long-term use. In contrast, CysLT₁ antagonists such as montelukast target upstream amplification while offering a more favorable safety profile for potential chronic use.^{8,37}

A major advantage is the biological overlap across seemingly unrelated ocular conditions, such as dry eye, DR, glaucoma, AMD, retinal ischemia, and uveitis.¹ Despite different triggers, they involve shared processes in which leukotrienes play a central role. Thus, modulating this pathway could deliver benefits across multiple diseases rather than being limited to one indication.

From a practical standpoint, drug repurposing of an already-approved, well-tolerated agent such as montelukast is highly appealing. It aligns with modern pathway-focused pharmacology and could accelerate innovation in a field where new drug development is expensive and slow.^{8,85}

Accordingly, caution is warranted. Most supporting data remain preclinical, and the importance of leukotriene signaling likely varies across diseases and patients. Leukotriene modulation is unlikely to be a universal solution but may prove especially valuable in precision approaches targeting inflammatory phenotypes that are most responsive to this pathway.

Why Montelukast? A Drug Repurposing Perspective

Drug repurposing offers an efficient path to innovation, especially in ophthalmology, where high costs and regulatory barriers slow traditional development. By leveraging approved drugs’ established safety and pharmacokinetic profiles, researchers can address shared inflammatory and neurodegenerative pathways in eye diseases. Montelukast stands out as a compelling candidate.⁸⁶

Moreover, with over two decades of clinical use for asthma and allergic rhinitis, this selective CysLT₁ receptor antagonist boasts a well-documented safety record across age groups, predictable dosing, and known drug interactions, advantages that streamline translational efforts while reducing early development risks.

Beyond its primary action, montelukast also exhibits broad pleiotropic effects. According to evidence, it inhibits NF-κB activation, curbs pro-inflammatory cytokines and chemokines, mitigates OS, supports mitochondrial function, modulates immune cells, and reduces apoptosis. These actions closely conform to the multifactorial nature of chronic ocular conditions, where inflammation, vascular issues, oxidative damage, and neurodegeneration interconnect.⁸

Unlike therapies targeting single mediators (e.g., anti-VEGF or corticosteroids), montelukast’s multi-pathway influence could provide more comprehensive disease modification. It complements existing treatments by

operating through distinct mechanisms, potentially improving outcomes in retinal disorders with persistent inflammation or ocular surface conditions where long-term steroid use poses risks.

This interest mirrors advances in systems biology, revealing leukotriene signaling's wider roles in neuroinflammation, fibrosis, and tissue remodeling, extending far beyond airways.

Nonetheless, challenges remain. Optimal intraocular exposure from systemic dosing needs clarification, along with suitable biomarkers and dosing for eye indications. The boxed warning of the U.S. Food and Drug Administration on rare neuropsychiatric events requires careful patient selection and risk-benefit assessment for long-term off-label use.⁸⁷

These gaps highlight priorities for future work, pharmacokinetic studies, stratified trials, and iterative translation, rather than barriers. Montelukast's profile positions it well for network pharmacology in precision ophthalmology, where agents modulating interconnected pathways hold growing promise. In addition, its value lies in matching modern disease understanding with a versatile, accessible agent.⁸⁸

Pharmacological Advantages and Current Limitations

Successful drug repurposing hinges on more than strong biology; it demands practical feasibility, including safety, delivery, cost, and real-world applicability. Montelukast offers clear strengths here, tempered by notable gaps that define the path forward.⁵⁸

Its greatest advantage is its two decades of global clinical use. This real-world experience across different age groups has yielded a well-characterized pharmacokinetic profile, straightforward once-daily oral dosing, minimal monitoring requirements, and well-mapped drug interactions, all of which sharply lower barriers to use compared with novel agents.⁸⁹

For chronic ocular conditions, the oral route provides systemic modulation of inflammation that may complement local therapies, potentially improving adherence compared with frequent eye drops or intravitreal injections. As a low-cost generic, it also reduces the economic burden in resource-variable settings where repeated biologic treatments or procedures strain healthcare systems.⁹⁰

Montelukast's pleiotropic actions, spanning cytokine networks, OS, endothelial function, and cell survival, suit the interconnected pathology of retinal and ocular surface diseases better than single-target drugs.⁸ This multi-pronged profile supports broader disease modification without replacing current standards of care.

Nonetheless, limitations are significant. Ocular pharmacokinetics following standard oral doses remain poorly defined; it remains unclear whether therapeutic concentrations reliably reach the retina or posterior segment in humans.⁹¹ Existing formulations target systemic rather than ocular delivery, leaving opportunities for innovation in topical, sustained-release, or targeted systems, although these approaches remain in the early

stages of development.⁹²

Clinical evidence lags behind mechanistic data. Most of the available evidence comes from preclinical models, with few robust human trials available to guide dosing, duration, patient selection, or meaningful endpoints. Safety also warrants vigilance. Although montelukast is generally well-tolerated, neuropsychiatric risks have led to regulatory warnings, necessitating careful monitoring during off-label, long-term ophthalmic use, especially in vulnerable patients.⁹³

Therapeutic Opportunities Across Ocular Diseases

Leukotriene signaling acts as an upstream driver of chronic inflammation, OS, endothelial dysfunction, neuroinflammation, and pathological angiogenesis, processes that are central to many ocular conditions.⁹⁴ These mechanisms position montelukast as a versatile adjunct rather than a disease-specific cure, with its greatest potential in conditions where these pathways overlap and reinforce one another.

This reflects a shift from narrow, downstream therapies, including antihistamines for allergy, lubricants for dry eye, corticosteroids for uveitis, or anti-VEGF for neovascularization, toward network-level modulation that targets inflammatory pathways and may complement existing treatment options in complex chronic disorders.⁹⁵

Allergic conjunctivitis and vernal keratoconjunctivitis offer the most direct potential applications. By blocking CysLT₁-mediated eosinophil recruitment, mast cell activation, and vascular permeability, montelukast could benefit patients who continue to experience persistent symptoms despite standard care.

In dry eye disease, montelukast may interrupt the vicious cycle of epithelial injury, hyperosmolarity, oxidative damage, and innate immune activation, potentially improving tear stability and barrier function beyond providing symptomatic relief.

Posterior segment opportunities are particularly promising. In DR, it could address leukostasis, BRB breakdown, microglial activation, and OS, key drivers beyond pure microvascular damage. Studies in models show reduced inflammation and superior retinal preservation.⁹⁶

For AMD, especially non-neovascular forms, the effects of montelukast on chronic para-inflammation, oxidative injury, and RPE dysfunction may complement anti-VEGF therapy by supporting long-term retinal homeostasis.^{84,97,98}

In glaucoma, where neuroinflammation, mitochondrial dysfunction, and microglial activation contribute to ganglion cell loss, montelukast may offer potential neuroprotective effects alongside intraocular pressure-lowering therapies. Similar logic applies to retinal ischemia and optic nerve injury, where it may help limit secondary inflammatory cascades and apoptosis.^{99,100}

Combination Therapy and Precision Ophthalmology

Modern ophthalmic care is increasingly moving beyond single-agent "magic bullets" toward rational combination approaches that address interconnected disease networks

involving inflammation, OS, vascular issues, and neurodegeneration while embracing precision medicine.¹⁰¹

Montelukast fits well within this framework. Its leukotriene antagonism, coupled with its effects on OS, endothelial function, and innate immunity, complements rather than overlaps with established therapies such as anti-VEGF agents or corticosteroids.^{96,97}

In neovascular retinal diseases, adding montelukast may help address persistent inflammation and microglial activation that can limit anti-VEGF responses in some patients, potentially improving fluid resolution and long-term control. When used with corticosteroids, it provides a steroid-sparing option, reducing risks of cataract, glaucoma, or infection in chronic surface disease and uveitis.^{3,97}

Moreover, future regimens might pair montelukast with antioxidants, mitochondrial protectors, complement inhibitors, or neuroprotective agents, guided by emerging delivery technologies such as sustained-release implants or nanoparticles in order to achieve targeted ocular concentrations while limiting systemic exposure.¹⁰²

Precision ophthalmology further elevates its potential. Clinically similar conditions frequently differ molecularly; patients with prominent leukotriene-driven inflammation, eosinophilic activity, or microglial activation are more likely to benefit than those dominated by other pathways. Biomarker development, measuring cysteinyl leukotrienes in tears/aqueous, cytokine profiles, or imaging signs of inflammation, combined with artificial intelligence-driven multimodal analysis, could enable tailored selection.¹⁰³

Challenges to Clinical Translation

Strong biology alone rarely guarantees clinical success, as many promising agents falter in translation. For montelukast in ophthalmology, several practical hurdles must be overcome before it can progress from experimental interest to routine clinical use.^{58,104}

Ocular pharmacokinetics remains a major knowledge gap. Although plasma levels are predictable, the distribution of montelukast into retinal, choroidal, vitreous, and aqueous tissues following oral dosing is poorly characterized, making it unclear whether approved respiratory doses achieve meaningful target engagement in ocular tissues.¹⁰⁵

Drug delivery poses another barrier. The eye's tight barriers limit drug penetration, while conventional oral formulations were not designed for ocular use. Exploring nanoparticles, liposomes, implants, hydrogels, or sustained-release systems could enhance local efficacy while reducing systemic exposure.¹⁰²

Validated biomarkers remain lacking. Tools to measure leukotriene pathway activity, microglial activation, or OS in ocular fluids or tissues are required for patient selection and monitoring, both of which are essential for precision approaches.¹⁰⁶

Patient heterogeneity further complicates this issue. Diseases such as DR, AMD, glaucoma, and dry eye encompass diverse molecular endotypes; thus, montelukast will likely benefit specific inflammatory subtypes rather

than producing uniform effects across all patients.¹⁰⁷

Clinical trials must evolve beyond preclinical histological findings or changes in cytokine to include vision-related outcomes (visual acuity, optical coherence tomography metrics, and visual fields), quality-of-life measures, and integrated biomarkers. The optimal positioning of montelukast, whether as adjunct, steroid-sparing agent, or maintenance therapy, also requires further definition.¹⁰⁸

Regulatory and safety considerations include existing neuropsychiatric warnings, necessitating vigilant long-term monitoring, especially in older populations. Although repurposing may accelerate the approval process, robust evidence of efficacy and ocular safety data remain essential.⁸⁷

Diabetic Retinopathy

DR is now understood as a neurovascular disorder in which low-grade chronic inflammation accelerates vascular damage and neuronal loss. Preclinical studies in streptozotocin-induced diabetes and related ischemia models have confirmed that montelukast reduces leukostasis, limits vascular permeability, dampens OS, and protects retinal ganglion cells from apoptosis. These benefits appear to be linked to the modulation of microglial activation and preservation of the BRB.^{3,96}

Clinical evidence is still sparse, with no large randomized controlled trials currently available. Some observational data hint at lower odds of DR among patients taking montelukast, although confounding factors limit the interpretation of these findings. The drug may hold value as an adjunct to anti-VEGF therapy, particularly in patients with prominent inflammatory components. Accordingly, future work should prioritize ocular pharmacokinetics and inflammation biomarkers to identify responsive subgroups.¹⁰⁹

Glaucoma

Beyond elevated intraocular pressure, glaucoma involves progressive retinal ganglion cell loss driven by neuroinflammation, OS, and mitochondrial dysfunction. Experimental models of retinal ischemia-reperfusion and optic nerve crush have demonstrated that montelukast attenuates microglial activation, reduces oxidative damage, and improves ganglion cell survival, with these effects appearing to be partly independent of pressure lowering.^{110,111}

Human data remain essentially nonexistent, with no dedicated clinical trials conducted to date. Montelukast could be explored as a targeted neuroprotective add-on for patients who continue to progress despite adequate pressure control. Therefore, biomarker-driven studies incorporating structural and functional imaging will be essential to evaluate this concept.

Dry Eye Disease

Dry eye disease is a self-perpetuating inflammatory disorder of the ocular surface. In animal models of desiccating stress, montelukast has been shown to decrease inflammatory cell

infiltration, suppress pro-inflammatory cytokines, and help maintain corneal epithelial integrity and goblet cell density. Likewise, its antioxidant effects appear to play a supportive role.¹¹²

Clinical studies remain limited and heterogeneous. The drug may offer benefit in inflammatory-dominant subtypes, especially those with eosinophilic features. Topical formulations (e.g., eye drops or nanoparticle carriers) could enhance local efficacy while minimizing systemic exposure.

Allergic Conjunctivitis

Allergic conjunctivitis, particularly vernal keratoconjunctivitis, provides the strongest clinical evidence for the use of montelukast. Several trials have reported improvements in itching, redness, tearing, and overall symptom scores, especially when this drug is used with antihistamines. The agent effectively targets the late-phase allergic response.¹¹³

However, montelukast is not considered a first-line therapy and is most useful in moderate-to-severe cases or when allergic rhinitis is also present. The development of topical ocular preparations could further expand its therapeutic utility.

Retinal Ischemia and Optic Nerve Injury

Models of retinal ischemia-reperfusion and optic nerve crush provide some of the most consistent preclinical support. Montelukast reduces microglial activation, stabilizes the BRB, limits oxidative injury, and enhances neuronal survival. These multifaceted effects create a plausible therapeutic window for secondary injury prevention after acute ischemic events.¹¹¹

No clinical trials have been conducted so far. Given the acute nature of these conditions, combination approaches incorporating reperfusion strategies and advanced intraocular delivery systems warrant further exploration.

Age-Related Macular Degeneration

In AMD, chronic para-inflammation and OS contribute to RPE and photoreceptor degeneration. Limited preclinical work suggests montelukast can reduce microglial activation, preserve mitochondrial function, and modestly influence inflammatory angiogenic pathways.⁹⁷

This remains an exploratory area. Although montelukast might eventually serve as an adjunct in neovascular AMD or in dry AMD, robust pharmacokinetic and biomarker data are required before clinical testing.

Uveitis

Experimental models of endotoxin-induced and autoimmune uveitis demonstrate that montelukast decreases leukocyte infiltration, cytokine levels, and oxidative damage while supporting BOB integrity. Similarly, its potential as a steroid-sparing agent is particularly appealing.^{114,115}

Clinical evidence is limited. This drug could be considered for chronic non-infectious uveitis as part of

a multimodal regimen aimed at reducing corticosteroid dependence. Patient stratification based on inflammatory endotypes will be critical in future studies.

Conclusion

The expanding understanding of leukotriene biology has fundamentally reshaped our perception of inflammatory mechanisms in ocular disease. Once regarded primarily as mediators of allergic airway inflammation, cysteinyl leukotrienes are now recognized as multifunctional regulators that integrate innate and adaptive immunity, OS, endothelial dysfunction, mitochondrial impairment, and neurodegeneration.¹¹⁶ These interconnected processes are shared across a remarkably broad spectrum of ocular disorders, including allergic conjunctivitis, dry eye disease, uveitis, DR, age-related macular degeneration, glaucoma, and retinal ischemic injury.^{8,83} Consequently, leukotriene signaling should no longer be viewed as a disease-specific pathway but rather as a common inflammatory network linking anterior and posterior segment pathology.

Within this framework, montelukast represents the most clinically accessible pharmacological tool for interrogating the therapeutic potential of leukotriene inhibition in ophthalmology. Beyond its established role as a selective CysLT₁ receptor antagonist, accumulating evidence demonstrates that this drug exerts pleiotropic biological effects extending to the suppression of NF- κ B-mediated inflammation, attenuation of OS, preservation of mitochondrial function, stabilization of vascular barriers, modulation of microglial activation, and inhibition of apoptosis.⁹⁶ These complementary mechanisms closely parallel the pathological processes underlying retinal neurodegeneration and chronic ocular inflammation, providing a compelling biological rationale for repurposing the drug in age-related macular degeneration.⁶⁸

The strength of current evidence, however, varies substantially across disease entities. Allergic conjunctivitis possesses the most mature clinical evidence base, whereas DR, glaucoma, and retinal ischemia display the strongest convergence of mechanistic plausibility and reproducible preclinical efficacy.^{8,117} By contrast, evidence supporting the use of montelukast in age-related macular degeneration and uveitis remains largely exploratory, emphasizing the need for further mechanistic and translational investigation. Importantly, this heterogeneity should be viewed as a reflection of different stages of therapeutic development across the ophthalmic disease spectrum, rather than being interpreted as inconsistency.

Despite the growing body of experimental evidence, translation into clinical ophthalmology has remained limited. This gap appears to reflect pharmacological and technological challenges instead of a lack of biological relevance. High plasma protein binding, uncertain intraocular pharmacokinetics following systemic administration, and the lack of optimized ophthalmic formulations may restrict effective drug exposure in posterior segment tissues.¹⁰⁵ Thus, a central conclusion emerging from this review is that the principal barrier to

clinical implementation is not target validation but rather efficient ocular drug delivery. Hence, future advances in sustained-release systems, biodegradable nanoparticles, liposomal carriers, hydrogel platforms, microneedle technologies, and suprachoroidal or intravitreal delivery may substantially enhance retinal bioavailability while minimizing systemic exposure.⁵⁹

Equally important is the transition from empirical treatment toward precision ophthalmology. Increasing recognition of the biological heterogeneity underlying ocular diseases suggests that leukotriene-directed therapies are unlikely to benefit all patients equally.¹⁰³ Accordingly, integration of tear and aqueous humor lipidomics, inflammatory biomarker profiling, single-cell transcriptomics, spatial transcriptomics, multimodal retinal imaging, and artificial intelligence-assisted phenotyping may enable the identification of patients with leukotriene-driven inflammatory signatures who are most likely to respond to targeted intervention.⁹⁷ Moreover, such biomarker-guided approaches have the potential to transform montelukast from a broadly administered anti-inflammatory agent into a precision therapeutic tailored to specific molecular disease endotypes.¹¹⁶

The future of leukotriene-targeted therapy will almost certainly extend beyond montelukast itself. Advances in medicinal chemistry and drug discovery are rapidly expanding the therapeutic landscape to include selective CysLT₂ receptor antagonists, dual leukotriene receptor inhibitors, 5-LOX and lipoxygenase-activating protein inhibitors, RNA-based therapeutics, gene-editing technologies, and next-generation targeted delivery systems.¹¹⁸ These emerging strategies may overcome many of the pharmacokinetic and pharmacodynamic limitations associated with current therapies while providing more comprehensive modulation of leukotriene signaling within ocular tissues.¹¹⁹

In general, the available evidence supports a conceptual shift in ophthalmic pharmacology. Rather than representing a niche pathway confined to allergic disease, leukotriene signaling appears to function as a central regulator linking inflammation, OS, vascular dysfunction, and neurodegeneration across multiple ocular disorders. Likewise, montelukast provides a valuable proof-of-concept for the therapeutic modulation of this pathway, although its greatest contribution may ultimately lie in establishing the biological validity of leukotriene-directed intervention instead of serving as the definitive therapeutic agent. Future progress will depend on rigorous mechanistic studies, optimized ocular drug-delivery platforms, biomarker-guided patient selection, and well-designed randomized clinical trials capable of translating compelling experimental findings into clinically meaningful outcomes. If these challenges are successfully addressed, targeting leukotriene signaling may emerge as a novel disease-modifying strategy that complements existing therapies and broadens the therapeutic armamentarium for both anterior and posterior segment diseases.

Artificial Intelligence Use Disclosure

During the preparation of this work, QuillBot was employed to correct grammar errors and improve the clarity and coherence of the language. Moreover, ChatGPT was used to draw a better visualization of the graphical abstract. The authors carefully examined and revised the content after utilizing this tool or service. Finally, they wholeheartedly accept responsibility for the publication's content.

Authors' Contribution

Conceptualization: Safieh Amiraslanzadeh, Mojtaba Ziaee
Data Curation: Safieh Amiraslanzadeh, Hamid Mahmoudpour
Investigation: Safieh Amiraslanzadeh, Hamid Mahmoudpour
Supervision: Mojtaba Ziaee
Validation: Mojtaba Ziaee
Writing—Original Draft: Safieh Amiraslanzadeh
Writing—Review & Editing: Hamid Mahmoudpour, Mojtaba Ziaee

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