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Nano formulations of quercetin for ocular delivery

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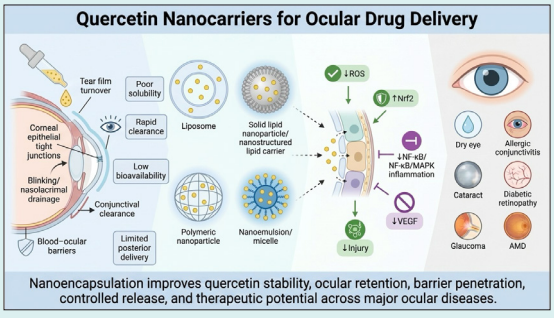
Abstract

Quercetin (QUE), a bioactive flavonoid with potent antioxidant, anti-inflammatory, and neuroprotective properties, has emerged as a promising therapeutic candidate for age-related macular degeneration, diabetic retinopathy, cataracts, glaucoma, dry eye disease, and allergic conjunctivitis. Its therapeutic effects are primarily mediated through modulation of key molecular pathways, including direct scavenging of reactive oxygen species (ROS), activation of Nrf2-dependent antioxidant responses, inhibition of NF-κB and MAPK signaling, and downregulation of pro-inflammatory cytokines and angiogenic mediators such as VEGF. However, effective ocular delivery of QUE remains challenging because anatomical and physiological barriers severely limit drug penetration and retention, and because QUE itself exhibits poor aqueous solubility, chemical instability, rapid clearance, and a narrow therapeutic window at the tissue level. Recent advances in nanotechnology-based delivery systems including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, micelles, and polymeric nanoparticles have shown considerable potential to enhance corneal and scleral permeability, prolong ocular residence time, improve QUE stability and bioavailability, and enable more controlled local exposure. This review critically evaluates recent progress in QUE-loaded nanocarriers for ocular drug delivery, integrating mechanistic insights, formulation strategies, and preclinical and emerging clinical data, and discusses key challenges and opportunities for the safe and effective clinical translation of quercetin-based ocular nanotherapeutics.



Introduction

The complex structural and physiological features of the human eye pose significant challenges for the effective delivery of therapeutic agents in ocular pharmacology.[1] These challenges arise chiefly from the eye's complex defence mechanisms, which comprise both dynamic and static barriers.[2] The dynamic barriers such as choroidal and conjunctival blood flow, lymphatic drainage, and rapid tear film turnover further obscure drug delivery by successively diluting and removing topically administered formulations, while the static barriers, including the cornea, sclera, and retina, along with the blood-aqueous and blood-retinal barriers, considerably restrict drug penetration to the target tissues.[3-5] Standard ophthalmic dosage forms, such as eye drops, display low bioavailability, typically below 5%, mainly because of pre-corneal drug loss and inadequate corneal penetrability. The corneal epithelial layer serves as a selective barrier that reduces the transit

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time of small lipophilic agents and entraps hydrophilic drugs, which often remain restricted within stromal partitions.[6,7] These physical barriers underscore the need to develop sophisticated ocular drug delivery systems capable of achieving and maintaining therapeutic levels at the target site.

Over the past decade, quercetin has attracted growing interest in ophthalmology as a pleiotropic small molecule capable of modulating oxidative stress, inflammation, angiogenesis, and fibrosis across multiple ocular tissues.[8,9] Preclinical studies now span a wide spectrum of indications, including age-related macular degeneration, diabetic retinopathy, glaucoma, cataract, dry eye disease, and allergic conjunctivitis, and encompass both free quercetin and an expanding array of nanoengineered formulations.[9,10] At the same time, several clinical and translational studies have begun to explore oral and topical quercetin-containing products in patients with dry eye–related symptoms, allergic conjunctivitis, and age-related macular degeneration, underscoring the need to integrate mechanistic, formulation, and early clinical data into a coherent framework.[11,12] Despite this broad pharmacological profile, the clinical translation of quercetin in ophthalmology remains limited. Its poor aqueous solubility, low chemical stability, extensive first-pass metabolism, and short biological half-life reduce ocular exposure when administered using conventional formulations such as eye drops or systemic supplements.[8,10,13-15] Moreover, preclinical data suggest that quercetin may exert concentration-dependent cytotoxicity in ocular cells, including human lens epithelial and retinal pigment epithelial cells, highlighting a narrow therapeutic window at the tissue level and the importance of tightly controlled local delivery. These biopharmaceutical and safety constraints, combined with the eye's anatomical and physiological barriers, create a strong rationale for advanced delivery systems that can both enhance quercetin bioavailability and modulate intraocular exposure over time. Further clinical studies indicate that quercetin is generally well tolerated as an oral supplement at daily doses up to 1000–1250 mg, yet preclinical data show that high local concentrations can be cytotoxic to human lens epithelial and retinal pigment epithelial cells, promoting apoptosis and DNA damage.[8,10,13-15] These findings underscore the importance of delivery systems that achieve therapeutically effective, but not excessive, intraocular levels, reinforcing the rationale for nanoformulations designed to control local concentrations and release profiles at the ocular surface and posterior segment.Nanotechnology-based drug delivery systems have garnered attention for addressing these hurdles, including pre-corneal elimination, corneal shielding, and the blood-ocular barrier.[5] Nanoformulation techniques for loading lipophilic and hydrophilic drugs have shown tremendous promise in enhancing ocular permeability, prolonging coating residence time, and improving stability and bioavailability.[3,6] These nanocarriers also accelerate targeted drug release, increase solubility, and aid site-specific delivery, aligning with the urgent need for new treatments and the integration of therapeutic drugs into these cutting-edge technologies. This study reviews current developments in QUE nanoformulation techniques, emphasising the design and utilisation of a range of nanocarriers, including solid lipid nanoparticles (SLNs), liposomes, nanoemulsions, and polymeric nanoparticles. By enabling controlled, prolonged drug release via targeted administration to specific ocular tissues, these novel delivery systems have demonstrated the capacity to enhance QUE's ocular penetration. Several reviews have discussed either the general pharmacology of quercetin or the broader field of ocular nano-drug delivery, but none, to our knowledge, has systematically integrated quercetin's disease-specific mechanisms of action with up-to-date nanoformulation strategies and emerging clinical evidence in ophthalmology.

The present review aims to fill this gap by (i) mapping quercetin's molecular and cellular effects onto the pathophysiology of major ocular diseases, (ii) critically analyzing recent advances in quercetin-based nanoformulations for anterior and posterior segment delivery, and (iii) highlighting translational challenges related to toxicity, dose control, regulatory requirements, and clinical trial design. By clearly linking mechanistic insights, formulation choices, and early clinical data, this review provides a focused framework to guide the rational development of quercetin-based ocular nanotherapeutics and to identify priority areas for future research.

Quercetin and ocular diseases

The human eye, a complex organ responsible for vision, is commonly affected by severe conditions such as age-related macular degeneration (AMD), cataracts, diabetic retinopathy, and glaucoma.[16] The aetiology of many of these ailments is the same: persistent inflammation and oxidative stress, which damage eye cells, impair their function, and eventually lead to vision loss.[17-20] Taken together, QUE, a widespread natural flavanol derivative found in numerous fruits, vegetables, and herbs, has recently drawn attention for its robust anti-inflammatory and antioxidant effects.[21-23] However, the therapeutic application of QUE is significantly hampered by its inherent limitations. QUE is challenging to use as a treatment because it doesn't dissolve well in water, isn't readily absorbed by the body, and degrades quickly. These difficulties are compounded by the eye's protective structure, which limits how well drugs can reach their target areas.[24-27] These factors highlight the acute need for advanced delivery systems that can augment QUE's stability, solubility, and targeted transport to ocular tissues.

The human eye's ocular anatomy and conditions that QUE's efficient administration could improve. Conjunctivitis, dry eye, keratoconus, cataract, Graves' orbitopathy, retinoblastoma, optic neuropathy, diabetic retinopathy, and proliferative vitreoretinopathy are associated eye conditions.[9] Retinoblastoma (RB) causes prevalent malignancy and they usually occur in under the age of 5 years old. QUE was formerly identified to impede

tumor growth in certain malignancies by induced cell apoptosis and oxidative stress.[9]

Molecular mechanisms of quercetin's action in ocular tissues

QUE's capacity to regulate both oxidative stress and inflammatory signalling pathways is a major contributor to its therapeutic success in ocular diseases.[28] Oxidative stress, arising from an imbalance between the body's antioxidant defences and the generation of ROS,[29] is a leading cause of ocular tissue damage and disease progression. By directly scavenging ROS, quercetin reduces oxidative damage to cellular components and thereby provides protection.[28] Furthermore, it enhances endogenous antioxidant defences by activating the enzyme paraoxonase 2 (PON2) and the Nrf2-ARE pathway, both of which help reduce oxidative and inflammatory stress.

Solid quercetin (Q-SD) treatment dramatically decreased ROS and MDA levels in animal models of dry AMD while restoring the activity of glutathione peroxidase (GSH-Px), catalase (CAT), and superoxide dismutase (SOD), three essential antioxidant enzymes, in both blood and retinal tissues. These defence mechanisms were tightly linked to Nrf2 activation.[30] Moreover, Q-SD increased Nrf2 mRNA expression and promoted its nuclear translocation, which in turn increased the expression of downstream antioxidant genes such as GCL, HO-1, and HQO-1.[31] Quercetin protects ocular cells from oxidative damage largely through the stimulation of endogenous antioxidant enzymes.

In addition to its antioxidant properties, QAE has potent anti-inflammatory effects. Diabetic retinopathy and AMD are two visual disorders significantly influenced by chronic inflammation in their onset and progression. By inhibiting the activation of the nuclear factor-kappa B (NF-κB) pathway, a key regulator of pro-inflammatory cytokine and chemokine production, QAE primarily reduces inflammation. Studies have shown that QAE downregulates multiple inflammatory mediators, including IL-6, IL-8, IP-10, IL-1β, IL-18, and TNF-α.[8,32] In retinal pigment epithelial (ARPE-19) cells, QAE reduced inflammatory signalling by inhibiting the mitogen-activated protein kinase (MAPK) pathway and decreasing CREB phosphorylation. Likewise, in a rat model of diabetic retinopathy, QAE dramatically reduced the overproduction of pro-inflammatory cytokines in retinal tissues, including interleukin-1β, interleukin-18, interleukin-6, and tumour necrosis factor.[33] These anti-inflammatory properties are essential for sustaining visual function and retinal structure.[34]

Therapeutic potential of QAE in ocular diseases

QAE's diverse molecular mechanisms contribute to its broad therapeutic applications in ophthalmic disorders.

Glaucoma

Oxidative stress is a primary contributor to the development and progression of glaucoma. As QUE suppresses inflammatory responses and boosts endogenous antioxidant defences, it may confer neuroprotective benefits to ocular tissues affected by this illness.[35] Although few clinical studies specifically evaluate QUE in glaucoma, its ability to reduce oxidative damage and inflammation makes it a promising adjuvant therapeutic option.[28] In glaucoma, retinal ganglion cell loss is closely linked to mitochondrial dysfunction and chronic oxidative and inflammatory stress at the optic nerve head.[36] Quercetin's capacity to preserve mitochondrial function, enhance endogenous antioxidant enzymes, and modulate microglial activation suggests a direct neuroprotective role that could complement intraocular pressure-lowering therapies.[36] While human glaucoma trials of quercetin have not yet been reported, these mechanistic insights support its investigation as an adjunctive neuroprotective agent, particularly using sustained-release intraocular or periocular Nanoformulations.[36]

Diabetic retinopathy

Diabetic retinopathy is a serious microvascular complication of diabetes characterised by chronic inflammation, abnormal neovascularisation, and progressive retinal neuronal apoptosis.[37] QUE shows potential to preserve retinal structure and function in diabetic retinopathy by inhibiting neovascularisation, preventing retinal cell death, reducing pro-inflammatory cytokines, and increasing neurotrophic factor levels.[33] In a rat model of streptozotocin-induced diabetic retinopathy, QUE markedly increased retinal cell layer thickness, increased ganglion cell count, and decreased pro-inflammatory cytokine levels. The study demonstrated that QUEs upregulate heme oxygenase-1 (HO-1) expression, which has a neuroprotective role in diabetic retinopathy. QUE also suppresses the overexpression of TLR4 and NF-κB p65, as well as pro-angiogenic factors such as VEGF and sICAM-1, which reduces abnormal blood vessel growth in diabetic retinopathy.[33] Building on the antioxidant and anti-inflammatory mechanisms described above, quercetin preserves retinal structure and function in diabetic retinopathy by limiting neovascularisation and neuronal apoptosis, which translates into increased retinal layer thickness, higher ganglion cell counts, and reduced inflammatory and pro-angiogenic markers in experimental models.

Age-related macular degeneration

By activating Nrf2 and dampening inflammatory chemokines, quercetin mitigates RPE damage and Bruch's membrane thickening in dry AMD models, consistent with its previously outlined antioxidant and anti-inflammatory actions.[21,30] Conventional pre-treatment with QUE shows promises as an effective strategy for controlling retinal inflammation and preserving visual function in AMD *in vivo*.[38] A solid dispersion of QUE has been shown to reduce retinal pigment epithelial deposits and Bruch's membrane thickness in a mouse model of dry AMD, activate Nrf2 signalling, and upregulate antioxidant enzymes.[30] These antioxidant, anti-inflammatory, and anti-angiogenic actions are particularly relevant for early and intermediate dry AMD, where oxidative stress, para-inflammatory activation, and subclinical choroidal neovascularisation drive disease progression.[36] Although clinical evidence

remains preliminary, quercetin is now being evaluated in combination with resveratrol and curcumin in a phase 2 oral trial for dry AMD, aiming to determine whether sustained targeting of oxidative stress and inflammatory pathways can slow functional decline beyond what is achievable with the current standard of care.[36] Such efforts underscore the translational potential of quercetin-based strategies, especially when coupled with delivery systems that achieve therapeutic levels at the retina and retinal pigment epithelium.[36]

Allergic conjunctivitis

Allergic conjunctivitis (AC) is a common eye condition caused by allergens such as pollen and dust, which can irritate the conjunctiva.[39-41] Symptoms include itching, photophobia, eyelid swelling, redness, and increased tearing. Current treatments include antihistamines, mast cell stabilisers, anti-inflammatory drugs, steroids, and immunosuppressants.[42] However, chronic steroid use can lead to serious adverse effects such as glaucoma and Cushing's syndrome, and antihistamines and mast cell stabilisers do not address neutrophil and eosinophil activity. QAE is a naturally occurring antioxidant with strong anti-inflammatory and anti-allergic properties, according to studies. It has been shown to inhibit specific inflammatory cytokines and protect eye cells from UV-B-induced oxidative damage. Animal studies further demonstrate that QUE can alleviate allergic responses in AC models. This protective action is mediated primarily by suppressing excessive immune responses and downregulating pro-inflammatory cytokine production. Together, these findings highlight QUE's potential as a promising therapeutic candidate for the management of ocular inflammatory disorders.[9] Mechanistically, quercetin's inhibition of Lyn kinase and downstream PLCγ/IP3R–Ca^{2+} signaling reduces mast-cell degranulation and IgE-mediated mediator release, directly targeting pathways that drive conjunctival itching, hyperemia, and tear film instability in allergic conjunctivitis.[12,43] Consistent with this, oral administration of a bioavailable quercetin phytosome formulation (500 mg/day) as add-on therapy in adults with allergic conjunctivitis improved validated ocular symptom scores and tear film stability. It helped prevent clinical exacerbations despite tapering topical antihistamines, indicating that these molecular effects can be leveraged to alleviate clinical signs and symptoms.

Dry eye disease

Dry eye disease (DED) is a prevalent ocular disorder that substantially impairs visual function and overall quality of life by causing persistent discomfort and visual instability.[44] Studies show that conventional topical QUE can improve ocular surface conditions in dry-eyed mouse models. It increases tear volume and the number of goblet cells. Its anti-inflammatory action may also help restore normal lacrimal gland function.[45] QAE eye drops have been shown to reduce ocular surface inflammation in DED models.[9]

Beyond preclinical models, quercetin's antioxidant modulation of the lacrimal functional unit has begun to show relevance in humans; oral quercetin supplementation lengthened tear film breakup time and reduced oxidative DNA damage marker 8-OHdG in tears, suggesting that Nrf2-mediated redox control in the lacrimal gland can translate into measurable improvement in tear film quality in clinical settings.[11,46-48] These findings support the concept that nanoformulations designed to deliver quercetin to the ocular surface and adnexal glands may not only restore tear quantity and goblet cell density, as shown in animal models, but also improve tear stability and oxidative stress profiles in patients with DED.

Cataracts

Cataracts arise from a combination of factors, including genetics, environmental exposure, and lifestyle habits.[49] They also involve structural and functional changes in lens proteins. Key mechanisms include oxidative stress, excessive apoptosis of lens epithelial cells, and alterations in lens proteins. The protective effects of QUE against cataract induction have been confirmed in in vitro and in vivo laboratory studies, consistent with its antioxidant and chelating properties.[50]

This prevents protein aggregation and maintains the lens's clarity. It also inhibits damaging enzyme activity that may contribute to eye injury. QAE may also be beneficial in preventing cataract onset by regulating intracellular calcium homeostasis and reducing oxidative stress[9]. QAE applies to various eye diseases. Its potent anti-inflammatory and antioxidant properties make it a practical choice for addressing issues such as dry eye disease, allergic conjunctivitis and cataracts. Since lens opacification is driven by oxidative damage, calpain activation, and protein aggregation, quercetin's metal-chelating and anti-oxidative effects directly address core pathogenic mechanisms of cataractogenesis.[15,36] In vivo, quercetin-rich formulations have been shown to delay cataract formation in experimental models. At the same time, early senotherapeutic approaches combining dasatinib and quercetin slowed choroidal neovascularisation in AMD, suggesting that targeting senescent, pro-oxidant cells may also be relevant to age-related lens pathology.[15,36] Although controlled clinical trials of quercetin for cataract prevention are not yet available, these mechanistic data justify further evaluation of topical and systemic quercetin, especially in nanoformulations able to reach lens epithelial cells.[15,36]

Collectively, these pathways map onto distinct stages of major ocular diseases: Nrf2-driven reinforcement of antioxidant defences is central to limiting photoreceptor and RPE damage in AMD and oxidative injury in cataract and DED; inhibition of NF-κB and pro-inflammatory cytokines is critical in diabetic retinopathy, DED, and allergic conjunctivitis; and suppression of VEGF and related angiogenic mediators directly targets neovascular processes in AMD and proliferative diabetic retinopathy. By aligning specific molecular actions with disease-defining mechanisms, quercetin provides a mechanistically coherent framework for multi-target therapy, which can now begin to be tested in clinical and translational studies, particularly when delivered via optimised ocular nanoformulations.

Human clinical and translational studies of quercetin in ocular conditions

Human evidence for quercetin in ocular disorders remains preliminary but clinically relevant, particularly for ocular surface symptoms, allergic conjunctivitis, and dry AMD. As summarized in Table 1, the available clinical and translational studies primarily focus on oral quercetin or quercetin-containing nutraceutical formulations rather than ophthalmic quercetin-loaded nanocarriers. Therefore, these studies should be interpreted as early human evidence supporting quercetin's biological relevance in ocular disease, but not yet as direct clinical validation of ocular nano formulations.

One pilot human study showed that oral intake of quercetin-rich onion powder was associated with detectable quercetin-related metabolites in tears and improvement

Table 1. Human clinical and translational studies of quercetin in ocular conditions

Study / indication	NCT / registry identifier	Phase	Date	Country	Design / population	Intervention	Key ocular endpoints	Key details / findings
Oral quercetin-rich onion powder and tear function / dry-eye-related tear quality	UMIN (UMIN000037092)	Not applicable	Published: 6 Oct 2022	Japan	Pilot human study in healthy volunteers; double-blind crossover component with 7 healthy volunteers	Onion powder with high vs low quercetin content, short-term intake	Tear quercetin/metabolite levels, tear film breakup time, tear oxidative stress marker 8-OHdG	Quercetin and metabolites were detected in tears after oral intake; high-quercetin onion intake improved tear film stability and reduced tear oxidative stress markers. This should be described as a pilot human translational study, not a registered clinical trial.[11]
Quercetin-containing supplement for allergic rhino-conjunctivitis / pollinosis	UMIN000038765; no NCT identified	Not applicable	Registered/start: 3 Dec 2019; last follow-up: 4 Apr 2020; published: 2022	Japan	Randomized, double-blind, placebo-controlled, parallel-group trial; 66 adults with pollinosis/allergic symptoms	Quercetin phytosome-containing supplement, 200 mg/day, vs placebo for 4 weeks	Japanese Rhino-conjunctivitis Quality of Life Questionnaire, eye itching, tearing, nasal symptoms, VAS, QOL	The quercetin group showed improvement in several JRQLQ items, including ocular itching and allergy-related QOL. Use the UMIN identifier because this trial was registered in Japan rather than ClinicalTrials.gov.[51, 52]
Oral quercetin phytosome as add-on therapy in allergic conjunctivitis	No NCT reported	Not applicable	Received: 10 Oct 2022; published: 11 Nov 2022	Italy	Human case series; 15 subjects / 30 eyes with allergic conjunctivitis	Quercefit™ quercetin phytosome 500 mg/day for 2 weeks, with olopatadine 0.1% eye drops; quercetin continued after topical therapy suspension	Total Ocular Symptom Score, non-invasive tear breakup time	TOSS and tear-film stability improved after supplementation. Because this was a small case series without placebo/randomization, it should be listed as a clinical case series, not as a phased clinical trial.[54]
RQC for preventing progression in age-related macular degeneration	NCT05062486	Phase 2	Study start: 4 Oct 2021; estimated completion: 7 Nov 2024; status reported as completed in 2025 databases	United States	Open-label, randomized, two-arm, single-blind Phase 2 study in dry AMD; registry lists 55 participants	RQC: resveratrol 100 mg BID, quercetin 120 mg BID, curcumin 1000 mg BID vs curcumin 1000 mg BID for 24 months	Drusen volume, geographic atrophy growth, progression to moderate vision loss, progression to advanced AMD, safety	This is the key registered quercetin-containing ocular trial. Update the manuscript from "ongoing" to "completed/reported as completed" if using current registry status.[53]

in tear film stability, supporting the concept that orally administered quercetin can reach the lacrimal functional unit and influence tear physiology. This finding is relevant to dry eye disease because oxidative stress in the lacrimal gland and ocular surface contributes to tear film instability and ocular discomfort. However, because this was a pilot translational study rather than a large randomized ophthalmic trial, its findings should be presented cautiously and used mainly to support mechanistic plausibility.

Clinical evidence is comparatively stronger for allergy-related ocular symptoms. A randomized, placebo-controlled, double-blind, parallel-group study (UMIN000038765) evaluated a quercetin-containing supplement in Japanese adults with allergic symptoms of the nose and/or eyes. The study was registered on 3 December 2019, conducted from 3 December 2019 to 4 April 2020, and enrolled 66 adults with allergic symptoms assessed using the Japanese Rhino-conjunctivitis Quality of Life Questionnaire.[51,52] The intervention used a quercetin phytosome formulation, and improvements in allergy-related symptoms, including ocular itching, were reported. This study supports the anti-allergic and anti-inflammatory relevance of quercetin in rhino-conjunctivitis, although it was not specifically designed as an ophthalmic drug-delivery trial.

Additional clinical support comes from a small case series evaluating oral quercetin Phytosome™ as an add-on approach in adults with allergic conjunctivitis. In this study, 15 subjects with allergic conjunctivitis received 500 mg/day quercetin Phytosome™ for 2 weeks alongside topical olopatadine, followed by continued supplementation after the suspension of topical therapy. Outcomes included Total Ocular Symptom Score and non-invasive tear breakup time, and the authors reported improvement in ocular symptoms and tear film stability.[51,52] Nevertheless, the lack of placebo control, small sample size, and case-series design limit the strength of the evidence, so this study should be described as exploratory clinical evidence rather than confirmatory efficacy data.

For posterior-segment disease, the most relevant registered clinical trial is NCT05062486, a Phase 2 study evaluating resveratrol, quercetin, and curcumin (RQC) compared with curcumin alone in AMD. The registry lists the study as completed, with a study start date of 4 October 2021, an estimated completion date of 7 November 2024, and a study site in Chicago, Illinois, United States.[53] The intervention includes oral RQC containing resveratrol, quercetin, and curcumin, while the main outcomes include drusen volume, geographic atrophy growth, progression to moderate vision loss, and progression to advanced AMD. This trial is important because it shifts quercetin from ocular surface symptom control toward retinal disease modification.[53] However, it evaluates quercetin as part of a polyphenol combination rather than as an isolated quercetin formulation or ocular nanocarrier.

Overall, current human studies suggest that quercetin may improve tear film-related parameters, reduce allergy-associated ocular symptoms, and contribute to antioxidant or anti-inflammatory strategies in dry AMD. However, the available evidence remains limited by small sample sizes, reliance on oral supplementation, heterogeneous formulations, and the absence of completed clinical trials directly testing quercetin-loaded ocular nanocarriers. Future studies should therefore prioritize well-designed ophthalmic trials that evaluate topical or intraocular quercetin nanoformulations, define ocular pharmacokinetics, compare nanocarriers with conventional formulations, and assess clinically meaningful endpoints, including tear stability, corneal staining, retinal imaging outcomes, visual function, dosing frequency, and long-term ocular safety.

These investigations, summarised in Table 1, demonstrate that quercetin can beneficially modulate tear film stability, allergic ocular symptoms, and oxidative stress markers, and is now being prospectively evaluated in dry AMD, thereby providing a critical bridge between the molecular mechanisms discussed above and their potential clinical impact.

Conventional delivery challenges and the need for nanoformulations

QAE shows great therapeutic potential; however, its application to ocular diseases is restricted by formulation development and delivery issues.[55,56] These problems are mainly due to classical drug administration forms, but also to the inherent physico-chemical limitations of this compound, such as low water solubility, low chemical stability, and low bioavailability.[57] Moreover, the eye has a sophisticated architecture, which makes drug delivery one of the most difficult; natural protective systems (e.g., rapid turnover of tears, nasolacrimal drainage, and a selective, permeable corneal epithelial barrier) significantly reduce drug absorption and retention.[58,59] The consequence is that, with standard formulations, for example, eye drops, bioavailability is less than 5% (i.e., only noticeable to marginal amounts of the drug reach the back of the eyes) (Fig. 1). This translates into a formidable challenge in treating such cases as diabetic retinopathy and AMD, wherein efficient drug delivery to the posterior segment of the eye is uncertain.

Nanotechnology-based delivery approaches may serve as a valuable adjunct to address these issues. Nanocarriers, such as SLNs, polymeric nanoparticles, microemulsions, nanostructured lipid carriers (NLCs), and nanofibres, offer marked advantages for the ophthalmological application of medicinal agents.[58,60] These nanosystems enable targeted delivery to, specifically ocular tissues, sustained and controlled release, and a remarkable improvement in QAE's solubility and chemical stability. In addition, nanoencapsulation helps reduce particle size, which is critical for improved drug-loading efficiency and retinal permeability. Similarly, ultrafine nanoemulsions have been shown to increase solubility and potent transcorneal permeation.[61] Innovative nanocarrier systems help maintain a therapeutically effective QAE concentration at the site of action by circumventing ocular barriers,

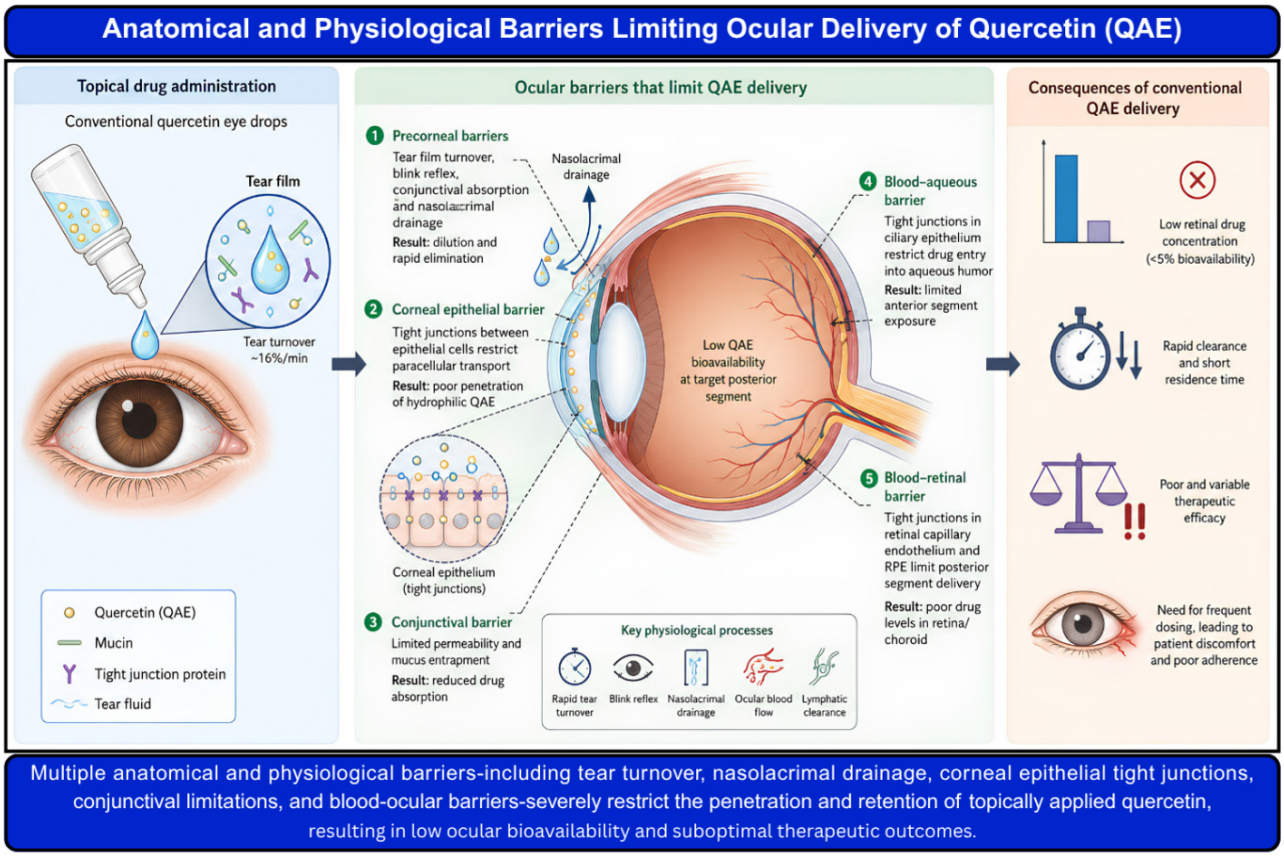


Figure 1. Anatomical and physiological barriers limiting ocular delivery of QAE. Tear turnover, corneal epithelial tight junctions, conjunctival clearance, and blood-ocular barriers drastically reduce drug penetration and retention, resulting in low bioavailability of conventional topical formulations.

prolonging drug retention, and improving absorption and efficacy. Together, these innovations suggest a generalised shift towards predictive and targeted treatments of ocular conditions.[27] Moreover, a considerable portion of a topically administered dose drains through the nasolacrimal duct. It is absorbed through the nasal and conjunctival mucosa, leading to clinically relevant systemic exposure despite the small administered volume.[62,63] This is well documented for several ophthalmic agents, such as beta-blocker eye drops, which have been associated with systemic cardiovascular and respiratory adverse effects, underscoring that inefficient targeting not only limits ocular efficacy but also increases the potential for off-target toxicity.

Nanoformulation strategies for enhanced ocular delivery of QAE

Liposomal nanocarrier for QAE ocular delivery

Liposomes are tiny vesicles composed mainly of phospholipids. They are effective at delivering QUE to the eye.[64] Their double-layered structure closely resembles natural cell membranes, making them highly biocompatible. Notably, they retain both hydrophilic and hydrophobic drugs. Owing to these characteristics, liposomes enhance penetration through ocular barriers and significantly increase the bioavailability and therapeutic efficacy of QAE in ocular tissues.[56] Liposomes can encapsulate both hydrophilic and hydrophobic drugs. They act as a protective outer layer, shielding the drugs from degradation and enhancing their penetration into ocular tissues.[65] Modifying the structure of the lipid bilayer in liposomes can slow drug release. This helps in eye treatments by keeping the drug active for longer and reducing how often it needs to be applied. Research shows that liposomal forms of QUE improve drug stability and provide controlled release, helping maintain effective levels in the eye.[66]

For quercetin specifically, SLN-based eye drops and gels have generally outperformed simple solutions and some liposomal formulations in terms of sustaining therapeutic levels on the ocular surface, owing to their solid lipid core, higher physical stability, and reduced susceptibility to oxidative degradation. Compared with polymeric nanoparticles, quercetin SLNs tend to show somewhat higher initial burst release but simpler compositions, more established excipients, and manufacturing processes that are closer to existing ophthalmic lipid products, which may facilitate regulatory translation. When contrasted with nanoemulsions and micelles, SLNs and NLCs typically provide slower onset but more prolonged exposure and better protection of the active, making them particularly suitable for chronic conditions such as dry eye disease, allergic ocular surface inflammation, and early macular pathology where frequent instillation is a barrier to adherence.

The recent study reported that functional twin liposomes (TLs) were produced by linking avidin-anchored and

biotin-anchored single liposomes via avidin-biotin interactions. They first used the liposome magnetoporation method to generate pores in the liposome surface, enabling encapsulation of QUE or laccase (LAC) without organic solvents. In a recent formulation approach, the liposomal pores were sealed with pH-sensitive glycol chitosan grafted with 3-diethylaminopropylamine (GDEAP) and functionalised with avidin or biotin. This framework facilitated effective interactions among separate liposomes specifically, those containing QUE and biotin–GDEAP, and those bearing LAC with avidin–GDEAP. The resulting tandem liposomes (TLs) enabled more sustained release of both QUE and LAC in mildly acidic environments (pH 6.8). This led to increased LAC-mediated QAE oxidation and a marked enhancement of cytotoxicity towards tumour cells over normal ones.[67] Such a concept opens up multiple opportunities for the regulatory and gradual activation of prodrugs.

Furthermore, tissue-specific targeting could be achieved by designing specific surface modifications of liposomes. For instance, given the broad applicability of the liposomal system for organ-selective action, a coating material has been used, specifically developed and directed towards liver cells, and galactosylated with chitosan. QAE-loaded liposomes have shown good physicochemical stability under various storage conditions, protecting QAE against degradation and enabling prolonged drug release, which is a key requirement for a prolonged ocular therapeutic effect. Fig. 2 summarizes the structural organization of ocular liposomes, common preparation approaches, surface-engineering strategies, and their expected delivery advantages for quercetin.

Solid lipid nanoparticles and nanostructured lipid carriers for enhanced ocular bioavailability

Second-generation lipid-based nanoparticles, including self-emulsifying drug delivery systems (SEDDS), SLNs and NLCs, have attracted attention for ocular delivery of QUE. Due to their biocompatibility, biodegradability and ability to markedly enhance drug penetration and bioavailability, they are applicable for ocular purposes.[68] SLNs comprise only solid lipids, whereas NLCs incorporate both solid and liquid lipids, providing a more flexible and potentially more stable matrix for drug entrapment. However, these formulations have low and variable bioavailability, and there is limited control over drug release. On the other hand, SLNs and NLCs of hydrophilic and lipophilic drugs

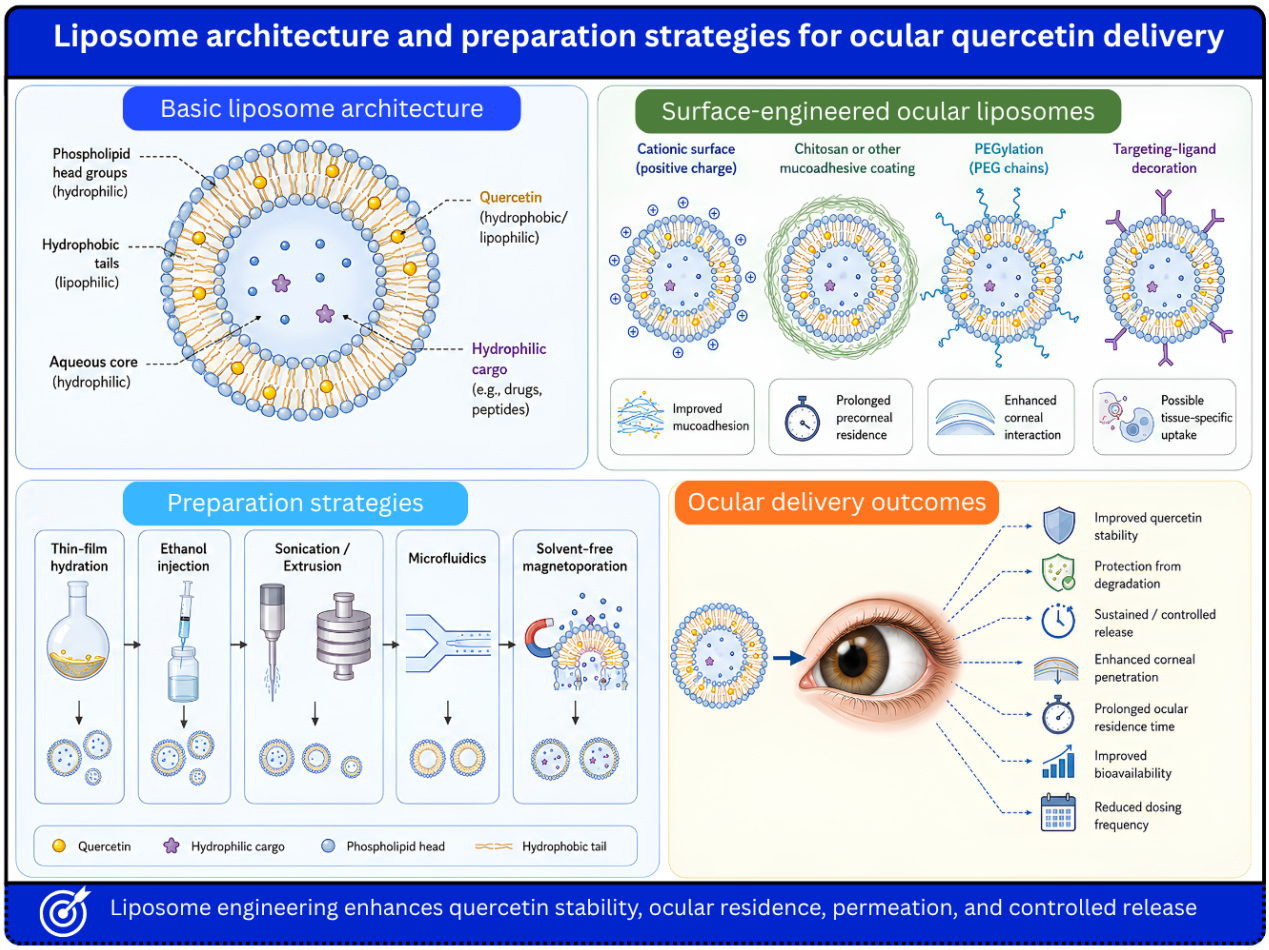


Fig. 2. Liposome architecture and preparation strategies for ocular quercetin delivery. Quercetin can be incorporated into the phospholipid bilayer of liposomes because of its hydrophobicity, while the aqueous core can accommodate hydrophilic agents. Surface engineering using cationic lipids, mucoadhesive polymers, PEG, or targeting ligands may improve precorneal retention, corneal interaction, and tissue-specific delivery. Common preparation approaches include thin-film hydration, ethanol injection, sonication/extrusion, microfluidics, and solvent-free liposome magnetoporation. These strategies collectively improve quercetin stability, controlled release, and ocular bioavailability

have also exhibited enhanced corneal penetration and high ocular bioavailability, indicating their strong potential as carriers for QAE-loaded formulations. This helps counter one of QUE's weakness.

Beyond their general advantages for ophthalmic delivery, several investigations have specifically evaluated quercetin-loaded SLNs for ocular application. In one seminal study using ex vivo porcine eyes, quercetin was encapsulated in SLNs and nanoemulsions and compared for delivery to the cornea and sclera.[69] SLNs provided the highest corneal flux (approximately 158 μg cm^{-2} at 24 h), the lowest cytotoxicity toward corneal and retinal ganglion cells, and efficient protection of ocular cells from hydrogen peroxide-induced oxidative damage, underscoring the value of the rigid lipid matrix for stabilizing quercetin. More recently, squalene-based NLCs loaded with quercetin have been developed for dry eye disease, achieving small particle sizes, high loading, and a biphasic release profile in which more than 70% of the drug was released within 1 h, followed by sustained release for up to 6 h.[70] These NLCs increased ex vivo corneal permeation by roughly 2.5-fold and extended tear film half-life, area under the curve, and mean residence time compared with free quercetin, while maintaining favorable ocular tolerance in modified Draize and HET-CAM assays. Taken together, these studies indicate that quercetin-loaded SLNs and NLCs can simultaneously improve chemical stability, modulate release, and enhance anterior segment exposure relative to conventional solutions or simple dispersions, making them strong candidates for chronic treatments such as dry eye, allergic ocular surface disease, and early macular pathology.[36,71]

Age-related macular degeneration is a debilitating eye disease caused by choroidal neovascularisation (CNV), characterised by rapid vision loss and posing an intractable treatment challenge. In a recent study, SLNs were functionalised with an Asp-Gly-Arg (NGR) peptide to enable targeted delivery of microRNA-150 (miR-150) and the anti-angiogenic compound QUE directly to endothelial cells implicated in pathological neovascularisation.

The nanoparticles, approximately 200 nm in size, showed efficient miR-150 uptake in vitro and successfully targeted the eye's fundus in vivo. In mouse models, they significantly reduced CNV for up to two weeks without causing retinal toxicity. Combined delivery of miR-150 and QUE suppressed abnormal angiogenesis, reduced lesion size, and lowered expression of key markers, including HIF-1α and CXCR4. These findings indicate that NGR-modified nanoparticles could serve as a promising platform for combined AMD therapy, particularly for pairing nucleic acid and small-molecule drugs for safe intravitreal use. However, this theory remains to be validated in larger animal models.[72] Collectively, mechanistic and preclinical data suggest that quercetin-loaded SLNs and NLCs occupy an intermediate position between fast-acting nanoemulsions and more slowly releasing polymeric nanoparticles, offering prolonged exposure and protection from degradation while retaining relatively simple compositions and established excipients that are compatible with ophthalmic translations.

Polymeric nanoparticles for controlled ocular drug delivery

Polymeric nanoparticles (PNPs) represent another robust strategy for QUE ocular delivery, recognised for their biodegradability, biocompatibility, and ability to achieve sustained and targeted delivery. PNPs can encapsulate a variety of bioactive compounds, and their small size enables efficient delivery to sites of action.[73] In recent studies, a thermosensitive gel formulation was developed for the ocular delivery of two potent antioxidants, QAE (QUE) and epigallocatechin gallate (EGCG). QAE was encapsulated in poly(lactic-co-glycolic acid) (PLGA) nanoparticles using the solvent displacement technique, which markedly improved its solubility, stability, and sustained-release profile. The antioxidant potential of QUE-loaded nanoparticles was synergistic with EGCG. They were further assessed for their ability to inhibit intracellular ROS and scavenge free radicals. The nanoparticle-gel system efficiently suppressed ROS generation in human corneal epithelial (HCE) cells. It exhibited optimal gelation characteristics suitable for ocular application, thereby signifying its potential as a favourable antioxidant delivery platform for ocular therapy.[31] Equally, in an earlier study, the inhibitory effects of several polyphenols including QAE, baicalein, and resveratrol on Cu^{2+}-induced aggregation of γD-crystallin were investigated. Among the examined compounds, QAE showed the most effective performance but was limited by poor solubility and low bioavailability. To overcome these challenges, QAE was encapsulated in chitosan-based nanocarriers (CS-TPP and CS-PLGA) and characterised by dynamic light scattering (DLS) and transmission electron microscopy (TEM). The encapsulated QAE considerably reduced protein aggregation, suggesting that such nanoparticle formulations could serve as a non-surgical method for inhibiting cataract formation by neutralising metal-induced oxidative destruction of lens proteins.[74]

Additionally, a pectin–QAE conjugate nanoparticle (NPQ) system loaded with azithromycin (AZI) was developed to enhance ocular bioavailability and treat bacterial infections, particularly those caused by *Staphylococcus aureus*. The nanoparticles, with sizes of 124–178 nm and a negative surface charge, exhibited excellent stability, mucoadhesive properties lasting up to 24 hours, and sustained drug release following zero-order kinetics. The enhanced formulation (NPQ3) achieved approximately 70% drug permeation and improved pharmacokinetic performance compared with pure AZI. Comprehensive characterisation by DSC, XRD, TGA, and FTIR confirmed formulation stability, while in vitro antibacterial assays verified significant inhibition of *S. aureus*. By incorporating the natural antimicrobial and antioxidant properties of QAE with the mucoadhesive and biocompatible characteristics of pectin, this nanoparticle system enhanced the solubility, stability, and ocular retention of AZI, providing an efficient strategy for the management of ocular infections.[75]

Improvements in nanoemulsion and micellar systems for enriching ocular drug infusion and bioavailability

Nanoemulsions and micellar systems offer substantial advantages for the ocular delivery of QUE, primarily by increasing solubility and supporting permeation across ocular barriers, owing to their nanoscale dimensions and promising physicochemical characteristics.[76] Nanoemulsions are thermodynamically stable, transparent, and isotropic mixtures comprising water, oil, and surfactants, with droplet sizes typically ranging from 10 to 100 nm. Their extremely small droplet size, low interfacial tension, and excellent diffusion across the corneal surface accelerate drug diffusion and markedly increase ocular bioavailability.[77]

This study introduces a strategically designed, QUE-loaded squalene nanostructured lipid carriers (QS-NLCs) were shown to enhance the treatment of dry eye disease (DED). Prepared by the melt emulsification method, the optimised QS-NLCs exhibited a small particle size (~93.74 nm), high drug loading (~44%), and stability for over 90 days. QS-NLCs demonstrated biphasic drug release, with over 70% released in the first hour, followed by sustained release for up to 6 hours, and showed approximately a 2.5-fold improvement in corneal permeation compared with free QUE. The formulation-maintained moisture retention comparable to glycerine and exhibited strong anti-inflammatory activity with reduced cytotoxicity. Pharmacokinetic studies showed increased tear production, a 2.79-fold longer half-life, 3.02-fold greater AUC, and 2.88-fold higher mean retention time, indicating enhanced ocular bioavailability. With good ocular tolerance and improved pharmacological effects, QS-NLCs offer a promising strategy for DED treatment, though further scale-up and optimisation are needed.[3]

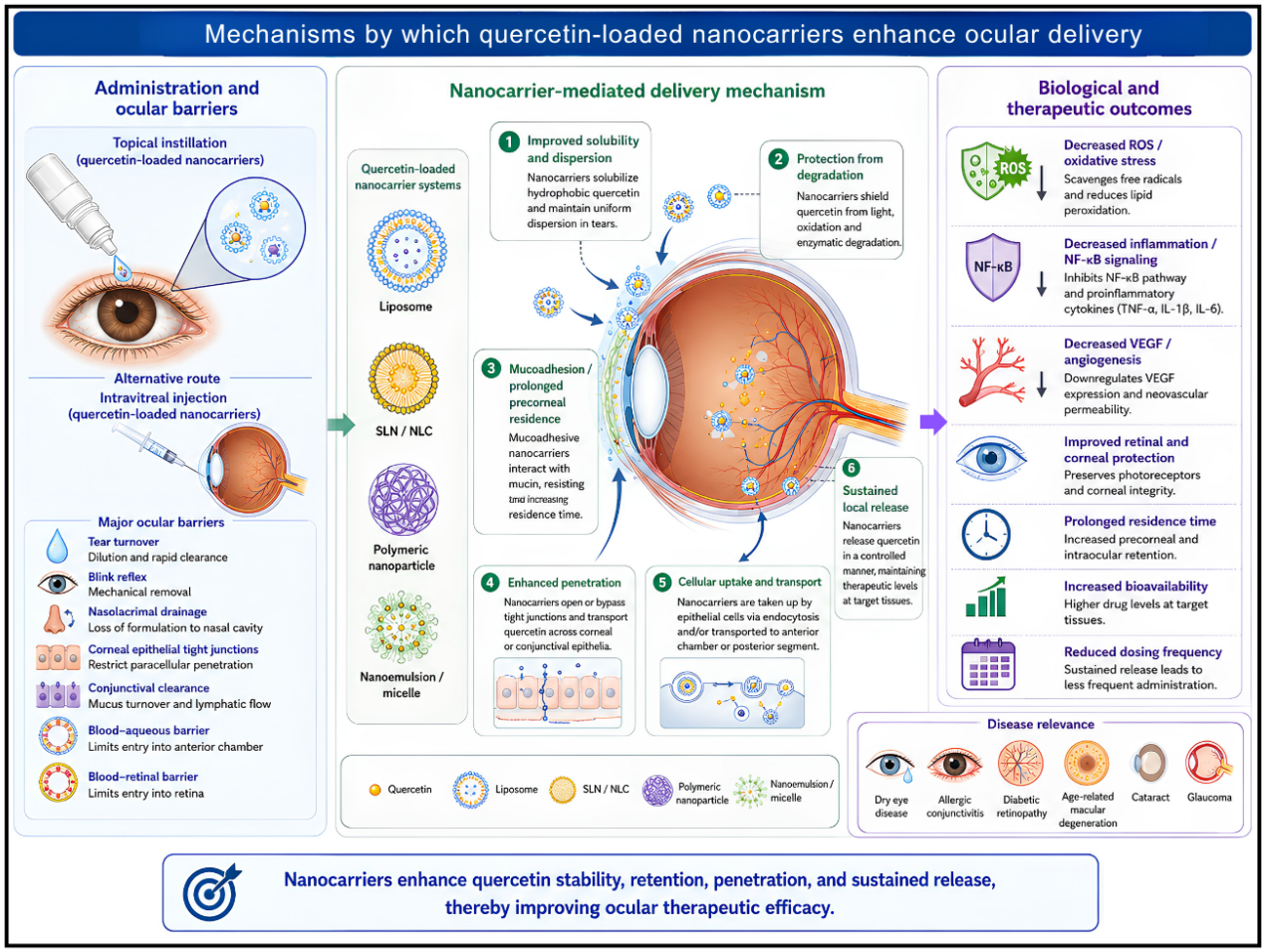
Thermoresponsive QUE nanoemulgels (T-QNE-Gs) were developed for intravitreal injection. The optimised formulation, containing Pluronic F127 and F68 in a 2:1 ratio with hydroxypropyl methylcellulose (HPMC), formed a solution at room temperature and transitioned to a gel at the posterior eye segment temperature (35 ± 1 °C). The sterilised version, S–2F127–1F68, retained its physicochemical properties post-sterilisation and demonstrated significant anti-angiogenic activity in vitro by inhibiting human umbilical vein endothelial cell (HUVEC) migration and tube formation, and by downregulating VEGF-A gene and protein expression under hypoxic conditions. These results underscore the potential of QAE as a promising intravitreal therapeutic for the management of vasoproliferative retinopathies and highlight the need for further preclinical investigations to validate its efficacy and safety.[78]

Cataract remains one of the leading causes of visual impairment globally. A state-of-the-art therapeutic strategy has been proposed using hybrid micelles (Q/siP-c-M) for the co-delivery of QUE and PARP-1 siRNA. These micelles are surface modified with an RGD peptide, exhibit a consistent particle size, high encapsulation efficiency, and exceptional physicochemical stability. Their nanoscale design enables superior transcorneal permeation and sustained retention, permitting efficient delivery of therapeutic agents into deeper corneal layers. Q/siP-c-M therapy markedly increased catalase activity and ATP levels in selenite-induced cataract models, while decreasing PARP-1 protein expression, lipid peroxidation, and malondialdehyde accumulation.

Furthermore, QAE attenuated inflammatory responses by efficiently inhibiting neutrophil extracellular trap (NET) formation and downregulating pro-inflammatory cytokine expression. In lens epithelial cells, the combined formulation also demonstrated anti-apoptotic properties. Taken together, these results point to Q/siP-c-M micelles as a potent therapeutic platform for the management of cataracts by improving drug bioavailability and, at the same time, addressing inflammation, oxidative stress, and apoptosis in the lens.[79] To overcome the limitations associated with conventional ocular drug delivery, nanotechnology-based systems have been widely explored for improving QAE bioavailability and targeted ocular transport. Various nanocarriers including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, and nanoemulsions have demonstrated enhanced corneal penetration, prolonged ocular residence time, and controlled drug release. These advanced delivery systems significantly improve therapeutic outcomes in ocular diseases by protecting QAE from degradation and facilitating efficient drug transport across ocular barriers (Fig. 3).

Addressing stability issues in ocular QAE-based nanoformulations

The stability of QUE nanoformulations is pivotal to their therapeutic effectiveness, shelf life, and clinical applicability. Therefore, given QUE's intrinsic instability, encapsulation within nanocarriers is indispensable to counteract degradation and preserve pharmacological activity. Nevertheless, challenges such as low drug-loading capacity and inadequate formulation stability persist, delaying the development of QUE-based nano delivery systems. Environmental factors, including light exposure, temperature fluctuations, and interactions with metal ions, can also influence the stability of free QUE and its liposomal formulations. The limits of protection currently achievable by liposomal encapsulation, even with a small additional physical barrier such as the lipid vesicle wall, are common to preservation chemistries. The stability of these nanocarriers is critically influenced by their physicochemical properties, such as particle size, surface charge, and the type of excipients incorporated. For example, true-yield lipid-based nanoparticles have demonstrated enhanced stability of QUE-loaded particles, whereas nanoemulsion systems enhance aqueous solubility and drug stability. Similarly, unless the sacrificial carbon source is fully converted into hollow structures, it can still serve not only as a robust template but also as structural support for these hollow silica nanoparticles, ensuring resistance to structural collapse upon drug loading.



Fi. 3. Mechanisms by which quercetin-loaded nanocarriers enhance ocular delivery. Nanocarriers improve ocular quercetin delivery by increasing solubility, protecting quercetin from degradation, prolonging precorneal residence, enhancing corneal or conjunctival penetration, and enabling sustained local release. Following cellular uptake, released quercetin may suppress oxidative stress, inflammatory signaling, angiogenesis, and retinal or corneal cell injury, thereby supporting therapeutic effects in dry eye disease, diabetic retinopathy, age-related macular degeneration, cataract, and allergic conjunctivitis.

However, the formulation step often requires fine-tuning and can be technically challenging. Without adequate stability, the benefits of increased bioavailability and therapeutic effectiveness offered by nanoformulations cannot be fully realised. Therefore, appropriate material selection and targeted optimisation of the manufacturing process are mandatory for the successful development of strong, robust ocular nanoformulations.

Comparative performance of quercetin nanocarriers in ocular delivery

Although diverse nanocarrier systems have been explored for the ocular delivery of quercetin, their performance profiles differ. Liposomes offer excellent biocompatibility and the ability to encapsulate both hydrophilic and lipophilic drugs, and cationic or mucoadhesive surface modifications can markedly prolong precorneal residence and enhance corneal uptake; however, they may suffer from limited drug-loading capacity and physical instability during long-term storage or sterilization. SLNs offer greater physical stability and better protection of labile quercetin against hydrolysis and oxidation. However, their highly ordered lipid matrix can limit drug loading and may promote drug expulsion during storage. NLCs partially overcome this limitation by incorporating liquid lipids into the solid matrix, increasing loading capacity, reducing drug expulsion, and allowing more flexible control of release kinetics, which has translated into superior corneal permeation and sustained ocular levels for several lipophilic drugs, including quercetin.

Nanoemulsions and micellar systems generally achieve smaller droplet or aggregate sizes and higher interfacial surface area, which favor rapid transcorneal permeation and high apparent bioavailability; however, they are often less suitable when prolonged residence or tight control over release is required and can be more sensitive to surfactant-related irritation. Polymeric nanoparticles (e.g., PLGA or chitosan-based systems) can offer highly tunable and sustained release, robust protection of quercetin, and facile surface functionalization for targeting. However, they may involve more complex fabrication, scale-up, and regulatory evaluation compared with lipid-based carriers. In practice, the optimal nanocarrier choice for ocular quercetin delivery depends on whether the primary objective is to maximize corneal penetration and rapid onset (favoring nanoemulsions and some micelles) or to achieve long-lasting, controlled delivery with a reduced dosing frequency (favoring NLCs, SLNs, liposomes, or

polymeric nanoparticles). Because ocular nanocarriers differ not only in composition but also in release kinetics and permeation behavior, Fig. 4 provides a conceptual comparison of the expected release and corneal permeation profiles of major quercetin nanocarrier classes (Table 2). When quercetin is used as the model drug, SLN-based systems generally outperform simple aqueous solutions and some liposomal formulations in sustaining ocular levels, largely because the solid lipid core shields quercetin from hydrolysis and photo-oxidation and allows tighter control over release.[15,71,80,81] Compared with nanoemulsions and micelles, quercetin SLNs and NLCs typically produce a slightly slower onset but more prolonged exposure on the ocular surface and in tear fluid, as evidenced by increased corneal flux, longer half-life, and higher area under the curve in preclinical models of dry eye disease.[15,71,80,81] Compared with polymeric nanoparticles, SLNs leverage pharmacopeial lipids and straightforward melt-emulsification or high-pressure homogenization methods, which may simplify scale-up and regulatory assessment, albeit at the cost of somewhat less extreme sustained release.[15,71,80,81] These contrasts provide a practical

Table 2. Comparative features of nanocarriers for ocular quercetin delivery

Nanocarrier type	Main strengths in ocular quercetin delivery	Key limitations / risks	Ref.
Liposomes	High biocompatibility and flexibility in loading hydrophilic and lipophilic drugs; surface charge and mucoadhesive coatings can extend precorneal residence and improve corneal penetration; enable relatively controlled release.	Potential physical/chemical instability (aggregation, leakage, oxidation) during storage and sterilisation; limited drug-loading capacity for some compositions; manufacturing and scale-up can be costly.	82, 83
SLNs	Good physical stability; protect quercetin from degradation; suitable for topical ocular use; can be formulated with cationic or mucoadhesive surfaces to increase residence time.	Highly ordered lipid matrix may restrict drug loading and cause drug expulsion on storage; sometimes show burst release followed by incomplete drug	81,84,85
NLCs	Higher loading capacity and reduced drug expulsion compared with SLNs due to inclusion of liquid lipids; more flexible modulation of release kinetics; favourable corneal permeation and sustained levels demonstrated in ocular models.	More complex optimisation of solid/liquid lipid ratios and surfactant composition; potential long-term stability issues if composition is not carefully tuned.	81,84,86
Nanoemulsions / micelles	Very small droplet/aggregate size promotes rapid corneal permeation and high apparent bioavailability; good for poorly soluble drugs like quercetin; relatively simple to scale.	Often provide faster release and shorter residence time than lipid nanoparticles; may require high surfactant concentrations, with potential for ocular irritation and tear-film disturbance.	82,86
Polymeric nanoparticles	Highly tunable, sustained release and strong protection of quercetin; easy to incorporate targeting ligands; can reduce dosing frequency and improve patient adherence.	More complex fabrication and sterilisation; potential concerns about polymer degradation products and long-term safety; regulatory pathways can be more demanding than for lipid-based systems.	83,87

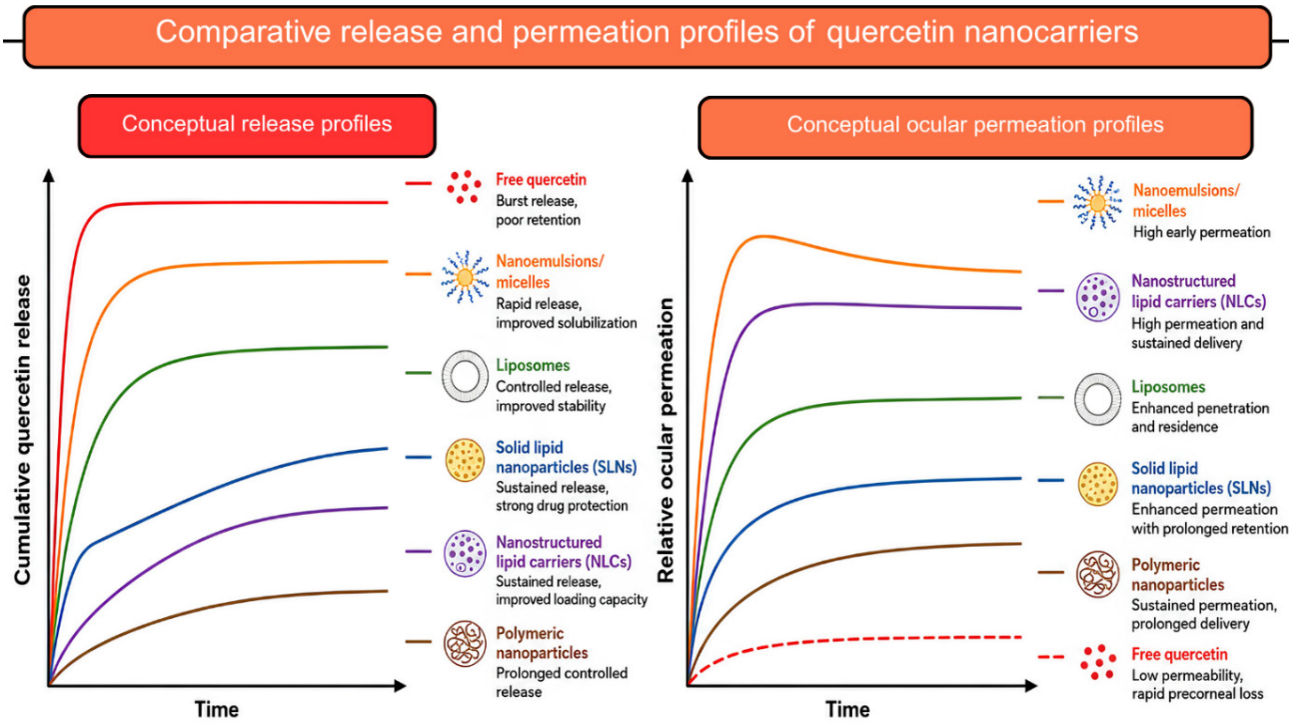


Fig. 4. Comparative release and permeation profiles of quercetin nanocarriers. Conceptual comparison of the expected release behavior and corneal permeation trends of quercetin-loaded nanocarriers.

framework for comparing SLN-based quercetin eye drops or gels with alternative delivery strategies in terms of onset of action, dosing frequency, and translational readiness.

Regulatory considerations and challenges in the development of ocular nanoformulated drugs

Expansion and appreciation of nanoformulations for ocular drug delivery face a unique and complex set of governing issues. However, nanoformulations offer a revolutionary enhancement in drug delivery, as they can surmount drawbacks such as poor solubility and systemic toxicity.[22,88] Authorities want the whole data thingy, including consistency, wear tests, and cost-to-efficacy bullshit. The absence of a defined regulatory horizon and an insufficient understanding of nanoparticles in clinical use pose significant challenges for the pharmaceutical industry. Particularly for ocular applications, the interaction of nanocarrier systems with biological entities raises potential toxicity risks and mandates close evaluation of nanoparticle size, shape, surface charge, and coating. The regulatory approval process is currently impeding rigorous in vivo and in vitro safety studies that validate the clinical relevance of nanocarriers. This is especially important in ophthalmic use, where the eye's delicate nature demands a stringent safety profile. Despite extensive preclinical data on quercetin-loaded nanocarriers for ocular diseases, clinical evidence remains scarce. Most studies to date have evaluated quercetin as an oral supplement or in simple topical formulations for ocular surface conditions, and only a few early-phase, small-scale trials and pilot studies are available, mainly in dry eye–related symptoms, allergic conjunctivitis, and nutraceutical combinations in dry age-related macular degeneration.[11,12,63] There are currently no completed, adequately powered randomized controlled trials of ophthalmic quercetin nanoformulations in humans, and very limited data on long-term safety, dose–response relationships, and comparative effectiveness versus standard of care, which represents a major gap that must be addressed before widespread clinical adoption can be considered.

Translating laboratory novelties into clinical use is extremely challenging, particularly in the areas of production scale-up and quality retention. Although new regulations and patents point in a certain direction, there remains a clear need for harmonised guidelines for nanoformulated ocular drugs. The Quality by Design (QbD) principles would offer a rational approach to optimising nanocarrier composition and the manufacturing process, which are important for safety and efficacy. However, the absence of comprehensive regulatory frameworks for nanomedicinal products, together with existing fears about nanotoxicity, continues to impede the clinical translation of QUE-based nanoformulations. From a regulatory standpoint, nano-enabled ophthalmic products are often classified as complex drug–device or drug–biologic combination products and must comply with stringent quality, safety, and efficacy requirements.[63,89,90] Regulators expect detailed characterization of nanocarrier composition and structure, in-depth in vitro and in vivo safety data (including immunogenicity and long-term ocular tolerability), and robust control strategies for critical quality attributes, all of which are more demanding than for conventional small-molecule eye drops.[63,89,90] Moreover, there is still a lack of harmonized, nanomedicine-specific guidance for ophthalmic products, and uncertainty regarding suitable bioequivalence and clinical endpoints, which increases development risk and may discourage investment in quercetin-based ocular nanotherapeutics despite their mechanistic and preclinical promise.

Future Perspectives

To bridge the gap between bench and bedside, future work must move beyond proof-of-concept animal studies toward well-designed phase 1/2 clinical trials of selected quercetin nanoformulations in defined ocular indications, with careful dose-finding, pharmacokinetic, and safety evaluation.[89] Parallel efforts are needed to develop scalable, GMP-compliant manufacturing processes and to align formulation development with evolving regulatory expectations for complex ophthalmic nanomedicines, ideally using QbD principles and early dialogue with regulatory agencies.[89] Addressing these clinical, technological, and regulatory gaps will be essential for real-world implementation of quercetin-based ocular nanotherapies. Despite the boundaries, the field of ocular QUE nanoformulations is advancing through novel methodologies and promising prospects. Polymeric nanoparticles, SLNs, NLCs, niosomes, and liposomes are the major nanocarriers developed to enhance the therapeutic efficacy of QUE in the ophthalmic field. Each methodology offers specific advantages in terms of drug retention, corneal penetration, and overall bioavailability. These nanocarriers facilitate controlled and targeted drug release, potentially improving therapeutic effects and patient adherence.

Decoding QUE nanoformulations from preclinical research to clinical practice poses several ongoing challenges, including low drug-loading capacity, formulation instability, and difficulties in large-scale production. New strategies are currently focused on stimuli-responsive nanocarriers that can release QUE in response to stimuli and physiological cues within ocular tissues. Additionally, combining gene and protein delivery systems with QUE-based formulations paves the way for therapeutic possibilities for multifactorial eye diseases.

Given the higher development costs, the use of complex analytical techniques is also indispensable for characterising these nanosystems, refining formulation reproducibility, and assuring clinical dependability. Another exciting prospect for QUE-based nanotherapeutics is the rising emphasis on precision medicine, which tailors' treatments to the unique characteristics of each patient. The concept of targeted ocular drug delivery, deeply rooted in oncology but currently under review in ophthalmology, is another area where nanoformulations show promise. The safety and clinical feasibility of these formulations will drive

further developments in nanotechnology aimed at reducing cytotoxicity and genotoxicity. Finally, interdisciplinary cooperation will be indispensable for future success.

Conclusion

Ocular drug delivery remains challenging due to anatomical barriers, tear turnover, and limited corneal permeability, compounded by the poor solubility and stability of QAE. To overcome these limitations, various nanoformulation strategies including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions, and micelles have been explored to enhance QAE's bioavailability and targeted delivery. These nanocarriers improve drug retention time, protect against rapid tear washout, enable sustained release, and facilitate corneal penetration, thereby maximizing QAE's antioxidant, anti-inflammatory, and neuroprotective effects in ocular disorders. Preclinical findings demonstrate promising therapeutic potential; however, successful clinical translation will require further optimization, large-scale validation, and long-term safety evaluation to ensure effective and noninvasive treatment options for vision-threatening diseases. Despite the encouraging preclinical results, the current evidence base for quercetin-loaded ocular nanoformulations in humans is extremely limited, with only small pilot studies and nutraceutical trials available for a few indications and no completed, adequately powered randomised controlled trials of ophthalmic nanocarriers. There is an urgent need for well-designed phase 1/2 clinical studies that systematically evaluate safety, tolerability, pharmacokinetics, dose–response, and comparative efficacy of selected quercetin nanoformulations against standard therapies in clearly defined ocular diseases. Only through such rigorous clinical evaluation, coupled with scalable manufacturing and clear regulatory pathways, can quercetin-based ocular nanotherapeutics move from promising laboratory concepts to reliable treatment options in real-world ophthalmic practice.

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Competing Interests

The authors declared no competing interests.

Declaration of AI-assisted Tools in the Writing Procedure

The authors declare that generative artificial intelligence (AI) tool ChatGPT were used to assist in improving the language and readability of the manuscript. The content was reviewed and verified by the authors to ensure accuracy and originality and the authors take full responsibility for the final version of the manuscript.

Ethical Approval

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