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ADVANCES IN POLYPHENOL-BASED OCULAR DRUG DELIVERY: MECHANISTIC INSIGHTS, FORMULATION INNOVATIONS, AND TRANSLATIONAL PERSPECTIVES

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ABSTRACT

Objective: To evaluate the therapeutic potential of plant-derived polyphenols for ocular disorders and to review advanced formulation strategies designed to overcome the limitations of conventional ocular drug delivery systems.

Methods: A comprehensive review of recent literature was conducted focusing on formulation approaches developed to enhance the ocular delivery of polyphenols. Various advanced drug delivery systems-including nanoemulsions, polymeric micelles, lipid- and polymer-based nanocarriers, in situ gelling systems, mucoadhesive platforms, stimuli-responsive systems, and other advanced delivery technologies targeting both anterior and posterior ocular segments-were analyzed. Their underlying mechanisms, pharmacokinetic and pharmacodynamic outcomes, as well as safety, manufacturing, and regulatory considerations were critically assessed.

Results: Advanced formulation strategies significantly improve the ocular delivery of polyphenols by enhancing retention time, corneal permeability, and sustained drug release. Mechanistic approaches such as improved mucoadhesion, modulation of paracellular transport, and promotion of endocytic uptake facilitate better drug penetration and distribution within ocular tissues. These systems demonstrate improved bioavailability and therapeutic performance compared with conventional delivery methods, while also offering potential for targeted delivery to both anterior and posterior ocular segments.

Conclusion: Emerging formulation technologies provide promising solutions to overcome the bioavailability and delivery challenges associated with polyphenol-based ocular therapies. Continued development and optimization of these advanced delivery platforms, along with addressing safety, manufacturing, and regulatory challenges, are essential for the successful clinical translation of polyphenol-based treatments for ocular diseases.

Keywords: Polyphenols, Ocular drug delivery, Nanoemulsions, Nanocarriers, Enhanced ocular penetration

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INTRODUCTION

The human eye is a highly specialised sensory organ that has overly complex structures depicting anatomy and physiological barriers that restrict drug penetration and retention [1]. The tear turnover, nasolacrimal drainage, and presence of blood ocular barriers drastically decrease the residence time of topically administered drugs, whilst the tight junctions between the corneal epithelium and retinal vascular endothelium further limit the intraocular drug penetration [2, 3]. Standard approaches for treating ocular disorders include topical eye drops, ointments and gels for anterior segment diseases, intravitreal or periocular injections, and systemic therapy for posterior segment diseases [4]. Despite their clinical success in treating many ocular diseases, topical methods are commonly associated with low drug bioavailability and frequent dosing administration [5]. Intravitreal injections have significant drawbacks, including endophthalmitis, retinal detachment, and cataract [6, 7].

The most common causes of visual impairment and blindness in the world include age-related macular degeneration (AMD), glaucoma, diabetic retinopathy, cataract, and dry eye disease. Ageing, genetic vulnerability, malfunction of the metabolism, oxidative stress, chronic low-grade inflammation, and, in certain cases, infection characterise their pathogenesis, which leads to the increased burden of visual impairment and blindness with cataract, diabetic retinopathy, and posterior segment diseases being significant contributors to preventable loss of vision and productivity[8-10]. Epidemiological reports indicate that the prevalence rate of visual disability and blindness is increasing in Malaysia and other areas of Southeast Asia [11]. Although surgical interventions, laser procedures, and pharmacological treatments are available, structural damage and visual loss continue to increase in many patients, which means that there is an unmet need to provide a strategy that offers long-term neurovascular protection of the ocular tissues [12, 13].

These gaps have led to increased attention in bioactive substances that can regulate oxidative stress, inflammatory signalling, and microvascular dysfunction in ocular tissues. Among the most widely studied candidates are polyphenols, which comprise a large and structurally diverse group of plant-derived secondary metabolites, including flavonoids, stilbenes, phenolic acids, tannins, and lignans [14, 15]. Quercetin, epigallocatechin gallate (EGCG), resveratrol, anthocyanins, rosmarinic acid, and gallic acid are polyphenols that have strong antioxidant, anti-inflammatory, anti-angiogenic, and neuroprotective activities *in vitro* and *in vivo* [16, 17]. They have been demonstrated to stabilise homeostasis of tear film, minimise oxidative injury/damage to corneal and lens epithelial cells, moderate microglial activation and pathological neovascularisation of the retina, and have been shown to increase the signs and symptoms of dry eye disease in clinical and preclinical studies [18, 19].

Nevertheless, polyphenols are exhibiting promising pharmacodynamic properties; translating them into practical clinical therapies is limited by low aqueous solubility, chemical instability at physiological pH, and extensive hepatic first-pass metabolism in the gastrointestinal tract and liver, resulting in a minimal and erratic systemic exposure after oral intake [20, 21]. Besides, they have other impediments when administered as conventional eye drops or suspensions, such as rapid precorneal loss, poor corneal permeability, and minimal stromal and deeper tissue diffusion, giving rise to low intraocular levels and low retention [1]. In the case of posterior segment diseases, systemic administration is further limited by the blood-retinal barrier, and repetitive intravitreal injections, which are effective in the delivery of drugs including anti-VEGF agents, have logistical limitations as well as non-trivial risks [2, 5, 22]. To overcome these limitations, extensive portfolio of formulation strategies has been explored including viscosity improved eye drops, cyclodextrin inclusion complexes, in situ gelling systems, nanoemulsions, solid lipid nanoparticles (SLNS), nanostructured lipid carriers (NLCs), polymeric nanoparticles, micelles, liposomes, ocular inserts, drug-eluting contact lenses, periocular depots and intravitreal implants to enhance ocular delivery of polyphenols [23-27]. However, these systems have shown better apparent solubility, longer precorneal residence time, increased corneal or scleral permeability and drug retention in anterior or posterior segment tissues of many polyphenols but the literature is still fragmented i. e. most studies have involved isolated formulations and describe them as promising but have not made systematic comparisons of different platforms, nor have systematically reported pharmacokinetic parameters such as ocular half-life, area under the curve (AUC) or C_{max}, and limited discussion has been made on long-term safety, scalability, sterilisation [24, 28].

This review extensively covers the polyphenols-loaded ocular preparations, starting with an overview of the key anatomical and physiological obstacles to the delivery of drugs to the anterior and posterior eye segments. This review also reveals the superior formulation strategies in a barrier-based system integrating traditional and nano-enabled systems [29]. It is focused on the processes that influence drug penetration, such as mucoadhesion, paracellular modulation, and carrier-mediated endocytosis, as well as on pharmacodynamics and pharmacokinetics outcomes. Lastly, the current review comments on the biosafety, manufacturing, and regulatory issues, which should be weighed out to introduce polyphenol-based ocular therapies into clinical practice.

Polyphenols in healthcare management and their therapeutic properties

Polyphenols have been defined as a large class of naturally occurring secondary metabolites, which are flavonoids, phenolic acids, tannins, lignans, coumarins, and similar compounds. These are abundantly found in fruits, vegetables, tea, coffee, and whole grains and are associated with diverse health benefits [14, 16]. Polyphenols exhibit a wide range of pharmacological effects that mediate their potential in the prevention and treatment of various diseases, including diabetes, cardiovascular diseases, and neurodegenerative diseases. However, as afore mentioned, reduced oral bioavailability, rapid metabolism, and limited absorption in the human body necessitate the development of new delivery approaches to enhance their pharmacokinetic and pharmacodynamic performance [20, 30].

The potent antioxidant activity of polyphenols is attributed to their chemical structure, consisting of aromatic rings bearing one or more phenolic hydroxyl groups. These hydroxyl groups permit direct scavenging of reactive oxygen species (ROS), such as anions of the superoxide (O_2^-), hydroxyl radical (•OH), and lipid peroxides, and breaking free-radical chain reactions, resulting in a reduction in oxidative stress, which impacts most chronic diseases [14, 31]. Resveratrol is an example that prevents lipid peroxidation of low-density lipoproteins (LDL) and cellular membranes, and quercetin promotes endogenous production of glutathione, which enhances the antioxidant defence mechanism [16, 30]. Polyphenols may also bind to transition metals e. g. iron, copper and inhibit Fenton-type reactions as well as prevent excess production of highly reactive hydroxyl radicals that damage cellular components. Eating large amounts of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), has been reported to improve the activity of antioxidant enzymes, which further decreases the oxidative injury [14, 16]. In addition to direct antioxidant activity, polyphenols control important pathways of inflammatory and cell-signalling processes. They modulate nuclear factor kappa B (NF-κB) and mitogen-activated protein-kinase (MAPK) signalling pathways (fig. 1), thereby suppressing the pro-inflammatory cytokines such as TNF-α and interleukins [32]. Polyphenol formulations also reduce the cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) pathways, decreasing the pro-inflammatory eicosanoid production. Curcumin, which is a key ingredient of turmeric, has been investigated extensively for its property to mitigate inflammatory responses (as in rheumatoid arthritis and atherosclerosis, in large part by inhibiting the action of macrophages) [33, 34]. Such systemic interventions relate specifically to ocular wellbeing. The ocular protective effects were due to the defensive nature of curcumin towards oxidative stress, chronic inflammation, and vascular dysfunction, which play a role in the pathogenesis of glaucoma, diabetic retinopathy, age-related macular degeneration, and other retinal disorders [9, 35]. Polyphenols enhance endothelial function, increase the bioavailability of nitric oxide (NO), and decrease platelet aggregation, which is beneficial to cardiovascular and microvascular health. Resveratrol and quercetin are reported to elevate the endothelial nitric oxide synthase (eNOS) activity, resulting in better vasodilation and tissue perfusion, both of which are also valuable in retinal circulation. Polyphenols preserve retinal microvasculature by decreasing LDL oxidation and reducing the less favourable lipid profile [30, 36].

Polyphenols have also been shown to have neuroprotective properties in Alzheimer's models, as well as Parkinson's disease model systems, where they alleviate oxidative stress and apoptosis in the brain tissues [14]. This phenomenon applies equally to the retina, where oxidative stress and programmed cell death contribute to loss of retinal ganglion cell (RGCs) in glaucoma and ischemic retinopathies. Green tea EGCG has been demonstrated to increase superoxide dismutase (SOD) activity and decrease oxidative damage in retina cells, and Ginkgo biloba extracts have the potential to improve ocular blood flow in glaucoma [19, 37, 38]. Ferulic acid is also reported to prevent cerebral ischaemia, as well which can be converted to prevention of ischaemic damage in retinal tissues [16, 39].

The modulation of glucose homeostasis and insulin sensitivity, which is pertinent to diabetic retinopathy, is also achieved by polyphenols [40]. Resveratrol is also active on Sirtuin 1 (SIRT1) to enhance mitochondrial performance and insulin signalling, and gallic acid and naringenin can reduce post-prandial hyperglycaemia by inhibiting 5-glucosidase [30]. Polyphenols may delay injury to the microvasculature in diabetic eye disease by minimising the oxidative and inflammatory destruction of microvascular endothelium triggered by hyperglycaemia. Irrespective of these favourable systemic and ocular effects on pharmacodynamics, their ultimate clinical utility lies in overcoming delivery barriers and enhancing bioavailability, especially to those tissues of the eye where delivery is closely controlled [20, 21].

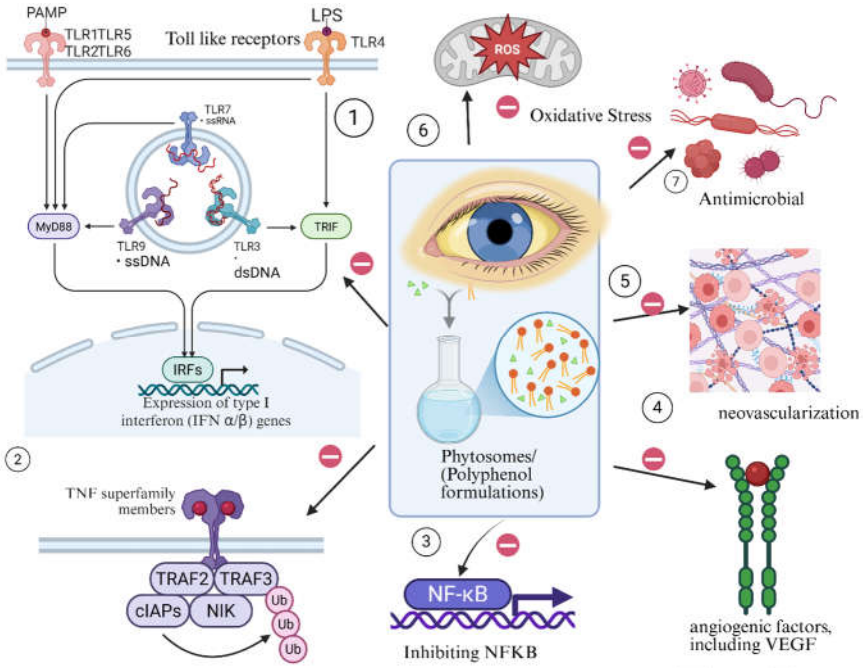

Fig. 1: Action of polyphenol ocular formulations

Polyphenolic formulations prevent eye diseases by means of their anti-inflammatory, anti-angiogenic, and antioxidant properties. Consequently, oxidative stress, which is associated with conditions such as cataract, glaucoma, and age-related macular degeneration (AMD), is mitigated by these naturally occurring compounds, including flavonoids, phenolic acids, and stilbenes, which neutralise reactive oxygen species and enhance antioxidant enzymes like catalase and glutathione peroxidase. These compounds suppress signalling pathways, such as through TLR (1) NF-κB and MAPK, which are linked to retinal degeneration and uveitis, and inhibit critical inflammatory mediators such as COX-2, TNF-α, and IL-1β. Additionally, polyphenols inhibit pathological neovascularization in diabetic retinopathy and moist AMD by modulating angiogenic factors, including VEGF. Furthermore, some polyphenols stabilise mitochondrial function and improve cellular resilience, thereby safeguarding retinal ganglion cells and photoreceptors. Various ocular disorders are prevented and managed by polyphenolic formulations, which are promising candidates due to their multi-targeted actions.

Challenges of polyphenols in ocular delivery

Although polyphenols have significant potential in preventing ocular tissues, numerous formulations and biological issues hinder their effective delivery to the eye [1]. These barriers are inherent to the physicochemical properties of polyphenols, including low aqueous solubility, chemical instability, and susceptibility to rapid metabolism and the complicated anatomical and physiological mechanisms that make up the ocular milieu. These challenges are addressed by systematic formulation research and strategic delivery approaches that consider ocular pharmacokinetics and unique physiological characteristics of anterior and posterior segmental tissues [22].

Several polyphenols with clinical significance, such as resveratrol and curcumin, are highly lipophilic and exhibit low solubility in tear fluid and aqueous-based ophthalmic vehicles [30]. Hence, traditional eye drops have a low percentage of deposition to the target site from the administered dose. Poor solubility and slow rate of dissolution decrease the concentration gradient driving corneal penetration, and high dosage or frequency of instillation might be needed to reach therapeutic levels, putting patients at risk of local irritation and impeding patient compliance. Moreover, polyphenols also undergo considerable phase I and phase II metabolism by ocular and systemic enzymes, which may result in shorter retention time of polyphenols at the site of action and decreased proportion of active component [16, 20].

The eye architecture offers crucial protection against environmental insults while simultaneously presenting formidable barriers to drug delivery. Upon topical administration, the loss of drug is high because of the turnover of tears, nasolacrimal drainage, and blinking; less than 5% of the instilled drug is usually delivered to intraocular tissues. The cornea is made up of various layers, which are the lipophilic epithelium, the hydrophilic stroma, the Bowman layer, the Descemet membrane, and the endothelium [1, 27]. The restrictive properties of the corneal epithelium to the permeation of more hydrophilic and larger molecules, and collagen-rich stroma to the more hydrophilic drugs in terms of diffusion, are also limiting factors in trans corneal transport of the majority of polyphenolic compounds. For hydrophilic or macromolecular polyphenols, resistance from the conjunctiva and sclera, together with efflux transporters and metabolic enzymes that are presented at the ocular surface, impeded the drug absorption [25].

There is an additional constraint of the blood aqueous barrier (BAB) and blood retinal barrier (BRB) to posterior segment delivery [8]. The BAB formed by tight junctions in the ciliary body and iris vasculature limits the diffusion of hydrophilic drugs and plasma proteins to the aqueous humour and restricts the posterior diffusion of systemically administered or topically applied molecules. The BRB is made up of retinal capillary endothelial cells and retinal pigment epithelium (RPE), which have tight junctions that restrict the flow between the circulation and the neural retina to restrict the penetration of numerous small molecules and biologics. These obstacles aid in supporting a state of retina homeostasis but pose a massive restraint to the delivery of polyphenols systemically or topically administered into the posterior segment [35].

Due to these limitations, most of the polyphenolics delivery into ocular tissues depends upon an invasive route such as intravitreal injection or periocular implants [7, 41]. Although intravitreal injection would be able to deliver large drug concentrations locally, it is also associated with several risks, such as endophthalmitis, retinal detachment, and cataract formation, and must be repeated every few weeks in case of chronic diseases. These shortcomings raise the significance of sustained-release systems and less invasive methods to reach sufficient concentrations in the posterior tissues with less frequent injections [22, 42]. One of the major formulation challenges is the chemical instability of polyphenols, which are prone to oxidation, photodegradation, and hydrolysis, resulting in the loss of activity and reduced shelf life [37]. Curcumin and quercetin are examples that are unstable

at physiological pH and therefore usually must be stabilised or encapsulated within protective matrices. Interactions between polyphenols and polymers should also be maximised carefully since excipients may affect drug loading, release kinetics, and bioactivity [25]. Nanocarrier systems like nanoemulsions, liposomes, noisome, and nanoparticles can alleviate some of these problems by enhancing solubility, preventing degradation of polyphenols, but they introduce new problems related to scale-up, batch-to-batch reproducibility, sterilisation, and regulatory approval [21, 23, 27].

Lastly, *in vitro*, *ex vivo,* and *in vivo* models are not standardised to determine the ocular pharmacokinetics and toxicity of polyphenol-loaded formulations. The variability in animal models, dosing regimens, and analytical methods causes comparison problems between the studies and hinders the establishment of robust structure-activity and formulation-response relationships [26]. An effective nanocarrier for ocular delivery of polyphenols needs to be able to incorporate adequate drug loading, controlled release, compatibility with ocular tissues, and be manufacturable under good manufacturing practice (GMP) conditions, and should generate reproducible pharmacokinetic and safety profiles that are acceptable to regulatory authorities [25].

Formulation strategies for ocular polyphenol delivery

Conventional formulations

Aqueous eye drops: solubility enhancement strategies

Aqueous polyphenol eye drops are the most studied formulation type because of their ease of administration, low cost, and clinical familiarity. However, their limitations include poor solubility of most polyphenols at physiological pH, quick elimination by tear turnover and blinking, and poor corneal penetration, resulting in only a small percentage of the instilled dose of the drug reaching intraocular target tissues [38, 43]. Aqueous preparations of unencapsulated quercetin require the 4-times daily dosing to demonstrate therapeutic efficacy in chronic dry eye animal models [24, 28]. Cyclodextrin complexation can significantly enhance the solubility and stability of polyphenols. Complexation of quercetin, resveratrol, or oleuropein with hydroxypropyl-β-cyclodextrin (HPβCD) enhances apparent aqueous solubility by 2-4fold and prevents hydrolysis and oxidative degradation on polyphenol cargo [33, 44]. The hyaluronic acid (HA) is a natural component of the tear film, which has a dual functionality in terms of giving longer tear film dwell time between 2-4 h in increase over minutes, with the addition of solution viscosity and intrinsic lubrication of the cornea as a way of preserving epithelial health. Other research studies demonstrated that HP-β-CD-polyphenols solutions containing a concentration of 0.2-0.3% HA retained more than 95% antioxidant activity in corneal cell models and exhibited 2-3-fold corneal penetration enhancement compared to non-complexed solutions [21, 44]. Nevertheless, HA-enriched cyclodextrin preparations remain limited by their inability to maintain the therapeutic concentrations beyond 2-4 h after instillation. Consequently, such formulations are insufficient as a mono-therapeutic option for chronic disease conditions that require sustained therapeutic levels over 8-12 h [24].

In situ gels: thermosensitive and mucoadhesive systems

In situ gelling systems represents paradigm shift in the delivery of actives to the anterior segment of the eye, in response to temperature-dependent, pH-dependent, or ion-induced solution-to-gel transitions [28]. These formulations are free flowing solutions at room temperature and are rapidly undergo phase transition into gel at the ocular surface due to temperature of the eye (32-34 °C) or pH of the tear fluid (6.8-7.4) or ions present in the eye (Na^{+}, k^{+}, Mg^{+2}, Ca^{+2}) and forming physical depots that resist drainage by the tears with a prolonged residence time of 8-24 h at the ocular surface. Thermo-responsive EGCG gels prepared based on poly(N-isopropylacrylamide)-gelatin or Pluronic F127 systems exhibit more favourable behaviour in comparison to aqueous drops due to two effects: extended precorneal residence time, which is about 8-fold longer than free solutions, and controlled-release kinetics due to gel matrix and not burst release due to simple solutions [45, 46]. Single instillations of EGCG thermos-responsive gels produced 40 per cent acceleration of healing in the corneal epithelium, 50 % of suppression of pro-inflammatory cytokines (IL-1β, TNF-α), and total maintenance of conjunctival goblet cell density in the preclinical models of drug in medically relevant disease animal models (dry eye disease). The main limitations of in situ gel systems include transient blurring of vision during gel residence (typically for 15-30 min), and the feeling of foreign bodies, which restricts thermos-responsive gels more in the status of adjunctive therapy at night or in specific situations where disease severity necessitates the continuous gel application [23].

The complementary mucoadhesion is achieved using non-thermosensitive polymers such as HPMC, CMC, chitosan, gelatin HA, which react electrostatically or by hydrogen-bond with negatively charged ocular mucins. Such interactions increase retention time 4-9 times over conventional formulations [25]. Curcumin-loaded in situ gels fabricated using a combination of mucoadhesive polymer (HPMC/CMC) exhibited 5.4-8.8-fold improvement in corneal penetration and therapeutic residence time, resulting in the dosing administration to daily once instead of 4-6 times daily of conventional drops. The use of cationic chitosan coating combined with gellan gum thermos-responsive matrix as hybrid thermosensitive-mucoadhesive formulations produced 9.24 fold increase in the area under the curve (AUC) and 3.38 fold increase in the peak concentration (C_{max}) compared to free drug suspensions [23, 46]. In the treatment of chronic anterior inflammation and dry eye syndrome, mucoadhesive in situ gels found to be superior to conventional eye drops by their ability to maintain therapeutic concentrations over 8-24 h with a single or twice-daily dose, thereby enhancing patient compliance. Nevertheless, the key gap which continues to be unfilled is that no prospective randomised controlled trials have directly involved the comparison of multiple mucoadhesive platforms (thermos-responsive or non-thermosensitive or hybrid) in the same groups of patients to allow an evidence-based clinical selection of the most cost-effective platform to support the advancement of regulatory modalities.

Semi-solid formulations

The use of ophthalmic ointments is still comparatively not used in delivering polyphenols despite the evident benefits in the nocturnal use and therapy. Ointment bases, including lipids, have the potential to offer extended residence (typically 8 h or longer), safeguard polyphenols against light- and oxygen-scale impact, and allow controlled diffusion of drugs through the semisolid structure of the base. Preliminary clinical and preclinical evidence with antioxidant-based ointments implies that chronic overnight exposure could have the effect of relieving ocular surface inflammation and enhancing the evidence of chronic eyelid disease without significant safety issues. These ointments should be placed in the system of polyphenols as a complementary treatment, but not as a daytime treatment alone. Perhaps the most logical option is to use daytime nano-enabled or mucoadhesive drops/gels, with a polyphenol-or vitamin E-enriched ointment in the lid margin at night, such that the daytime drops cover the entire day, but the effect of the blurred vision on the day-to-day activities is limited. Due to visual disturbance and greasiness, ophthalmic ointments cannot be used as daytime monotherapy other than in short-term rescue cases [24, 28].

Lipid-based nanosystems

Nanoemulsions: Enhanced penetration with stability limitations

Another formulation strategy involves oil-in-water nanoemulsions with a droplet size of approximately 5-25 nm. Nanoemulsions are composed of non-ionic surfactants (Tween 80, Transcutol P) that stabilize the nanoparticles and promote rapid penetration into the cells by temporarily disrupting tight junctions and facilitating diffusion through cells. Surfactants, through their mechanistic action, partition into lipid bilayers of the corneal epithelial cell membrane transiently: destabilising tight junction proteins and raising paracellular pore-ability; and stimulating uptake in the

transcellular membrane by oil-phase lipophilicity [47, 48]. Comparative permeability experiments measuring the fluxes of fluorescently labelled polyphenols across isolated rabbit cornea have shown that quercetin-loaded nanoemulsions achieved a 9-fold greater corneal flux compared with plain aqueous solutions. Curcumin nanoemulsion fabricated using Pluronic F127/TPGS with a loading density of 4-5 mg/ml and particle size below 20 nm demonstrated adequate retinal penetration to exert neuroprotective effects in glaucoma experimental models. These formulations resulted in 4-fold higher survival of retinal ganglion cells and improved preservation of retinal optic nerve structure than controls [21, 23]. Notwithstanding these benefits, nanoemulsions stabilised by surfactant have severe translation limitations. Most of them can often be characterised by intrinsic physical instability at storage due to lipid oxidation and coalescence, resulting in loss of biological activity in 2-4 w at room temperature. The non-ionic surfactants that are necessary to stabilise the emulsions may stimulate ocular irritation and allergy reactions when concentrations exceed 0.5-1.0 % [48]. Compared to more resistant solid lipid nanoparticle-based systems, nanoemulsions are superior in acute permeability but failures in long term shelf stability translational obstacles that have hindered clinical use though decades of preclinical success have indicated their success [49].

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)

SLNs and NLCs are lipid-based systems, in which solid or partly amorphous lipid phases are used, instead of liquid oil, to overcome the issue of stability that makes nanoemulsion translation into clinical application impossible [50]. SLNs are comprised of solid lipids (glyceryl behenate, cetyl palmitate), which create rigid nanoparticle matrices that release polyphenols in a sustained manner for a period of 8-24 h [48, 49]. SLNs loaded with curcumin exhibited 4.5-8.8 fold increment in corneal bioavailability compared to free curcumin suspension. Furthermore, nanoemulsions demonstrated superior chemical stability, with storage conditions indicating retention of 90% polyphenol loading over a period of 12 w at room temperature [50]. Penetration of SLNs can occur through transcellular uptake through endocytosis and through sustained release kinetics, intracellular delivery. NLCs substitute rigid lipid core with partially amorphous lipid mixtures (solid lipids+liquid oil in specific proportions) that enhance drug loading capacity (up to 80% drug content compared to 10-20% of SLNs) and have markedly superior chemical stability than that of nanoemulsions [50]. In preclinical models, highly drug-loaded NLCs were shown to have superior performance; quercetin-loaded NLCs produced a statistically significant (6.5 fold) increase in tear film lipid layer thickness and 45% less epithelial damage compared to conventional eye drops and demonstrated prolonged therapeutic effect for 12 h of dosing than conventional eye drops [49]. Table 1 presents an overview of lipid-based nanocarriers for ocular polyphenol delivery, with emphasis on release characteristics and therapeutic efficacy.

Table 1: Lipid-based nanocarriers for ocular delivery of polyphenols: release profiles and therapeutic outcomes

Polyphenol	Lipid matrix	Key innovation	Release profile (PK)	Therapeutic outcome (PD)	Reference
Curcumin	Glyceryl monostearate	Cationic DOTAP coating on SLNs	~90% release at 48 h	8.8-fold ↑ corneal permeability; neuroprotective retinal levels	[21, 33]
EGCG	Precirol® ATO 5	Hyaluronic acid surface modification	Zero-order release up to 120 h	~50% reduction in ROS in lens epithelium	[23, 51]
Mangiferin	Cetyl palmitate	NLCs with Transcutol® P as permeation enhancer	~75% release at 72 h	4.5-fold ↑ bioavailability vs. suspension; enhanced corneal permeation	[49]

Although the stability of SLNs and NLCs is significantly higher than that of the nanoemulsions, their scalable production under the GMP conditions has not yet been fully resolved. The commonly used fabrication processes, including high-pressure homogenization, ultra-centrifugation, and membrane extrusion, are expensive, time-consuming, and challenging to implement at an industrial scale [50]. An additional challenge of terminal sterilisation by gamma irradiation, which induces lipid peroxidation and coalescence, while ethylene oxide sterilisation poses the risks of residual gas contamination. These manufacturing limitations and lack of USFDA regulatory guidance specific to lipid nanoparticles have confined the development of SLNs and NLCs to early preclinical stages despite their high-performance [25, 26].

Polymeric nanosystems

Chitosan-based mucoadhesive drug delivery system

Chitosan nanoparticles represent an alternative polymeric drug delivery platform, which enables the drug release by dual pathways of surface retention and intracellular release. The intrinsic positive charge of chitosan at physiological pH also facilitates the electrostatic interaction with corneal mucins, which are negatively charged [22, 42]. Mucoadhesion studies concluded that chitosan nanoparticles exhibit prolonged residence time through adhesion for 8-12 h as opposed to 1-2 h of non-adhesive control nanoparticles. In addition to the surface adhesion, chitosan nanoparticles can also serve as intracellular polyphenol carriers via receptor-mediated endocytosis. A confocal microscopy study reveals that the chitosan nanoparticles labelled with fluorescent labels accumulated in corneal epithelial cells through the endocytic route, setting a benefit of intracellular delivery [23, 25]. Quercetin-loaded nanoparticles decorated with quaternary ammonium to chitosan attained 60-70% TNF-α and IL-1α (compared to 30-40% of free drug) and a similar result of increasing corneal antioxidant enzyme activity, superoxide dismutase, and catalase by 45-60% compared to free drug in quaternary ammonium-decorated chitosan quercetin nanoparticles in dry eye models [28].

PLGA and gelatin polymeric systems

PLGA (poly (lactic-co-glycolic acid)) nanoparticles allow the fine-tuning of the drug release for several days to several months by altering lactic-glycolic acid ratios, LA: GA ratios of 50:50 to 85:15. Curcumin-loaded PLGA nanoparticles fabricated using an LA: GA ratio of 755:25 controlled the drug release for 14 days. These nanoparticles demonstrated a significant *in vivo* effect in the cataract experimental model, producing 55% reduction in the lens opacity in cats when instilled twice a day compared to controls [22, 33]. Gelatin nanoparticles offer a naturally available and biodegradable alternative, having, in general, faster degradation kinetics (typically within 3-7 days). These attributes are particularly advantageous for the management of acute or subacute inflammatory responses, where shorter dosing schedules are acceptable [52]. Their biocompatibility, ease of preparation, and ability to be chemically crosslinked or surface-modified also further favour the loading of sensitive polyphenols. These modifications do not damage the structural integrity of loaded compounds and cause only minimal ocular irritation [23, 25].

Polymeric micelles

Polymeric micelles are a viable alternative in enhancing the apparent solubility of highly lipophilic polyphenols, but they pose significant concerns about the ocular stability and tolerability [16]. Examples include curcumin micelles of Pluronic F127/TPGS (such as curcumin C10, curcumin C8, curcumin C6, and curcumin C3), which have been reported to have a solubility rate (compared to dissolved solubility) approximately 40-fold higher (from approximately 3 g/ml to approximately 120 g/ml) [45, 47]. This enhanced solubilisation (table 2) has potential, in principle, to sustain higher drug loading in ophthalmic formulations and augment the amount of drug available for uptake by the cornea or conjunctiva [23].

Nevertheless, polymeric micelles have an intrinsic weakness as they are easily destabilised when instilled onto the ocular surface. The rapid dilution of the tear fluid may cause the concentration of the surfactant to become lower than the critical micelle concentration, causing the breakdown under osmotic pressure of the micelles and desorption of the surfactant. This may result in premature initial burst release of the drug instead of a sustained release that is typically predicted in pre-formulation studies [28]. Besides, the comparatively high concentration of surfactants is required to stabilise the micelles. For instance, Pluronic F127 at concentrations of greater than 1-5%w/v usually may cause eye irritation and discomfort upon chronic administration. Consequently, polymeric-micelle delivery systems are suitable mostly for short-term use or as adjunctive therapies, but not as unique long-term therapeutics unless their composition and dosage are carefully optimized [21, 23].

Table 2: Polymeric micelle systems for ocular delivery of polyphenols: Solubility enhancement and ocular retention

Polyphenol	Polymer system	Particle size (nm)	Solubility enhancement	Ocular retention/pk effect	Reference
Curcumin	Pluronic® F127/TPGS micelles	18.5±2.1	~40-fold vs free drug	Retinal accumulation ↑ ~4×; sustained RGC protection in EG models	[21, 39]
Quercetin	PEG–Poly(ε-caprolactone) micelles	25.3±1.8	~35-fold vs free drug	Tear film stability ~6 h vs rapid wash-out of solution	[25, 45]
Myricetin	Polyoxyl 15 hydroxystearate micelles	21.7±3.2	~28-fold vs free drug	Corneal flux ↑ ~9× compared with free drug	[21, 39]

Emerging drug delivery platforms for the posterior ocular segment

Intravitreal delivery and sustained-release systems

Direct intravitreal injection may provide rapid and high concentrations of polyphenols in the posterior segment by bypassing all the ocular barriers and directly delivering the drug into the vitreous humour and retinal tissues [7]. Experimentally proven biological activity and its potency have been demonstrated for intravitreal injections of curcumin and resveratrol, which significantly reduce the number of photoreceptor apoptosis, prevent pathological neovascularisation, and inhibit microglial activation in age-related macular degeneration, diabetic retinopathy, and uveitis models. Nonetheless, the therapeutic value of free polyphenols does not last long [36]. The rapid vitreous clearance of intravitreally administered drugs (usually within 4-6 days), requires frequent injections, which are associated with risks of endophthalmitis (-0.03-0.05 % injection), rhegmatogenous retinal detachment (-0.05-0.1 % injection), traumatic cataract and vitreous opacification, that may subsequently require a surgical intervention. Cumulatively, all these risks justify the development of sustained-release drug delivery systems in order to reduce the number of injections while maintaining the therapeutic concentration in the posterior segment of the eye [53].

Prodrug chemistry and nanoparticulate depot systems are emerging approaches for sustained intravitreal delivery of polyphenols [22]. A notable example is the water-soluble curcumin prodrug Cur-2p, which is administered via intravitreal injection. Although the conjugate is rapidly soluble in aqueous solution, it undergoes *in vivo* hydrolysis by tissue phosphatases at the site of injection to release free curcumin and subsequently induce the in-situ formation of nanoparticles. In rodent models of uveitis, a single injection of Cur-2p intravitreally showed effective control of inflammation and oxidative stress for 4-6 w. This sustained therapeutic property is superior to free curcumin, which requires repeated injections to achieve a similar effect [23].

Although preclinical findings are promising, there are no polyphenol-based intravitreal implants or sustained-release formulations currently undergoing clinical trials [53]. This gap indicates that several critical impediments in clinical translation, including attainment of reproducible production under GMP conditions, achievement of uniform drug loading and predictable release kinetic models, validated terminal sterilisation protocols without compromising polymer integrity or polyphenol stability, and producing long-term intraocular safety and tolerability data. Addressing these requirements often necessitates 12 mo or longer animal studies to meet regulatory specifications for intravitreal drug products [26, 42].

Systemic oral delivery

Oral polyphenol supplementation offers distinctive benefits of high accessibility and pan-ocular systemic support [30]. One of the earliest well-designed clinical trials provided robust clinical evidence that oral polyphenol supplementation significantly alleviated ocular dryness, reduced corneal staining, and stabilised the tear film lipid layer. It was found to be that these benefits were sustained and extended to the 6-month follow-up, demonstrating superior results compared with the placebo group. Anthocyanin-rich diets augment the accumulation of dietary anthocyanins in the ocular tissues, including the lacrimal gland and conjunctiva, where they mitigate oxidative stress and stimulate lacrimal gland secretion and subsequently reduce the tear film osmolarity [18, 19]. Oral intake of resveratrol ameliorated retinal blood flow (assessed by laser Doppler flowmetry), reduced microglial activation, and retinal ganglion cell death in experimental models of diabetic retinopathy and glaucoma, compared to control groups. EGCG oral supplementation improved the activity of retinal superoxide dismutase by 35-50 % and ischemic retinal injury in ischemia-reperfusion injury models [19, 51].

Despite the potential benefits of oral polyphenols, they still face several critical limitations. Most clinical investigations evaluating their effects on retinal diseases have been limited to small-scale pilot studies or case reports. To date. There are no prospective randomised control trials employing standardised ophthalmic outcomes (visual acuity, intraocular pressure, retinal function testing) that have been published to support the therapeutic efficacy of polyphenols against posterior segment retinal disorders. First-pass hepatic metabolism significantly marked the oral absorption of polyphenols, resulting in only 5-15 % of the ingested dose reaching the systemic [30]. This poor bioavailability indicates lower intraocular levels, usually 1-5 μM in retinal tissue upon oral administration, compared to 50-100+μM achieved through intravitreal injection. Systematically administered oral polyphenols are mostly useful as adjunctive therapies for chronic metabolic ocular diseases (dry eye, early AMD). However, they are unlikely to be effective as monotherapy for acute posterior segment disease or severe inflammatory diseases, which require high localized drug levels for potential therapeutic efficacy [21, 30].

Evidence-based hierarchical framework for anterior segment formulation development

Most immediately translationally viable

Mucoadhesive in situ gels and mucoadhesive gel-forming inserts (thermos-responsive or non-thermo-sensitive) demonstrate an optimal balance of therapeutic efficacy (5.4-9.2-fold improvement in bioavailability, supported by quantified pharmacokinetic data), manufacturing feasibility

(conventional polymer-based processes), and regulatory compliance (polymers such as hyaluronic acid and chitosan are already approved in multiple ocular products) [24]. For the management of chronic anterior inflammation and dry eye disorders, once-daily or twice-daily formulations represent the most immediately translatable platform for advancement into human clinical trials [46].

Prospective for future investigation

Hyaluronic acid-enriched cyclodextrin solutions are best on the excellent of mild prophylactic therapy and chronic ocular supplementation, owing to their simplicity of manufacture and well-established safety profile however, they are lacking therapeutic richness for the management of acute inflammatory disorders [44]. Chitosan nanoparticles have strong efficacy and a favourable manufacturing profile, but further optimisation is required in terms of loading efficiency and stability of the formulation before advanced translational development [25].

High efficacy with significant translational barriers

Nano emulsions exhibit potential acute corneal penetration, but have constraints of unaddressed formulation stability issues (typical degradation within 2-4 w) and surfactant-associated ocular irritation and lack of a robust long-term safety profile [48]. Complex lipophilic nanoparticle systems (liposomes, SLN/NLC, advanced PLGA formulations) demonstrate strong mechanistic performance and face substantial challenges related to manufacturing scalability and uncertainty in regulatory guidance. Notably, there are no point-to-point pharmacokinetic comparisons between mucoadhesive gels, nanoemulsions, and other advanced nanocarrier systems within the same disease models, which makes it difficult for evidence-based selection of an optimal formulation approach [23, 49]. A detailed summary of diverse polyphenols, formulation methods utilised for ocular delivery, and their therapeutic efficacy is presented in Supplementary File 1

Mechanistic basis, pharmacokinetic considerations, and future perspectives

Mechanisms of enhanced ocular penetration

Nanocarriers enhance ocular delivery of polyphenols in synergistic mechanisms that take place at the ocular surface and in the target tissues. Interaction between cationic and mucoadhesive systems and the negatively charged mucin layer and the epithelial glycocalyx at the tear/cornea interface enhances the residence time and enables tight adhesion to occur between the formulation and cell membranes [3, 23]. This is a long-term precorneal exposure, which is a precondition to relevant drug absorption. Lipid-based carriers and surfactant-stabilised vehicles promote transcellular transport by strongly enhancing the partitioning of lipophilic polyphenols into epithelial cell membranes, and, in certain instances, providing a temporary opening of tight junctions to regulate paracellular flux. The effects can significantly enhance the percentage of dose passing through the corneal epithelium and conjunctiva relative to plain solutions or suspensions [47, 54].

Depending on size, surface charge, and the ligand decoration, corneal, conjunctival, and retinal cells can internalise polymeric nanoparticles and micelles through either clathrin-or caveolae-mediated endocytosis, macropinocytosis, or receptor-mediated uptake. After endocytosis, the polyphenol is released by carrier disassembly in acidic endosomal vesicles triggered by pH dependence, which is followed by diffusion to mitochondria and other intracellular sites. This series of acute retention to the cytosol, cellular uptake, and regulated release of intracellular particles supports the prolonged antioxidant and anti-inflammatory actions described in several models of loading polyphenol into nanocarrier systems into the eye [31, 55].

Pharmacokinetic and pharmacodynamic parameters

There is limited quantitative pharmacokinetic information on ocular polyphenol formulations. investigations indicate that corneal and intraocular AUC and peak concentrations improve with nanoformulation versus simple solutions [22]. Hybrid thermosensitive-mucoadhesive gels of chitosan-gellan gum showed an AUC of about 9-fold increased and C_{max} of more than 3-fold increase compared to drug suspension in anterior segment models and residence prolonged to 8-12 h using chitosan-based nanoparticles. The lipid nanoparticles and micelles containing highly lipophilic polyphenols have been reported to have a long half-life in vitreous and retinal tissues in animal models, but the reported values are widely varied across several studies, and many are based on small samples. Prerequisite pharmacokinetic, systematic, and standardised studies with labelled polyphenols are urgently required. The pharmacodynamic analysis usually aims at oxidative stress biomarkers, inflammatory cytokines, neovascularisation biomarkers, and neuronal survival biomarkers. Nano-formulations, in comparison to equal doses of free polyphenols, yield reduced TNF-alpha and IL-1, enhance retinal ganglion cell or photoreceptor survival in most models, and enhance antioxidant enzyme protection [31]. Nonetheless, comparisons of various classes of nanocarriers in the same disease models are rarely made directly, and it is often hard to make definite hierarchies [23, 56].

Biosafety and manufacturing challenges

The ocular nano medicines continue to focus on biosafety. Though most excipients employed in lipid-and polymer-based systems (including phospholipids, some triglycerides, and PLGA) have a history of clinical use, recent surfactants, coating agents, and stimuli-responsive polymers need to be reconsidered in terms of toxicology [22, 48]. The potential risks are long-term low-grade inflammation, reduction of nanoparticles in the trabecular meshwork or retina, disturbance of outflow channels, and unexpected immune system or complement activation [5]. It is the expectation of regulators that the particle size distribution, surface charge, composition, degradation products, and protein-binding profiles should be completely characterised, as well as long-term ocular safety studies in pertinent animal models [57].

Another important bottleneck is manufacturing and sterilisation. Most polyphenol-loaded nanocarriers are developed in laboratory level, such as solvent evaporation, probe sonication/micro emulsification, which is not easily scaled reproducibly using a good manufacturing practice (GMP) environment. Nanostructure can be interfered with by terminal sterilisation methods (e. g. moist heat, gamma irradiation) and can trigger lipid polymorphic transitions or decompose chemically sensitive polyphenols, whereas ethylene oxide sterilisation can lead to leftover toxicants [26, 57]. An alternative is aseptic processing that demands a high control of bioburden, justified filtration, and closed manufacturing systems that have been tested in industrial level. Until effective, scalable, and validated procedures are in place and accompanied by definitive regulatory directions on ocular nanocarriers translation, translation of systems loading polyphenol above the first redevelopment stages is likely to be slow [23].

Regulatory pathways for clinical translation

Ocular nanomedicines do not have specific regulatory guidance. In most cases, ophthalmic drug products, injectables, and nanotechnology-based formulations are assessed by agencies like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) under an existing environment of ophthalmic drugs, injectables, and nanotechnology-based preparations, rather than specific guidance documents [1, 6]. In the case of polyphenol-based ocular nanocarriers, regulators usually require physicochemical characterisation (size distribution, surface charge, composition, degradation profile) to be comprehensive and substantiated by an analytical method requiring good manufacturing practice (GMP) conditions. Ocular biocompatibility and toxicity examinations in suitable animal frameworks are also conducted for several weeks or months to theoretically incorporate any chronic impact [25, 26].

Various regulatory pathways can be taken in the United States by polyphenol-based formulations based on the level of novelty. A 505(b)(2) development programme can be used on products that are close build-ups on an active ingredient that has already been approved or reference product, whereas highly novel system a, like a new depot formulation, new complex nanocarriers are less likely to be eligible on a 505(b) (2) pathway and would instead require a full development programme under 505(b) (1) [42]. The initial interaction with the regulators during pre-IND meetings is important to agree on what actions will be expected to be done in terms of manufacturing quality, non-clinical safety packages, and the clinical trial design [1].

In clinical development terms, placing polyphenol nanomedicines as an adjunct to already developed treatment would probably be more acceptable at an earlier stage than trying to find independent indications. The examples are the use of intravitreal prodrug-based depots together with the regular anti-VEGF in treating retinal disease, or the use of nano-enabled topical polyphenol formulations and traditional lubricants in dry eye [18]. These sorts of combination or add-on designs can show incremental recommendations whilst exploiting the current standards of care, as an effective way of working out the eventual integration of polyphenol-based nanomedicines into everyday ophthalmic activity [23].

Future perspectives

Future research in polyphenol-based ocular drug delivery should prioritise the rational integration of mechanistic insights with advanced formulation engineering to overcome persistent ocular barriers and variability in therapeutic response. The convergence of nanotechnology, stimuli-responsive systems, and bioinspired carriers offers significant potential to enhance ocular bioavailability, site-specific targeting, and sustained drug release across both anterior and posterior segments. Equally important is the establishment of standardised *in vitro–in vivo* correlation models, clinically relevant disease models, and robust safety assessments to accelerate translational progression. Advances in scalable manufacturing, regulatory harmonisation, and quality-by-design approaches will be critical for clinical adoption. Collectively, these efforts are expected to facilitate the transition of polyphenol-based ocular formulations from experimental.

CONCLUSION

Polyphenols are scientifically credible therapeutic candidates for ocular diseases due to their well-established antioxidant and anti-inflammatory effects in experimental models. However, clinical translation is limited by poor aqueous solubility, rapid precorneal clearance, and restricted ocular permeability. For anterior segment indications, mucoadhesive in situ gel systems represent the most feasible near-term translational strategy. These systems demonstrate validated bioavailability enhancement and benefit from GMP-compatible manufacturing and regulatory precedent. Accordingly, mucoadhesive gels for dry eye disease and anterior uveitis merit progression to randomized controlled clinical trials. No single optimal delivery route exists for anterior segment disorders, necessitating rational combination strategies. Integrated topical, oral, and sustained intravitreal approaches may be required for acute, severe, or chronic ocular diseases. Addressing gaps in pharmacokinetics, PK/PD relationships, manufacturing scalability, regulatory pathways, and clinical efficacy will be critical to enabling evidence-based clinical translation.

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CONFLICT OF INTERESTS

The authors declare no competing interests related to financial or personal perspectives

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