Clinical Interventions in Aging

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REVIEW

Targeting Senescence, Oxidative Stress, and Inflammation: Quercetin-Based Strategies for Ocular Diseases in Older Adults

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Abstract: Quercetin, a flavonol abundant in fruits and vegetables, has attracted significant attention for its senotherapeutic effects, which involve the selective elimination of senescent cells and the modulation of pro-inflammatory phenotypes that contribute to age-related dysfunctions. These actions, together with its antioxidant, anti-inflammatory, neuroprotective, and anti-angiogenic properties, make quercetin a promising strategy for ocular diseases associated with visual impairment in older adults such as age-related macular degeneration, cataract, diabetic retinopathy, and glaucoma. This review emphasizes the mechanisms by which quercetin exerts its protective effects, with particular attention to its ability to target cellular senescence, reduce oxidative stress, and modulate inflammation. Despite extensive preclinical evidence, the clinical application of quercetin remains limited due to challenges related to poor bioavailability, rapid degradation, and the absence of standardized ocular formulations. Progress in drug delivery systems, including nanoparticles, nanoemulsions, and solid lipid carriers, provides promising strategies to overcome these barriers. In addition, combining quercetin with established treatments, such as anti-vascular endothelial growth factor (VEGF) agents and neuroprotective drugs, may enhance its therapeutic potential in managing and possibly reversing age-related ophthalmic disorders.

Keywords: quercetin, senescence, age-related macular degeneration, cataract, diabetic retinopathy, glaucoma

Introduction

Quercetin is a flavonol, a subclass of flavonoids, found in vegetables and fruit. Quercetin is abundant in onions, curly kale, leeks, broccoli, blueberries, red wine, and green tea.[1,2] Known for its potent antioxidant properties, quercetin has attracted significant attention in both clinical and experimental research.[3–6] Its multifaceted bioactivity makes it a promising compound for potential therapeutic applications across common ocular diseases in older adults associated with visual impairment, including age-related macular degeneration (AMD), cataract, diabetic retinopathy, glaucoma.[7–11]

Visual impairment in older adults predominantly results from chronic and progressive ocular disorders, which become significantly more prevalent and severe with advancing age. Cataract, the leading cause of reversible blindness globally, involves the gradual opacification of the crystalline lens, primarily driven by cumulative oxidative stress and protein aggregation within the lens fibers.[12] Similarly, AMD, characterized by degeneration of the retinal pigment epithelium (RPE) and photoreceptor cells, is one of the main causes of irreversible central vision loss in the elderly.[13] Diabetic retinopathy, a prevalent complication of diabetes mellitus, contributes to visual impairment through chronic hyperglycemia-induced vascular alterations, resulting in retinal ischemia, inflammation, and leakage.[14] Glaucoma, which predominantly affects retinal ganglion cells and optic nerve fibers, manifests primarily through elevated intraocular pressure, oxidative stress, and vascular insufficiency, progressively leading to irreversible vision loss.[15]

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Emerging experimental evidence highlights the promising therapeutic potential of quercetin, particularly in AMD, through its anti-angiogenic effects, potentially slowing disease progression and modulating abnormal vascular responses. Moreover, the demonstrated neuroprotective and anti-inflammatory properties offer significant potential for cataract, diabetic retinopathy and glaucoma, conditions characterized by pronounced oxidative damage and inflammation.[4] Despite this, clinical evidence on the use of quercetin in ophthalmic disorders remains underexplored. However, several clinical trials have evaluated quercetin as a dietary supplement in various systemic disorders at doses ranging from 150–1000 mg/daily highlighting both the efficacy and safety profile of quercetin.[16–19]

Aging significantly exacerbates the pathological processes underlying these ocular diseases. Increased oxidative stress, persistent inflammation, mitochondrial dysfunction, and cellular senescence represent common age-associated mechanisms that amplify disease progression and severity, underscoring the necessity for targeted therapeutic approaches.[20,21] In this context, quercetin, through its antioxidant capability, effectively mitigates oxidative stress by scavenging reactive oxygen species (ROS), which play a critical role in initiating and accelerating ocular tissue damage. Furthermore, quercetin modulates inflammatory pathways, inhibits abnormal angiogenesis, and influences cell proliferation and senescence, collectively attenuating the pathophysiological progression in these age-associated ocular conditions.[22–24]

Notably, recent research highlights the significant senotherapeutic potential of quercetin. Senotherapeutics are compounds that selectively target senescent cells, either eliminating them (senolytics) or modulating their detrimental effects (senomorphics). By reducing cellular senescence and its associated secretory phenotype (SASP), quercetin could alleviate chronic inflammation and tissue dysfunction commonly observed in aging eyes, thereby potentially delaying or reversing the progression of ocular diseases such as AMD, diabetic retinopathy, glaucoma, and cataract. Given that cellular senescence is increasingly recognized as a pivotal contributor to ocular aging and disease, the senotherapeutic effects of quercetin warrant considerable attention in future therapeutic strategies.[25–29]

This narrative review aims to provide a comprehensive analysis of quercetin as potential therapeutic agent in ocular diseases in older adults associated with visual impairment. By synthesizing current research, it highlights the antioxidant, anti-inflammatory, and senotherapeuthic properties of quercetin, which may offer protective and restorative effects against these ocular diseases. The review also explores the pharmacokinetic challenges associated with quercetin, recent advancements in ocular delivery systems, and the potential of combining quercetin with other therapeutic agents.

Quercetin

Chemical Properties and Natural Sources

Quercetin is a flavonol, one of the most abundant subclasses of flavonoids within the polyphenol family, widely distributed in the plant kingdom and notable for its extensive range of biological activities. A flavone backbone characterizes the chemical structure of quercetin, specifically s 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromophene-4-ketone, also known as 3,3',4',5,7-pentahydroxyflavone, with the molecular formula C15H10O7 and a molecular weight of approximately 302.24 g/mol. Its structure comprises two benzene rings (A and B) connected by a three-carbon bridge that forms an oxygen-containing heterocycle (C ring).[30] The hydroxyl groups at positions 3, 5, 7, 3', and 4' are crucial for antioxidant activity, as they can donate hydrogen atoms to neutralize free radicals and chelate transition metal ions, thereby reducing oxidative stress.[31] The planar structure and extensive conjugation of quercetin allow it to interact with various biomolecules, including proteins and enzymes, influencing numerous biological pathways. The capacity of quercetin to form hydrogen bonds and engage in π-π stacking interactions enables it to modulate, mainly inhibiting, the activity of enzymes like cyclooxygenase (COX), lipoxygenase (LOX), and kinases, impacting inflammatory and cell signaling pathways involved in cancer.[24,32]

Natural sources of quercetin are abundant and diverse. High levels are found in capers (*Capparis spinosa*), onions (*Allium cepa*), especially red onions, apples (*Malus domestica*), berries such as cranberries (*Vaccinium macrocarpon*) and blueberries (*Vaccinium corymbosum*), and grapes (*Vitis vinifera*). Leafy green vegetables such as kale (*Brassica oleracea var. sabellica*), spinach (*Spinacia oleracea*), and broccoli (*Brassica oleracea var. italica*) also contribute significantly to dietary intake.[24] Additionally, quercetin is present in herbs such as dill (*Anethum graveolens*) and cilantro (*Coriandrum*

sativum), and in beverages such as green and black tea (*Camellia sinensis*) and red wine, derived from quercetin-rich grape skins.[30]

In foods, as shown in Figure 1, quercetin commonly exists as glycosides, where sugar moieties are attached to the hydroxyl groups, forming prevalent compounds such as quercetin-3-O-glucoside (isoquercitrin), quercetin-3-O-rutinoside (rutin), guaijaverin (quercetin-3-O-α-L-arabinopyranoside), avicularin (quercetin-3-O-α-arabinofuranoside), hyperoside (quercetin-3-O-β-D-galactopyranoside), quercitrin (quercetin-3-O-rhamnoside) and reynoutrin (quercetin-3-O-β-D-xylopyranoside).[33] Glycosylation enhances its hydrophilicity; for instance, the water solubilities of quercetin, rutin, and isoquercitrin are 0.001, 0.034, and 0.095 mg/mL, respectively.[34,35] Conversely, quercetin is more soluble than rutin and isoquercitrin in polar organic solvents.[36] Additionally, quercetin dissolves readily in acidic environments, and its solubility increases with rising pH levels.[37]

Bioavailability

Bioavailability refers to the fraction of an orally administered substance that is absorbed and becomes available for physiological activity or storage. Despite the prevalence of quercetin in foods, its bioavailability in humans is relatively low due to poor water solubility and extensive first-pass metabolism. Light, heat, and storage time all influence the stability and content of quercetin in the diet, thereby altering bioavailability. Its inadequate bioavailability remains the

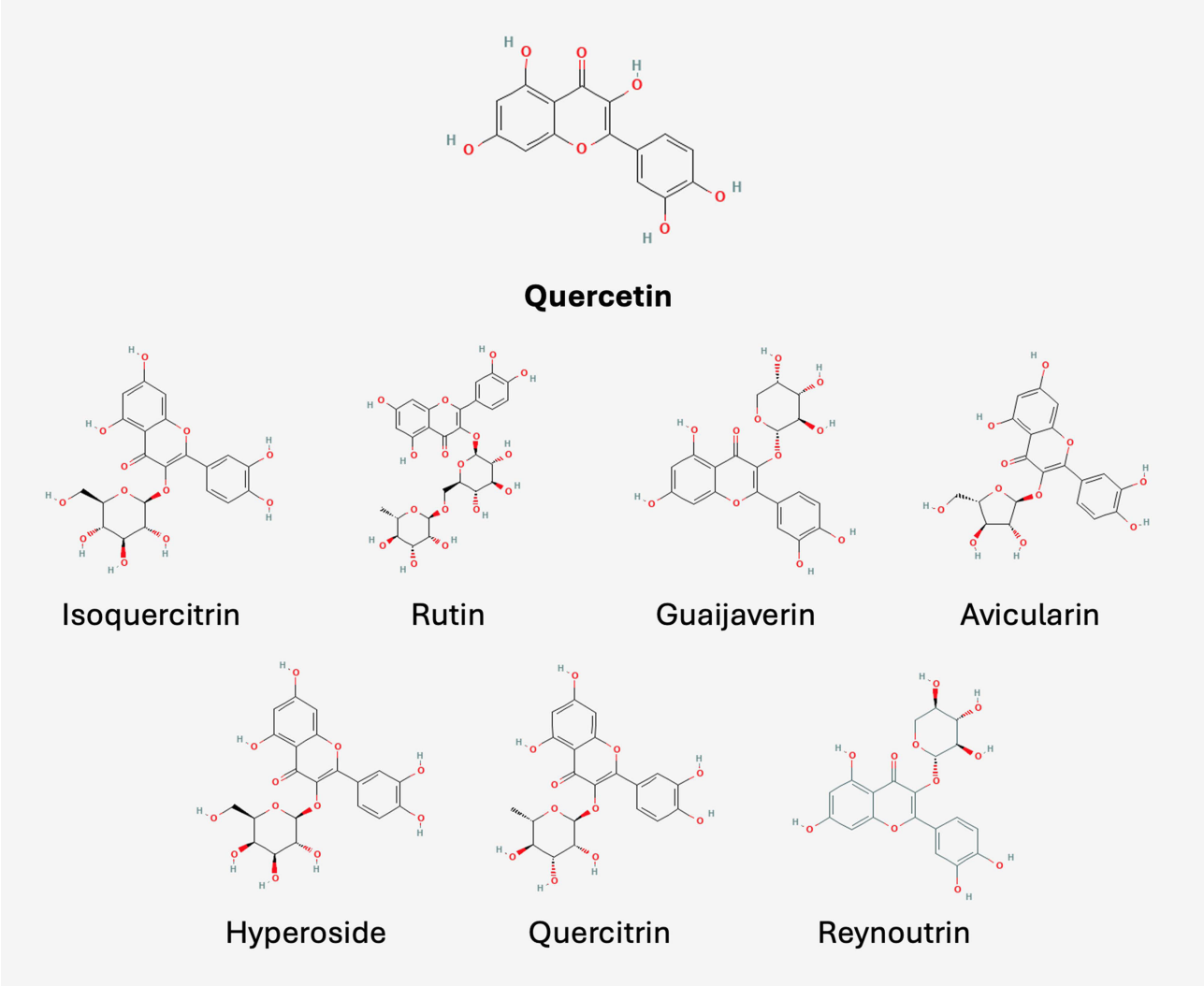

Figure 1 Chemical structures (obtained from PubChem) of quercetin and its glycoside derivatives.

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primary issue in using quercetin. Most published studies have reported the main factors affecting oral bioavailability, such as structure, food matrix, delivery system, and dosages of quercetin.[33] The half-life distribution and elimination of quercetin administered intravenously are 0.7–7.8 minutes and 3.8–86 minutes, respectively, while clearance and volume of distribution are 0.23–0.84 L/min/m² and 3.7 L/m².[38] These results indicate that quercetin is rapidly cleared and has a short half-life in the blood. The primary plasma metabolites are quercetin-3′-sulfate and quercetin-3-glucuronide, reaching peak levels at 0.8 and 0.6 hours, respectively.[39]

Multiple experiments have demonstrated that the sugar moiety is the principal determinant of quercetin absorption. In nine healthy human subjects who underwent ileostomy, the absorption rates were 24 ± 9% for quercetin aglycone, 17 ± 15% for quercetin rutinoside, and 52 ± 15% for quercetin glucosides from onions.[40] Quercetin enhances absorption when it interacts with glucose. Research involving Wistar rats indicated that the absorption efficiency of glycosylated quercetin compounds follows this order: isoquercitrin is absorbed most effectively, followed by quercetin, then rutin, and finally quercetin.[41] Studies on the anti-obesity effects of quercetin and isoquercitrin have shown that isoquercitrin is more effective than quercetin, largely because isoquercitrin has a bioavailability that is 235% higher compared to quercetin. In essence, increased bioavailability leads to enhanced bioactivity.[42]

The composition of the food matrix may significantly influence the bioavailability of quercetin and quercetin glycosides. Interactions between quercetin/quercetin glycosides and various food components during absorption and metabolism affect both the concentration and the duration that different metabolites remain in plasma or organs. In a single-blind, diet-controlled crossover study, consuming 10 mg of quercetin aglycone equivalents from onions was comparable to ingesting 166 mg of quercetin supplement.[43] Similarly, intake of 130 mg of cereal bars enriched with quercetin led to plasma quercetin concentrations up to five times higher than those achieved with the same amount administered via quercetin capsules.[18] Additionally, a clinical study revealed that a high-fat diet significantly increased both the maximum plasma concentration and the area under the curve of quercetin when compared to a low-fat diet.[44] These findings suggest that quercetin dispersed in a solid food matrix with a larger surface area is more readily transferred to the absorption site, thereby enhancing bioavailability.

Consistent and prolonged consumption of quercetin/quercetin glycosides appears to elevate bioavailability, possibly due to the extended presence in the gastrointestinal tract stimulating absorption. In a study where volunteers received 500 mg of quercetin daily for 12 weeks, serum concentrations increased by 385%.[45] In a subsequent double-blind trial, volunteers who took 1000 mg per day of quercetin for three months reached the highest serum concentration of the quercetin metabolite isorhamnetin-3-glucuronide, nearly 1000 ng/mL.[46] Lastly, the limited solubility of quercetin is a major obstacle to achieving high bioavailability. Therefore, strategies aimed at enhancing the water solubility and dispersion of quercetin/QG delivery systems are crucial for increasing circulating levels and improving bioavailability. For example, treatment with quercetin–nicotinamide cocrystals resulted in an approximately fourfold increase in the oral absorption rate of quercetin.[47] Additionally, pharmacokinetic studies in beagle dogs demonstrated that quercetin encapsulated in polymeric micelles significantly improved both the relative oral bioavailability and the half-life compared to the administration of free quercetin.[48]

Absorption, Metabolism and Excretion

After oral administration, quercetin is released from the food matrix and may form soluble aggregates with proline-rich salivary proteins via hydrogen bonds or hydrophobic interactions; this does not impede its absorption. In the acidic environment of the stomach, a small portion of quercetin degrades into phenolic acids like protocatechuic acid, which can be absorbed by the gastric epithelium. Quercetin glycosides, however, are neither absorbed nor metabolized in the mouth and the stomach and proceed to the small intestine for further processing.[49–51]

In the small intestine, enzymes such as lactase-phlorizin hydrolase (LPH) and cytoplasmic β-glucosidase (CBG) play crucial roles in quercetin glycosides' metabolism. Isoquercitrin is absorbed by intestinal epithelial cells via sodium-dependent glucose transporters and hydrolyzed to quercetin aglycone by CBG. Alternatively, QG can be deglycosylated by LPH to quercetin, which is then absorbed through passive diffusion.[52,53] Following absorption, quercetin and quercetin glycosides undergo Phase II metabolism—primarily glucuronidation, methylation, and sulfation—which enhances their hydrophilicity and reduces potential toxicity. Metabolites such as quercetin glucuronides are detected in the small intestine and duodenal fluid. These metabolites

enter the liver via the hepatic portal vein, while unmetabolized quercetin/quercetin glycosides are transported to the large intestine through multidrug-resistance-associated proteins.[54–56]

In the large intestine, residual quercetin/quercetin glycosides and their conjugates undergo extensive metabolism by the gut microbiota, transforming into various phenolic acids.[57] Microbial enzymes such as glycosidases, glucuronidases, and sulfatases release quercetin aglycones from conjugated forms.[53] Bacterial species such as *Bacillus* and *Bacteroides* degrade rutin to isoquercitrin and further to quercetin.[58,59] Quercetin is then converted into metabolites such as 3,4-dihydroxyphenylacetic acid by bacteria, including *Clostridium perfringens* and *Bacteroides fragilis* [75,76]. These metabolites can be absorbed and transported back to the liver for conjugation and eventual excretion in urine, or they may be eliminated in feces. Notably, quercetin and rutin have been detected in both fecal and urine samples.[60] In the liver, further phase II metabolism occurs, producing methylated derivatives such as isorhamnetin and tamarixetin. These compounds are then released into the circulatory system and bile via multidrug-resistance proteins. Biliary metabolites may be recycled back to the small intestine or excreted in feces.[35,61] Moreover, quercetin inhibits several cytochrome P450 (CYP) isoenzymes, including CYP3A4, CYP2C8, CYP2C9, and CYP1A2, potentially leading to interactions with other systemic drugs. These interactions can also result from quercetin modulation of P-glycoprotein (P-gp) efflux transporter, which is responsible for transporting drug molecules from the intracellular to the extracellular space.[62–64]

In the kidneys, circulating quercetin/QG and their metabolites are transported via organic anion transporters located in the renal proximal tubular cells. They are excreted into urine through multidrug-resistance-associated proteins (MRPs) and breast cancer resistance protein (BCRP). Urinary excretion includes various conjugated forms and phenolic acids such as quercetin-3-O-glucuronide, methyl quercetin diglucoside, isorhamnetin, and 3-hydroxyphenylacetic acid.[60,65]

The Role of Oxidative Stress, Inflammation and Senescence in The Aging Eye

Oxidative Stress and Inflammation

Ocular tissues are particularly susceptible to oxidative stress due to high metabolic rates, continuous exposure to ultraviolet (UV) radiation, and high concentrations of polyunsaturated fatty acids, especially in the retina. Phototransduction and metabolic processes principally generate reactive oxygen species (ROS) as byproducts, including superoxide anion ($O_2\bullet^-$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH). ROS are highly reactive molecules capable of altering and damaging cellular macromolecules, in particular DNA, proteins, and lipids.[66] To counter the harmful effects of ROS, ocular cells are equipped with a complex antioxidant defense system. This system includes enzymes such as superoxide dismutase (SOD), catalase (CAT), heme oxygenase (HO), and glutathione peroxidase (GPX), along with non-enzymatic antioxidants like vitamin E, vitamin C, and glutathione (GSH), which function as antioxidant scavengers. The gene expression of antioxidant enzymes is primarily regulated by the nuclear transcription factor known as nuclear factor erythroid 2-related factor 2 (Nrf2). Consequently, it is not surprising that Nrf2 down-regulation has been associated with numerous eye diseases related to oxidative stress.[67–70]

However, the excessive ROS production may impair the antioxidant defense systems, leading to oxidative damage of lipids, proteins, and DNA. In the retina, lipid peroxidation of photoreceptor outer segment membranes disrupts membrane integrity and function, contributing to cell death.[71] Oxidative DNA damage activates poly (ADP-ribose) polymerase (PARP), leading to NAD^+ depletion and impaired cellular metabolism.[72] Protein oxidation can result in enzyme inactivation and accumulation of misfolded proteins, triggering endoplasmic reticulum (ER) stress and unfolded protein response (UPR) pathways.[73]

Oxidative stress is closely linked to inflammation. ROS can activate redox-sensitive transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein-1 (AP-1), promoting the expression of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6 and chemokines. These mediators recruit immune cells and activate resident microglia, which release additional ROS and cytokines, creating a vicious cycle of inflammation and oxidative damage.[74,75] In AMD, oxidative stress accumulates drusen, deposits composed of lipids, proteins, and trace elements between the RPE and Bruch's membrane. Drusen contains oxidatively modified proteins and lipids that can induce immune responses, further contributing to chronic inflammation and complement system activation.[76,77] In glaucoma, elevated intraocular pressure causes mechanical stress

and oxidative damage in retinal ganglion cells (RGCs) and the optic nerve head. ROS-mediated activation of apoptotic pathways, including caspase-dependent and caspase-independent mechanisms, contributes to RGC loss.[78]

Cellular Senescence

Cellular senescence is a state of irreversible cell cycle arrest in response to various stressors. It has a dual role: it is beneficial in certain contexts, such as tumor suppression—where it inhibits the proliferation of cancer cells, including embryonic development, wound healing, and tissue repair. Senescent cells are highly metabolically active and secrete pro-inflammatory molecules known as SASP, which attract immune cells to promote their clearance. However, this beneficial process can be compromised in aged tissues, leading to an accumulation of senescent cells that may enhance tissue dysfunction through SASP, rich in pro-inflammatory cytokines and matrix metalloproteinases. Senescent cells exhibit specific features: significant morphological changes like enlargement and flattening due to cytoskeletal rearrangement; presence of senescence-associated heterochromatin foci (SAHF) in the nucleus; increased activity of senescence-associated β-galactosidase (SA-β-gal) reflecting greater lysosomal mass; elevated expression of antiproliferative molecules such as $p16^{INK4a}$; secretion of SASP components including cytokines, chemokines, extracellular matrix proteases, and growth factors; and significant changes in mitochondrial morphology, function, and metabolism, with increased mitochondrial biogenesis and respiration, while remaining metabolically active.[79]

In ocular tissues, senescent cells accumulate with age, causing or contributing to age-related diseases. In the RPE, senescence is induced by oxidative stress, mitochondrial dysfunction, and lipofuscin accumulation.[80] Senescent RPE cells secrete SASP factors like interleukins (IL-6, IL-8), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs), which promote inflammation, neovascularization, and extracellular matrix remodeling. Senescent cells can also propagate senescence to neighboring cells through SASP factors, exacerbating tissue dysfunction.[81,82] Molecular pathways involved in RPE senescence include activation of the $p53/p21^{Cip1}$ pathway, leading to cell cycle arrest and DNA damage response; inhibition of the $p16^{INK4a}$/retinoblastoma (Rb) pathway, preventing phosphorylation of Rb protein and maintaining cell cycle arrest;[83,84] and telomere shortening, which activates DNA damage responses leading to senescence[85,86] In the trabecular meshwork (TM), senescence impairs aqueous humor outflow due to extracellular matrix deposition and increased stiffness, elevating intraocular pressure and contributing to glaucoma.[86]

Senotherapeutic Effects of Quercetin

Antioxidant Properties

Quercetin exerts potent antioxidant effects through multiple mechanisms. As other flavonoids, it directly scavenges ROS and reactive nitrogen species (RNS) due to its 3'4'-dihydroxy B-ring and hydroxyl group at position 3 of the C-ring, which can donate electrons to neutralize free radicals such as superoxide anion, hydroxyl radical, and peroxynitrite, forming more stable phenoxyl radicals.[87–89] Quercetin also chelates transition metal ions such as Fe^{2+} and Cu^{2+}, inhibiting Fenton and Haber-Weiss reactions that generate hydroxyl radicals.[90]

Beyond direct scavenging, quercetin modulates the expression and activity of endogenous antioxidant enzymes. It upregulates the Nrf2 levels, leading to enhanced translocation of Nrf2 into the nucleus, where it binds to antioxidant response elements (ARE) in the promoters of genes encoding heme oxygenase-1 (HO-1), SOD, CAT, and glutathione S-transferase (GST). Quercetin enhances the cellular antioxidant defense system by upregulating these enzymes and the glutathione levels, providing sustained protection against oxidative damage.[91–94]

Quercetin has been shown to protect retinal ganglion cells from oxidative stress-induced death, inducing the synthesis of Nrf2 and Phase 2 antioxidant enzymes such as HO-1.[95] Similarly, quercetin showed a potent protective effect against oxidative damage in retinal tissue by upregulating antioxidant peroxiredoxins (PRDX) via activation of the Nrf2/Nrf1 transcription pathway and promoting PRDX3 and PRDX5 gene expression.[96] Quercetin may also downregulate photo-oxidative stress in retinal tissue, prevent heterodimer binding of c-Jun and c-Fos proteins at the activator protein (AP-1) transcription factor site, and protect against light-induced photoreceptor degeneration in rats.[97] Additionally, it decreases the formation of methylglyoxal adducts and reduces mRNA expression for receptors of advanced glycation end-products.

Quercetin preserves glutathione by preventing its reaction with photo-oxidized A2E, a blue light-excitable aging fluorophore, and, in rod outer segments incubated with all-trans-retinal to form bisretinoid and exposed to irradiation, lowers the release of the lipid peroxidation product 4-hydroxynonenal.[98] Moreover, in the sodium selenite-induced rat model of cataract, the antioxidant properties of quercetin glycosides may mitigate crystal turbidity caused by SeO_3^{2-} or Ca^{2+}, inhibit selenite-induced cataract formation, strengthen the lens antioxidant defense, and preserve lens structure. Through metal ion chelation, quercetin can reduce proteolytic enzyme activity and bind excess Ca ions, maintaining calcium balance and inhibiting calcium-induced lens opacification.[99]

Anti-Inflammatory Activity

The anti-inflammatory properties of quercetin involve the inhibition of key signaling pathways. It suppresses the NF-κB pathway by inhibiting IκB kinase (IKK), preventing phosphorylation and degradation of IκBα, thus keeping NF-κB sequestered in the cytoplasm and reducing transcription of pro-inflammatory genes. It may also suppress mitogen-activated protein kinase (MAPK) pathways, including ERK1/2, c-Jun N-terminal kinases (JNK), and p38 MAPK, attenuating the expression of inflammatory mediators and cytokines.[100] Moreover, quercetin suppresses COX-2 and LOX enzymes, reducing the synthesis of pro-inflammatory prostaglandins and leukotrienes.[101,102] Quercetin also inhibits MMP-9 activity, preventing extracellular matrix degradation and inflammation.[103] Indeed, it attenuates TNF-α-induced MMP-9 expression in human retinal pigment epithelial cells (ARPE-19) via the ERK1/2 and protein kinase C delta type (PKCδ)-JNK1/2-c-Jun or NF-κB pathways. Significant suppression of VEGF-induced excessive inflammatory response in retinal photoreceptor cells was promoted by quercetin through the inactivation of NF-κB signals via the inhibition of MAPKs and Akt.[22] Similarly, in a model of hyperosmolarity-induced human corneal epithelial cells, quercetin may reduce the expression of inflammatory factors, including IL-6 and TNF-α, by inhibiting the phosphatase and tensin homolog (PTEN)/ phosphatidylinositol 3-kinase (PI3K)/Akt pathway.[104] These data are confirmed by an in vivo model of retinal inflammation, where quercetin reduced the activation of NF-κB, the expression of IL-1β and TNF-α, and the infiltration of granulocytes in retinal tissues.[105]

Senotherapeutic Mechanisms

The term "senolytic" indicates the ability of a substance to target and kill senescent cells selectively, thereby restoring tissue function and reducing the adverse effects of senescence.[106] Quercetin is the only flavonoid with senolytic properties that has been investigated in clinical trials aimed at addressing cellular senescence, particularly in age-related diseases. The results from these trials show that quercetin, particularly in combination with dasatinib, mitigates age-related decline associated with senescence.[107,108] Quercetin exhibits this senolytic activity by targeting survival pathways in senescent cells (Figure 2). One key mechanism involves the inhibition of anti-apoptotic pathways. Senescent cells often upregulate proteins such as B-cell lymphoma-extra-large (Bcl-xL) and B-cell lymphoma 2 (Bcl-2) to evade apoptosis.[109] Quercetin binds directly to the BH3 domain of Bcl-2 and Bcl-xL proteins, thereby inhibiting their activity and promoting apoptosis by the dissociation of Bax from Bcl-xL. This flavanol may also downregulate these anti-apoptotic proteins, promoting apoptosis by decreasing Bcl-2 expression and increasing pro-apoptotic factors such as Bax. This shift induces mitochondrial outer membrane permeabilization, leading to caspase activation and cell death.[25–28] Additionally, quercetin modulates the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, which is crucial for cell survival and metabolism. In senescent cells, this pathway is often overactive, providing survival signals that prevent apoptosis. Quercetin inhibits Akt phosphorylation via SIRT5/PI3K/Akt or PI3K/Akt/mTOR and STAT3 signaling pathways, thereby sensitizing senescent cells to apoptosis by disrupting these survival signals.[110,111] Quercetin exhibits not only senolytic activity but also senomorphic effects, modulating the phenotype of senescent cells by suppressing the SASP without inducing cell death. These complementary actions classify quercetin as a senotherapeutic compound, capable of targeting both the presence and the harmful influence of senescent cells. Quercetin suppresses the activation of NF-κB, a transcription factor that regulates SASP components. In particular, the downregulation of miRNA-155-5p, possibly through the NF-κB signaling inhibition, quercetin reduces the secretion of pro-inflammatory cytokines and chemokines from senescent cells. This suppression alleviates chronic inflammation and diminishes autocrine and paracrine survival signals, making senescent cells more susceptible to apoptosis.[29]

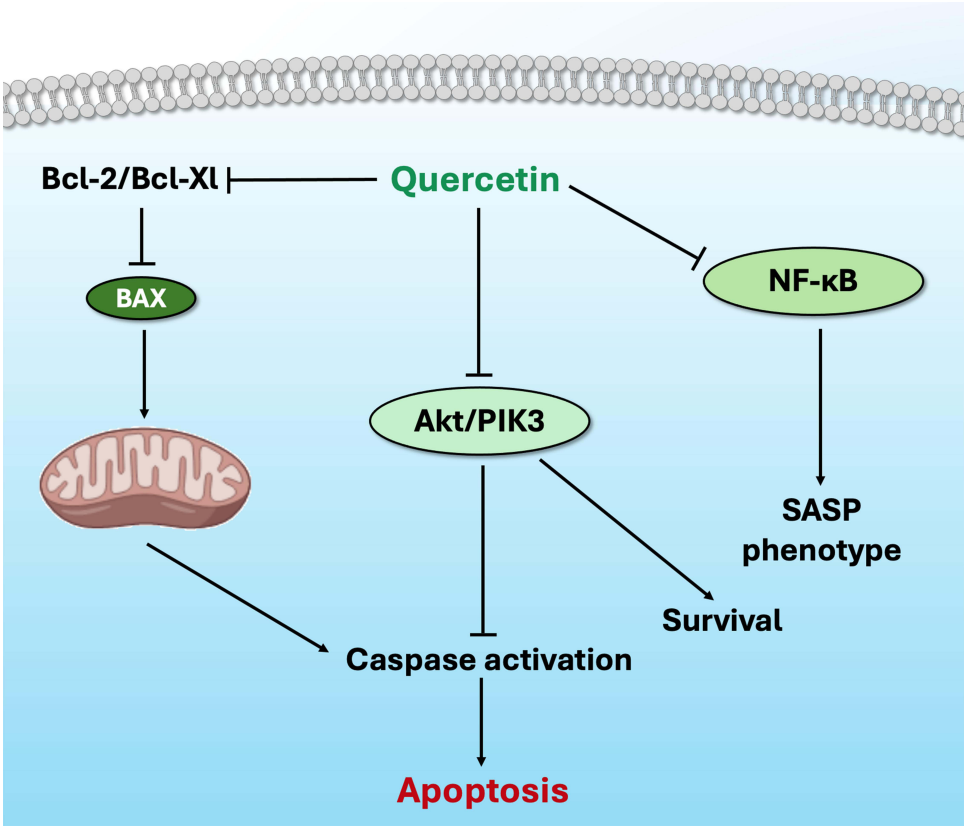

Figure 2 Senotherapeutic mechanisms of quercetin. Quercetin may inhibit anti-apoptotic factors Bcl-2/Bcl-XL and the Akt/PIK3 pathway, promoting caspase activation and apoptosis. Additionally, it may suppress NF-κB signaling, reducing the SASP.

Although quercetin is commonly associated with antioxidant properties that confer various health benefits, significant evidence points to its pro-oxidant potential as a crucial factor in anti-cancer effects. By inducing oxidative stress within tumor cells, quercetin disrupts the cellular redox balance, leading to apoptosis through specific signaling pathways. Its chemical properties, including susceptibility to autoxidation and its role as a co-catalyst in peroxidase-mediated reactions, may facilitate ROS production.[112] It is possible to believe that this anti-cancer characteristic can be extended to senescent cells, also considering the pro-apoptotic effects of quercetin. It may increase ROS in senescent cells, leading to oxidative damage and indirect activation of apoptotic pathways. Elevated ROS levels result in mitochondrial dysfunction and promote cell death in these cells.[113] Moreover, quercetin interferes with autophagy—a cellular process that degrades damaged organelles and proteins to support cell survival under stress. Senescent cells rely on autophagy for maintenance and survival. Quercetin may inhibit autophagic flux in senescent cells, leading to the accumulation of cellular debris and triggering apoptosis.[114,115]

In conclusion, quercetin exhibits senotherapeutic effects through multiple interconnected mechanisms, including the inhibition of anti-apoptotic proteins, modulation of survival signaling pathways, suppression of pro-inflammatory SASP factors, induction of oxidative stress, and interference with autophagy. These actions may collectively contribute to the selective elimination of senescent cells, offering a promising strategy for treating ocular degenerative diseases.

Quercetin and Age-Related Ocular Diseases

Age-Related Macular Degeneration (AMD)

AMD is a leading cause of vision loss in older adults, with an increasing trend of individuals affected worldwide.[13] The disease primarily affects the macula with drusen and pigmentary abnormalities in the initial stages, with eyes with large drusen having a 50% risk of developing late-stage complications (Figure 3). These complications include neovascular AMD or geographic atrophy.[116] The pathogenesis of AMD is multifactorial, with genetic and environmental factors involved.[117–119] Drusen and basal linear deposits, reticular pseudodrusen (RPD), also known as subretinal drusenoid deposits (SDD), and basal laminar

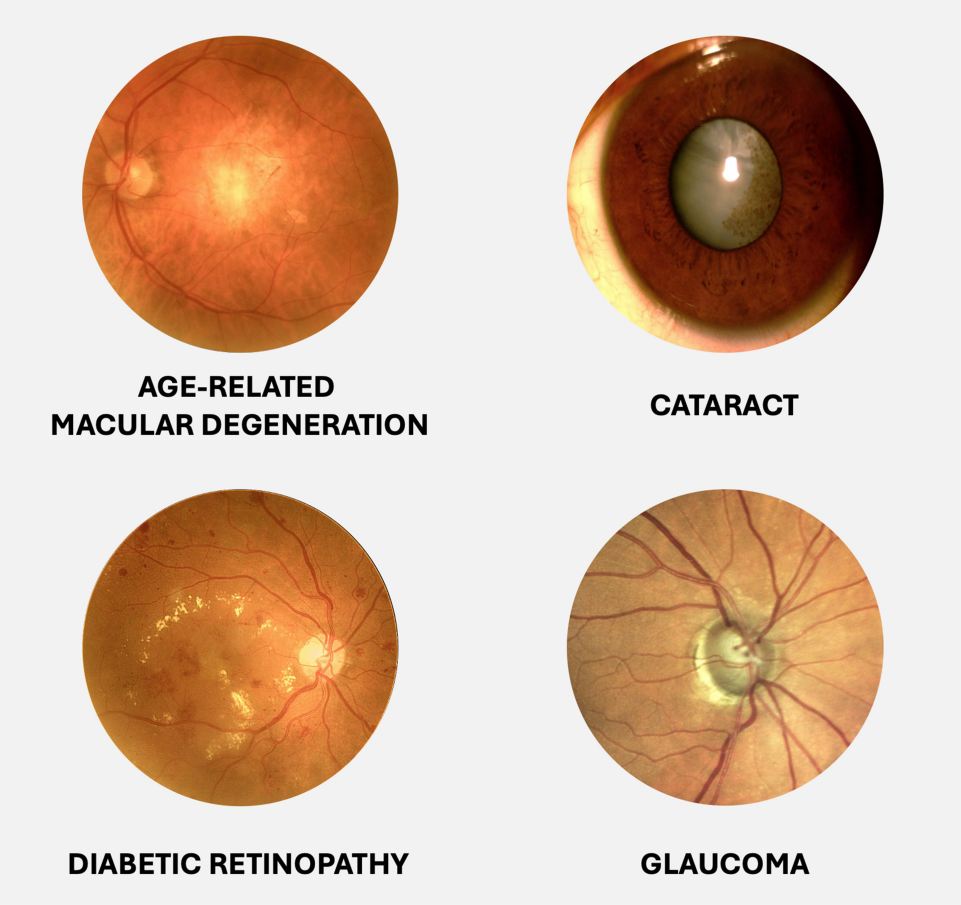

Figure 3 Representative color photographs of the anterior and posterior segment illustrating common age-related ocular pathologies associated with visual impairment. AMD, an advanced case characterized by subretinal fibrosis, perilesional atrophy, and pigmentary changes, indicative of progression to macular neovascularization evolved into fibrosis. Late-stage AMD results in irreversible photoreceptor damage, leading to central vision loss. Cataract is characterized by opacification of the crystalline lens, leading to significant visual impairment, particularly in the elderly population. Diabetic retinopathy shows microaneurysms, retinal hemorrhages, and exudates- hallmarks of microvascular damage caused by chronic hyperglycemia. Neuronal apoptosis is an early and key element of the disease, occurring before the onset of microvascular complications. Glaucoma is characterized clinically by optic nerve head cupping and thinning of the neuroretinal rim. These features are associated with progressive visual field loss due to retinal ganglion cell degeneration.

deposits (BLamD) represent hallmarks and risk lesions preceding the developing of end-stage complications characterized by RPE and photoreceptor irreversible loss.[120–123] Oxidative stress and inflammation demonstrated a crucial role in the AMD pathogenic cascade, involving several inflammatory mediators.[77,124] In the experimental model, quercetin demonstrated antioxidant properties that prevented the photooxidation of A2E.[125] A2E is the major fluorophore within RPE cells, which absorb light maximum at ~ 440 nm.[126] The photoexcitation of light on A2E produces singlet oxygen. The photooxidation of A2E through blue light can lead to several modifications that include DNA base lesions, lipid peroxidation of proteins, advanced glycation end-products (RAGE), proteasome stress, and ubiquitin accumulation.[127] Quercetin was superior to cyanidin-3-glucoside (C3G) in reducing the formation of oxidized A2E, also inhibiting MG RNAse A adducts and RAGE mRNA expression, and lipid peroxidation.[98]

Microglia residing in the plexiform layers, upon activation, migrate to the sub-retinal space and upregulate pro-inflammatory molecules. These cells can adopt different phenotypes involved in AMD pathogenesis, where the phenotype M1 is the one pro-inflammatory leading to the expression of CD16, IL-1β, IL-6, tumor necrosis factor-α, and inducible nitric oxide synthase,[128–130] while the M2 is the anti-inflammatory phenotype upregulating arginase1, mannose receptor, and IL-10.[131,132] In an experimental model, quercetin was shown to reduce the expression of M1 microglia and their pro-inflammatory mediators while promoting the upregulation of M2 cells and enhancing the anti-inflammatory response. The downregulation of M1 expression has several implications: it preserves the blood-retinal barrier (BRB), reduces vascular

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leakage, inhibits microglia proliferation and migration, suppresses the release of inflammatory cytokines, and suppresses the neuroinflammation, thereby preserving the photoreceptors. A lipophenolic formulation of quercetin (3-O-DHA-7-O-isopropyl-quercetin, Q-IP-DHA) was tested in albino ABCA4-/- and BALB/c mice via intravenous and oral route. Both formulations have demonstrated a protective effect against the light-induced damage to photoreceptors.[133]

Among the various molecular properties of quercetin with potential as therapeutic targets for AMD—such as neuroprotection, antioxidant, and anti-inflammatory effects—its anti-angiogenic activity is also highly relevant.[3,23] This was also supported by a clinical study showing that patients with neovascular AMD undergoing anti-VEGF treatment who reported higher baseline intake of flavonols, including quercetin, epigallocatechin, epigallocatechin-3-gallate (EGCG), and tea, had better visual outcomes and improved fluid resolution at 12 months.[134] In vitro, the anti-angiogenic effects of quercetin included inhibiting endothelial cell proliferation and migration, suppressing endothelial nitric oxide synthase, arresting the cell cycle in the early M phase, and reducing oxidative damage.[2,3,135,136] This anti-angiogenic effect was further confirmed in vivo in a rat model of laser-induced choroidal neovascularization (CNV), where administering 1% quercetin eye drops three times daily inhibited CNV and increased choroidal blood flow.[3]

More recently, a senolytic intravitreal drug designed to eliminate senescent RPE cells composed of 10 ng/μL dasatinib and 50 ng/μL quercetin was tested on a rat model.[137] Dasatinib is a potent tyrosine kinase inhibitor involved in mediating cellular proliferation, cytokines production, and T-cell response.[138] The combination of dasatinib plus quercetin appeared to slow the progression of laser-induced CNV in rats, likely through downregulation of the pro-inflammatory response[137] This finding further underscores the potential of senolytics as a novel therapeutic approach to managing age-related disorders, such as AMD. As demonstrated in an experimental mouse model, the use of peptide-based senolytics has shown promise by reducing senescence RPE cells, improving visual function, but more importantly slowing the progression of geographic atrophy.[139] Furthermore, it has been proven that senescent macrophages are responsible for subretinal drusenoid deposit accumulation. Senolysis acts through removing senescent macrophages in the subretinal space, representing a viable therapeutic approach in preventing and/or reversing AMD acting on drusen biogenesis.[140]

Cataract

Cataract remains the leading cause of legal blindness worldwide, especially in low-income countries, where it accounts for 50% of all cases of blindness (Figure 3).[12] Cataract formation appears to be closely linked to oxidative stress, which leads to several key changes in the lens. These include a reduction in reduced glutathione (GSH) levels in the nuclear region, protein oxidation, crosslinking of polypeptides, and posttranslational modifications to proteins.[141]

The role of quercetin has been investigated to reduce protein aggregation and the oxidative stress responsible for cataract formation. Experimental models have confirmed the role of quercetin in preventing γD-crystallin aggregation and selenite oxidative stress and protein lysis.[99,142–144] In a rat model, quercetin showed the greatest inhibition of crystalline lens turbidity because of selenite-induced oxidation and/or proteolysis by calcium-depended calpains causing lens turbidity. The protective effect of quercetin against lens opacification is hypothesized to result from its antioxidant capacity, particularly its action on selenite ions. For calcium-induced opacification, quercetin may exert protective effects by inhibiting calpain activity or binding excess calcium ions.[99]

Diabetic Retinopathy

Diabetic retinopathy is a sight-threatening complication of diabetes mellitus affecting working-age individuals.[145] Neurodegeneration plays an early and critical role in the pathogenesis of diabetic retinopathy, often preceding overt microvascular damage. Retinal neuronal loss, glial activation, and dysfunction of the neurovascular unit contribute to visual impairment independently of, and synergistically with, vascular abnormalities (Figure 3).[146] Microvascular alterations observed during clinical examination include microaneurysms and exudative changes such as hard exudates (lipoprotein leakage) and hemorrhages. As the disease progresses, ischemic changes may affect the inner retina, leading to infarcts in the nerve fiber layer known as cotton wool spots, as well as intraretinal microvascular abnormalities and venous beading. In advanced stages, proliferative changes develop, configuring the proliferative stage of diabetic retinopathy.[147,148] Proliferative diabetic retinopathy (PDR) is an advanced stage of diabetic retinopathy, a leading

cause of vision loss among individuals with diabetes. Characterized by the abnormal growth of new blood vessels on the retina and fibrous proliferation. These late sequelae, resulting from chronic retinal ischemia, are responsible for severe complications, including vitreous hemorrhage and retinal detachment.[148,149]

In vitro experiments on human retinal microvascular endothelial cells (HRMECs) indicated that quercetin can inhibit cell viability, migration, and tube formation under high glucose conditions.[150,151] Additionally, quercetin significantly inhibited the nucleotide-binding oligomerization domain-like receptors 3 (NLRP3) inflammasome signaling pathway, including the suppression of NLRP3, apoptosis-associated speck-like protein (ASC), and caspase 1, while also reducing the expressions of IL-1β and IL-18. All these effects were shown to be dose-dependent.[151] Similar results were reported on rats, where intraperitoneal quercetin (150 mg/kg) downregulated the pro-inflammatory response, reducing IL-1β, IL-18, IL-6, and TNF-α. Furthermore, the results confirmed a reduced over-expression of NLRP3 inflammasome-related proteins, as well as high mobility group box 1 (HMGB1).[152] These anti-inflammatory effects are particularly relevant in light of the pathogenic changes in diabetic retinopathy, where activated microglia and adherent inflammatory cells produce inflammatory cytokines, including TNF, IL-1β, and CC-chemokine ligand 2 (CCL2). Moreover, the Müller cell activation amplifies the pro-inflammatory response through microglia activation and purinergic receptors, leading to neuroinflammation and microvascular damage.[153]

In diabetic rats, quercetin also influenced pro-angiogenic cytokines and neurotrophic factors, reducing the expression of VEGF and ICAM-1 while enhancing neuroprotection by upregulating brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF).[152] Additionally, serum levels of matrix metalloproteinase-9 (MMP-9) and VEGF were significantly decreased in rats treated with 150 mg/kg of quercetin administered via intragastric injection compared to controls.[154] The neuroprotective effect of oral quercetin (50 mg/Kg/day) was confirmed in Wistar albino rats, where it modulated the expression of BDNF, NGF, but also of tropomyosin-related kinase B (TrkB), synaptophysin, and phosphorylation of Akt. Moreover, the authors indicated a beneficial effect on modulating pro-apoptotic caspase-3 and cytochrome c and increased the expression of anti-apoptotic Bcl-2.[155] In streptozotocin-induced diabetic rats, oral administration of quercetin was performed at two dosages: 25 mg/kg and 50 mg/kg. Notably, both doses demonstrated neuroprotective effects, preserving ganglion cells and maintaining a globally thicker retina, particularly in the inner and outer nuclear layers, compared to controls. This neuroprotective effect appeared to be associated with enhanced antioxidant activity, including increased levels of GSH, SOD, and CAT. Additionally, the reduced inflammatory response was evident through the downregulation of TNF-α and IL-1β, alongside an antiapoptotic effect marked by decreased NF-κB expression in the inner retina and reduced expression of aquaporin 4 (AQP4) in Müller cells.[156] The effect on AQP4 is crucial to prevent macular edema, as the increased levels of aquaporin and Kir4.1 channels have been implicated in the increasing permeability and angiogenesis.[153,157]

Glaucoma

Glaucoma is a neurodegenerative disorder characterized by irreversible loss of retinal ganglion cells (RGCs), leading to progressive peripheral visual field loss (Figure 3).[158–161] Glaucoma can happen at any age but is more common in older adults, representing one of the leading causes of blindness for people over the age of 60.[158–160,162] Preclinical evidence has shown the role of quercetin in improving RGC dysfunction and promoting cellular survival. This protective effect of quercetin has been attributed to the increasing expression of the anti-apoptotic protein Blc-2 and the downregulation of cleaved caspase-3 expression.[4,161] In a rat model, the administration of intravitreal quercetin improved the retinal function, which was evaluated through functional electroretinography. This study suggested a potential protective effect of quercetin on RGC dysfunction, likely through inhibiting glutamate from nerve terminals, thereby reducing the excitatory neurotoxicity.[163] Another potential effect of quercetin regards the senolysis on RGCs.[95] Targeting senescent RGCs with senotherapeutic drugs can protect healthy RGCs, preserving further cellular loss and visual function. This potential therapeutic strategy in glaucomatous eyes has shown promising results without affecting intraocular pressure, the progression of visual field damage, or producing adverse ocular effects.[164] A formulation of quercetin in resveratrol-loaded chitosan-nanoparticles and polyethylene glycol (PEG) modified was tested in vitro and in vivo. This compound demonstrated a significant intraocular pressure-lowering effect in a rabbit model compared to the formulation of

resveratrol alone. This confirmed a possible synergistic effect of resveratrol and quercetin in corneal permeation and intraocular pressure reduction, reaching a maximum reduction of 5.5 ± 0.5 mmHg.[165]

Safety, Delivery Systems, and Combination Therapies

Clinical Safety

Clinical trials have investigated the role of quercetin in several systemic pathologies, including diabetes mellitus, metabolic syndrome, and cardiovascular diseases.[166] However, despite robust preclinical evidence (Table 1), no clinical trials have yet investigated the effects of quercetin on ophthalmic disorders. In the clinical trials conducted on systemic disorders, quercetin has been administered as oral supplementation with variable dosages from 150 mg/day to 500 mg/day.[17,167,168] A dose of 500 mg per tablet of pure quercetin aglycone was equivalent, based on urinary excretion levels of quercetin glycoside conjugates, to the amount found in 100 grams of fresh red onion.[43]

The dose of 500 mg per tablet of pure quercetin aglycone was the equivalent assessed through urinary excretion of quercetin as glycoside conjugates contained in 100 gr of fresh red onion. The safety of quercetin supplementation assessed on blood routine showed no significant differences compared to placebo.[168] No adverse effects were noted for repeated daily intake of 500 mg of quercetin for 4–8 weeks, 730 mg for 4 weeks, or 1000 mg for 12 weeks. Countries applied different regulations regarding the maximum daily dose of quercetin, considered a safe dosage, reaching a maximum of 1250 mg per day. However, some concerns were raised from animal models where the administration of high doses of quercetin for a long period demonstrated adverse effects on the gastrointestinal and renal tracts, while the potential toxicity on the thyroid and carcinogenesis was not confirmed.[17,169–172]

Table 1 A Summary of the Potential Beneficial Effects of Quercetin in Common Neurodegenerative Ophthalmic Diseases in Older Adults

Ocular Diseases	Effects		References
Age-related macular degeneration (AMD)	Antioxidant	↓ A2E photo-oxidation	[99]
	Anti-inflammatory	↓ Expression of the pro-inflammatory microglia M1	[136]
	Anti-angiogenic	↓ Endothelial cells proliferation and migration	[2,3,136]
	Senolysis	Targeting senescent RPE cells (in combination with dasatinib)	[137]
Cataract	Antioxidant	↓ cristallin lens turbidity ↓ γD-crystallin aggregation	[99,142–144]
Diabetic retinopathy	Antioxidant	Modulation of GSH, SOD, and CAT	[156]
	Anti-inflammatory	↓ NLRP3 inflammasome signaling pathway and microglia activation	[150–152]
		↓ TNF-α and IL-1β	[156]
	Anti-angiogenic	↓ Cell viability, migration, and tube formation	[150,151]
		↓ MMP-9 and VEGF	[154]
		↓ AQP4	[156]
Glaucoma	Neuroprotection	Protection and survival of RGC	[163]
	Intraocular pressure	↓ Corneal permeation and intraocular pressure	[165]
	Senolysis	Modulation of apoptotic proteins in senescent cells	[25–28]

Abbreviations: AQP4, aquaporin-4; CAT, catalase; GSH, glutathione; IL-1β, interleukin-1 beta; MMP-9, matrix metalloproteinase-9; NLRP3, NOD-like receptor family pyrin domain-containing 3; RGC, retinal ganglion cells; RPE, retinal pigment epithelium; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

Nanoformulations for Quercetin Delivery

As stated above, quercetin exhibits limited bioavailability due to its poor solubility, leading to slow absorption, which hinders its efficacy when administered in traditional forms. Additionally, quercetin is both chemo- and thermo-labile, degrading rapidly in alkaline conditions, under light exposure, and at elevated temperatures, posing significant challenges for its formulation.[173]

Recent advancements in nanoformulation technologies have effectively addressed these issues, enhancing the therapeutic efficacy of quercetin. Nanoformulations were extensively characterized for physicochemical properties, including particle size, zeta potential, encapsulation efficiency, stability under storage conditions, and in vitro release profiles. These characterizations significantly correlate with improvements in quercetin pharmacokinetics, bioavailability, and therapeutic efficacy across various preclinical disease models[174] (Table 2).

Lipid-based nanocarriers such as liposomes or liposome-based, nanostructured lipid carriers (NLCs), and solid lipid nanoparticles (SLNs) have been extensively investigated to improve oral absorption, stability, and bioavailability of quercetin due to their cell membrane-like structures. Liposomes composed of lecithin and cholesterol, modified through PEGylation or ligand functionalization (such as galactosylated chitosan and folic acid), exhibited enhanced bioavailability, controlled release, and targeted delivery. Experimental details include preparation methods such as thin-film hydration, ethanol injection, and freeze-thaw techniques, with size reduction methods such as extrusion or sonication. Particle sizes generally ranged from 100 to 250 nm, achieving encapsulation efficiencies (EE) typically over 90%. Dosages used in preclinical studies varied from 10–100 mg/kg/day, showing significant anti-inflammatory and antioxidant activities in models including diabetic nephropathy, osteosarcoma, and acute liver injury, demonstrating improved therapeutic outcomes compared to free quercetin.[175–192]

Polymeric nanosystems, including polymeric micelles, nanoparticles, and hydrogels, provide distinct advantages for quercetin encapsulation and release. Polymeric micelles based on Soluplus and Pluronic copolymers improved quercetin bioavailability and exhibited controlled release kinetics, with particle sizes typically between 20–80 nm and high EE (up to 95%). Quercetin loading in these micelles ranged from 5–7%. These micelles enhanced antioxidant and anticancer efficacy both in vitro (such as MCF-7 tumor cells) and in vivo (glioma and breast cancer models), with quercetin dosages

Table 2 Biological Benefits of Quercetin Lipid-, Polymer-, Surfactant, Cyclodextrin-Based Nanosystems

Type		Key Biological Benefits	References
Lipid-based Nanocarriers	**Liposomes and Liposome-based**	↑ Solubility, ↑ EE, ↑ bioavailability, facilitation of the uptake into cells, ↑ anti-inflammatory properties, ↑ antioxidant activity	[175–185]
	SLNs and NLCs	↑ Solubility, co-loading with other actives, sustained release	[186–192]
Polymer-based Nanosystems	**Polymeric Micelles**	↑ Solubility, ↑ EE, co-loading with other actives, ↑ bioavailability, controlled release, ↑ stability, facilitation of the uptake into cells, ↑ anti-inflammatory properties, ↑ antioxidant activity	[48,193–195]
	Polymeric Nanoparticles	↑ Solubility, ↑ EE, co-loading with other actives, ↑ bioavailability, controlled release, ↑ stability, facilitation of the uptake into cells, ↑ anti-inflammatory properties, ↑ antioxidant activity	[196–199]
	Hydrogels	↑ Solubility, controlled release	[200–202]
Surfactant-based Nanoparticles	**Niosomes**	↑ Solubility, ↑ bioavailability, ↑ anti-inflammatory properties, ↑ antioxidant activity	[203–208]
	Nanoemulsions	↑ Solubility, sustained release	[209–214]
Cyclodextrin-based Nanoparticles		↑ Solubility, pH-responsive release	[215–218]

Abbreviations: EE, entrapment efficiency; NLC, nanostructured lipid carrier; SLN, solid lipid nanoparticle.

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between 20–50 mg/kg administered in animal studies. Polymer-based nanoparticles such as Eudragit® S100 and poly (n-butylcyanoacrylate) demonstrated targeted delivery with pH-sensitive release, suitable for colon cancer treatment, featuring particle sizes around 65–165 nm and EE ranging from 42–79%. Hydrogel formulations incorporating sodium alginate, poly(vinyl alcohol), and karaya gum achieved sustained quercetin release (over several days) and high loading capacities (up to 88%), with quercetin concentrations typically around 1–2% w/w, showing therapeutic potential in osteoarthritis treatment and transdermal applications.[48,193–202]

Additional nanocarriers explored include niosomes, nanoemulsions, and cyclodextrin-based systems, offering alternative administration routes, improved solubility, and targeted quercetin delivery. These systems typically demonstrate controlled release profiles and improved penetration, and bioavailability compared to conventional formulations.[203–218]

Advances in Ocular Delivery Methods: Preclinical Studies

Despite the intense and growing body of preclinical research focused on novel quercetin-based delivery systems, preclinical studies evaluating these nanoformulations remain extremely limited (Table 3). In a preclinical study, an intravenous formulation of a new lipophenol quercetin-based drug, 3-*O*-DHA-7-*O*-isopropyl-quercetin (Q-IP-DHA), (30 mg/kg) was tested using polymeric micelles formed with Kolliphor® HS 15 to increase the solubility (mean size of 16 nm, drug loading of 95%). The authors hypothesized that intravenous use should be considered in rare diseases, while oral administration should be preferred in chronic retinal disorders, such as AMD. Indeed, a solution of Q-IP-DHA was

Table 3 Recent Preclinical Studies on Quercetin Nanocarriers in Experimental Ocular Disease Models

Nanocarrier	Quercetin Formulation and Dose	Other Compounds	Animal Model	Administration Route	Effects Observed	References
Polymeric Micelles (Kolliphor HS15)	Q-IP-DHA, 30 mg/kg	None	Albino ABCA4$^{-/-}$ mice (retinal degeneration with light stress) and BALB/c	Intravenous	↑ retinal protection, ↑ ONL, ↑ photoreceptor survival, ↑ half-life,	[133]
PEG-modified chitosan nanoparticles	50 μLwith 1 mg/mL quercetin	Resveratrol	Normotensive rabbits	Eye drops	↓ intra ocular pressure	[165]
LNCs	Q-IP-DHA, 50–75-100 mg/kg	None	Albino ABCA4$^{-/-}$ mice (retinal degeneration with light stress) and BALB/c	Oral	↓ photoreceptor degeneration, ↑ ONL/INL thickness, ↑ retinal protection	[133]
SLNs	2 μL with 0.6 μg quercetin	mR-150, targeting asparagine-glycine-arginine peptide	Male C57BL/6 mice	Intravitreal	↑ targeting, ↓ angiogenesis, ↓ CXCR4/angiogenic markers	[23]
QS-NLCs	~30 mg/kg quercetin	None	Male albino rabbits (tear study), Goat (ex vivo cornea)	Topical, Ex vivo	↑ anti-inflammatory, ↑ corneal permeation, ↑ bioavailability, ↑ tear production	[219]

Abbreviations: CXCR4, C-X-C Motif Chemokine Receptor 4; INL, Inner Nuclear Layer; LNCs, Lipid Nanocapsules; ONL, Outer Nuclear Layer; Q-IP-DHA, 3-O-docosahexaenoyl-7-O-isopropyl-quercetin; PEG, polyethylene glycol; QS-NLCs, Quercetin-loaded Squalene Nanostructured Lipid Carriers; SLNs, Solid Lipid Nanoparticles.

formulated for oral use using lipid nanocapsules at 100 mg/kg, but a protective effect was also noted for a dosage of 75 mg/kg in 87% of cases.[133]

Chitosan-based nanocarriers encapsulating quercetin have been proposed as effective formulations to enhance transport across the BRB and improve stability in aqueous environments.[143,220] In a rabbit model, topical administration of resveratrol and quercetin co-encapsulated in PEG-modified chitosan nanoparticles effectively reduced intraocular pressure. The formulation showed significant and sustained therapeutic effects compared to control groups, suggesting enhanced ocular bioavailability and prolonged action of quercetin in combination with resveratrol.[165] Furthermore, an innovative approach involved the development of SLNs co-loaded with quercetin and micro-RNA-150 (mR150), further modified with the asparagine-glycine-arginine peptide for enhanced targeting and functionality. This multitarget nanocarrier system administered through intravitreal injection (2 μL co-loaded with 0.6 μg quercetin and 1 μg mR-150) demonstrated promising results in potentiating the anti-angiogenesis therapy. In this regard, mR150 downregulates C-X-C chemokine receptor type 4 (CXCR4) and other angiogenic targets co-acting with quercetin to improve the response to macular neovascularization treatment.[23] A recent study developed quercetin-loaded squalene-based NLCs (QS-NLCs) using a melt emulsification method to treat dry eye disease. The QS-NLCs had a particle size of approximately 93.7 nm, and 43.8% drug loading, and remained stable for 90 days under various conditions. Structural and morphological characterization (DSC, FTIR, XRD, TEM) confirmed no agglomeration and good colloidal stability. The system showed a burst drug release (>70% in 1 hour) followed by sustained release up to 6 hours. Ex vivo experiments demonstrated a 2.5-fold increase in corneal permeation compared to free quercetin. QS-NLCs also showed anti-inflammatory activity and were non-cytotoxic to human corneal epithelial cells (HCECs). In vivo, the formulation significantly enhanced tear production and improved bioavailability parameters with high ocular tolerance.[219]

To date, these experimental models have not been translated into clinical trials yet, but they pose a significant basis for future research.

Combination Therapies

Combined with conventional treatments, quercetin may enhance therapeutic outcomes by reducing oxidative damage and inflammation while mitigating drug-induced side effects. For instance, pairing quercetin with Age-Related Eye Disease Study 2 (AREDS2) supplements could improve retinal protection in AMD, slowing the disease's progression into late-stage complications. Another promising application of quercetin includes its use alongside anti-VEGF therapies for diabetic macular edema and neovascular AMD, providing additional anti-angiogenic and anti-inflammatory benefits.[220,221] This approach is particularly important in light of the increasing demand for long-lasting anti-VEGF therapies to alleviate the treatment burden and achieve sustained, stable, and long-standing disease control.[222] By complementing anti-VEGF agents, quercetin could help reduce treatment-related complications, minimize disease fluctuations and recurrences, and ultimately improve long-term visual outcomes.

In glaucoma, quercetin may complement neuroprotective agents such as citicoline (cytidine 5'-diphosphocholine) to further enhance the neuroprotection of RGCs cells. This combination may offer a synergistic effect in preserving retinal health and function, potentially slowing disease progression. While oral administration of quercetin has been explored, there is significant potential for developing topical formulations, such as eye drops, to directly target the ocular tissues, increase local bioavailability, and minimize systemic interactions.[223–226]

Conclusion

Quercetin shows strong potential as a therapeutic compound for common ocular diseases in older adults associated with visual impairment, thanks to its anti-inflammatory, antioxidant, and anti-angiogenic properties. These biological activities are particularly relevant in ocular diseases such as AMD, cataracts, diabetic retinopathy, and glaucoma, which are driven by senescence, oxidative stress, chronic inflammation, and vascular dysfunction.

The neuroprotective and senotherapeutic potential of quercetin may help counteract the impact of aging and cellular senescence, two central mechanisms involved in the pathophysiology of these ocular diseases. By targeting senescent RPE cells and retinal ganglion cells, quercetin may contribute to slowing disease progression and preserving visual function. This effect is especially important in older individuals, who are frequently affected by these conditions, where vision loss can lead to a significant decline in autonomy and quality of life.

Although clinical research is still limited and quercetin is known to suffer from low bioavailability and poor pharmacokinetics, recent in vitro and preclinical studies have introduced a wide variety of innovative nanocarrier systems. These include polymeric micelles, hydrogels, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and cyclodextrin-based platforms. Such systems have been shown to enhance quercetin's solubility, stability, and tissue-specific delivery, opening the door to new therapeutic strategies for the management of ocular diseases in the aging population.

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