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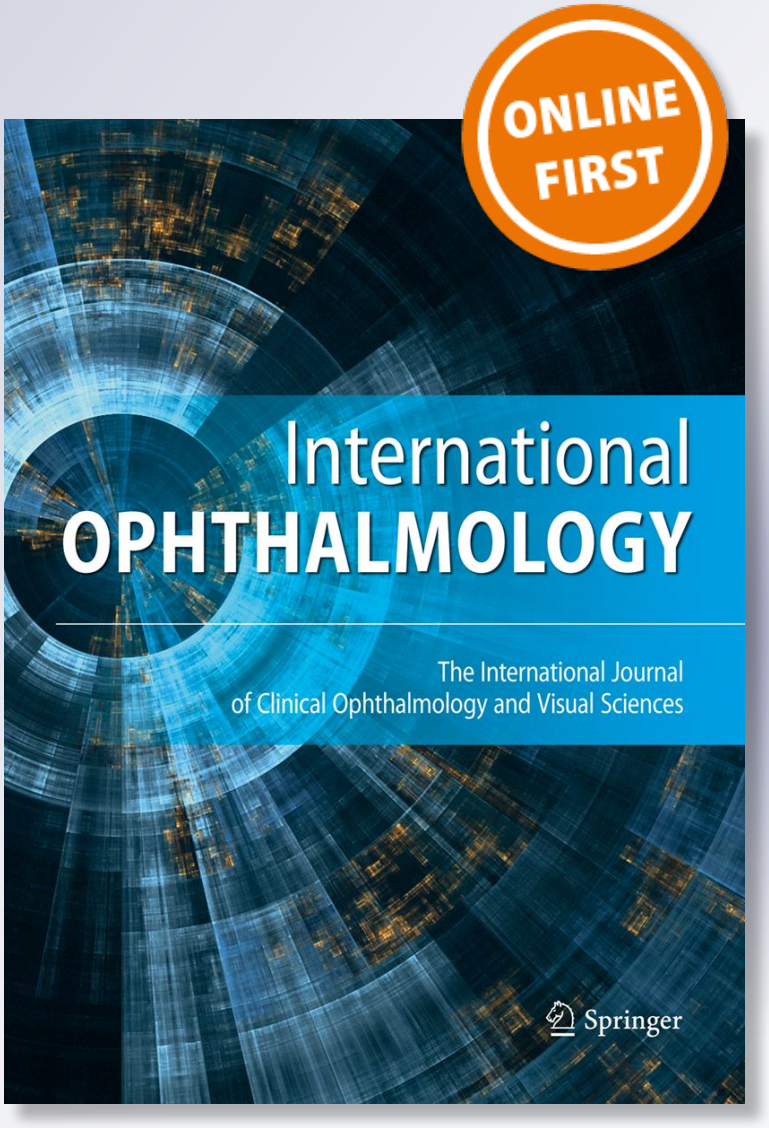

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REVIEW

Therapeutic potential of curcumin in major retinal pathologies

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Abstract
Purpose The retina is continually exposed to free radicals from its rich blood supply, numerous mitochondria, and photons of light which strike its surface. Most pathological processes that take place in the retina, such as inflammation, cell apoptosis, or angiogenesis, can hence involve free radicals directly or indirectly. Since inflammatory and oxidative stress pathways underlie retinal pathology, compounds that address these factors are therefore natural choices for treatment. This review article summarizes and provides commentary on curcumin's therapeutic potential use in ophthalmology with principal focus on retinal dosorders.
Methods Curcumin (diferuloylmethane) is a compound of the Indian spice turmeric (*Curcuma longa*) that has been found to be efficacious in preventing and treating a number of inflammatory diseases and neoplastic processes. Curcumin exerts anti-inflammatory, anti-tumor, antioxidant, and VEGF inhibition properties through modulation of numerous biochemical mediators. This makes curcumin particularly effective in retinal disorders.
Results Curcumin has found a role in slowing, and in some cases even reversing, age-related macular degeneration, diabetic retinopathy, retinitis pigmentosa, proliferative vitreoretinopathy, and retinal cancers.
Conclusions However, studies on curcumin's efficacy have been limited mostly to animal studies. Moreover, the biomedical potential of curcumin is not easy to use, given its low solubility and oral bioavailability—more attention therefore has been given to nanoparticles and liposomes.

Keywords Anti-inflammatory drug · Antioxidant drug · Anti-tumor drug · *Curcuma longa* · Curcumin · Retinal diseases

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Introduction: structural aspects and details of curcumin

The retina is continually exposed to free radicals from its rich blood supply, numerous mitochondria, and photons of light that strike its surface. The outer segment of the rods has a high content of polyunsaturated fatty acids that are particularly sensitive to

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peroxidation given their number of double bonds. The inner segments of the rods are particularly rich in mitochondria, which contain activated oxygen species that may cause damage if they leak out of cells. The blood supply to the choroid is the richest in the retinal body, with vertebrate retinas having a sevenfold higher rate of oxygen consumption per milligram of protein than other areas tested. Furthermore, the light that hits the retina may trigger photooxidative processes. Visible light in the blue wavelength forms the toxic compound A2E which targets cytochrome oxidase and induces irreversible DNA damage in RPE cells. Most pathological processes that take place in the retina, such as inflammation, cell apoptosis, or angiogenesis, can hence involve free radicals directly or indirectly [1–3].

Because inflammatory and oxidative stress pathways underlie retinal pathology, compounds that address these factors are therefore natural choices for treatment. One such compound is curcumin (diferuloylmethane), the orange and water-insoluble pigment extracted from turmeric. It is derived from the rhizome of *Curcuma longa*, a spice that belongs to the *Zingiberaceae* family. Chemically, curcumin incorporates several functional groups. The aromatic ring systems or phenols are connected by two α,β-unsaturated carbonyl groups. The diketones form stable enols and are readily deprotonated to form enolates; the α,β-unsaturated carbonyl group is a good nucleophilic acceptor of a carbanion or another nucleophile [4].

The mechanism by which curcumin induces its effects is yet to be fully elucidated, but many studies have shown its relevance as a potent anti-inflammatory and immunomodulating agent. Curcumin is able to down-regulate the expression of genes involved in apoptosis, proliferation, and transformation, by inhibiting the nuclear factor κB (NF-κB) activation. Other studies demonstrated that curcumin may exert an anti-inflammatory effect through the activation of peroxisome proliferator-activated receptor-γ (PPAR-γ), a group of transcriptional factors that regulate gene expression. In addition, curcumin inhibits the free radicals production and so exhibits antioxidant properties [4].

Indeed, curcumin with its pleiotropic activities can modulate the expression and activation of many cellular regulatory proteins such as chemokines, interleukins, hematopoietic growth factors, and transcription factors, which in turn inhibit cellular inflammatory responses and protect cells (Table 1).

There has been a fair amount of work done assessing curcumin's potential in ocular pathology. A review by Pescosolido et al. touches on many features that make curcumin a strong therapeutic agent in many parts of the eye. Curcumin has found application in dry eye syndrome by reducing the inflammation created by increased tear osmolarity. In animal models of cataracts, curcumin was found to reduce the free radical damage and calcium influx that is responsible for the proteolysis causing clouding of the lens. In diabetic retinopathy (DR), curcumin was found to improve retinal microcirculation by inducing nitric oxide production. For age-related macular degeneration (AMD), curcumin may provide therapy through beneficial effects on microglial cells that are responsible for drusen formation [4]. Researchers have even hypothesized a possible therapeutic effect of the curcumin on protease inhibitors that help maintain cellular and tissue homeostasis (Table 2) [5, 6]. Some authors have even theorized a possible therapeutic effect of protease inhibitors in treatment of neovascularization and inflammation in animal models [5–7].

In light of its angiogenesis-modulating profile and anti-inflammatory properties, curcumin has great potential in the treatment of inflammatory and neovascular proliferative diseases of the retina.

This article will summarize and provide commentary on curcumin's therapeutic potential with a focus on primary retinal disorders.

Age-related macular degeneration

AMD is the leading cause of worldwide blindness in the elderly and is projected to cost $59 billion worldwide over the next 20 years [8]. It occurs when extracellular material, known as drusen or lipofuscin, builds up between Bruch's membrane and the retinal pigment epithelium (RPE). AMD may lead to geographic atrophy with loss of RPE and photoreceptors and may further progress to wet macular degeneration if new blood vessels bleed into the inner retinal layers. Evolving atrophic macular degeneration represents at least 80% of all AMD and is currently without an accepted treatment regimen [9, 10].

Table 1 Curcumin inhibits or down-regulates a number of biochemical mediators

▶**Curcumin inhibits directly or indirectly**
G-proteins
Lipo-oxygenase
Cyclooxygenase
Interleukin-1-6-8 (IL)
Tumor necrosis factor-α (TNF-α)
Free radicals production (antioxidant properties)
Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)
▶**Curcumin down-regulates directly or indirectly**
Down-regulate the expression of IκBα gene
Down-regulate the expression of prostaglandin E-2 (PGE-2)
Down-regulate the expression of genes involved in apoptosis
Down-regulate the expression of genes involved in cellular proliferation and transformation

Table 2 Molecules most commonly involved in maintaining cellular and tissue homeostasis

Proteases and protease inhibitors mainly involved in retinal and uveal diseases			
Iris and ciliary body	SLPI↑	MMPs↑	Calpain inhibitor↑
Endophthalmitis, vitreous and retina disorders	SLPI↑	MMPs↑	Calpain inhibitor↑
Angiogenesis, tumor, inflammation, oxidative stress (AMD), and fibrosis	SERPINA3 K↑	TIMP-3↓	Calpain inhibitor↑
Damage to: photoreceptors, RGCs (apoptosis), and ONFs. During: GL, MS, RD, RP, DR, PVR, etc.	Caspase 3 inhibitor↑	MMPs↑	Calpain inhibitor↑

SLPI secretory leukocyte protease inhibitor, *MMPs* metalloproteinases, *TIMP-3* MMP inhibitor-3, *RGCs* retinal ganglion cells, *ONFs* optic nerve fibers, *GL* glaucoma, *MS* multiple sclerosis, *RD* retinal detachment, *RP* retinitis pigmentosa, *DR* diabetic retinopathy, *PVR* proliferative vitreoretinopathy

AMD is primarily a heritable disease that occurs when gene mutations predispose the retina to oxidative stress and dysregulation of the complement cascade [11]. In fact, research indicates that AMD has a heritability of 71%, putting it on par with Alzheimer's and obesity [12]. There are two gene loci, complement factor H (CFH) and ARMS2/HTRA1, implicated in the development of AMD. Complement factor H has a tyrosine to histidine change in AMD that leads to chronic complement activation and reduces its ability to bind to oxidized lipids and clear apoptotic cells [12]. The other gene locus, ARMS2, appears to be involved in inflammation as well. Studies have shown that knockout mice, or mice without the gene, display lower expression of the pro-inflammatory markers C3, C5, interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF-α). AMD is also associated with chronic diseases such as abdominal obesity [13], high cholesterol [14], cigarette smoking, and hypertension [15] that can tip the body's homeostasis into a pro-inflammatory milieu. Other stressors include increased light exposure that damages photoreceptors [16]. These stresses can lead to free radical production and endothelial dysfunction in choroidal blood vessel walls as a part of a systemic vasculopathy [17]. Vitamins such as AREDS, fatty acid supplementation (DHA and EPA), as well as zinc additives, have proven helpful in dry AMD likely owing to their ability to reduce oxidative stress. Current translational and clinical studies are focused on enhanced photoreceptor neuroprotection, mechanisms to reduce local

oxidative stress, and even photoreceptor transplantation [11].

Curcumin decreases the transcription, translation, and expression of the genes that increase inflammation in AMD. One study that modeled AMD through a pulsed H_2O_2 induction of retinal pigment cell aging showed that curcumin lead to decreased apoptosis and thus higher cell viability. This study found that curcumin reduced free radical expression as well as gene expression of the oxidative biomarkers superoxide dismutase (SOD), maleic dialdehyde, and glutathione [18]. Another study showed that curcumin effects posttranscriptional regulation and silencing. Curcumin was found to up-regulate and down-regulate specific microRNAs (miRNAs) that regulate the antioxidant system [19]. Curcumin also boosts enzymes that serve as cellular defense mechanisms in AMD, such as heme oxygenase-1 [20], and increase cytoprotective proteins such as nuclear-related factor (Nrf2) [21]. These changes were consistent across different laboratory models of AMD. For example, in the light-induced retinal degeneration model of AMD, curcumin was found to inhibit nuclear factor- κB (NF-κB) and down-regulate cellular inflammatory genes [22]. Overall, laboratory studies have shown utility in preventing cell death across different cellular models of AMD. The mechanisms of action have been through decreasing apoptotic rates of retinal pigment epithelial (RPE) cells and decreasing overall inflammation. Curcumin works on multiple processes involved in transcription and animal data on curcumin and translation such as gene expression, nuclear translocation of proteins, and silencing through miRNAs.

Diabetic retinopathy

Diabetic retinopathy (DR) is the primary cause of blindness in patients from 25 to 74 years old in industrialized countries [23]. This metabolic disorder is a chronic inflammatory state that damages both the photoreceptors and the blood vessels of the retina [24]. Diabetes affects the vasculature by causing local hypertension and basement membrane thickening that disrupts the tight connections between the pericytes. This results in pericyte apoptosis and the release of cellular mediators that promote angiogenesis [25]. Biochemically, a cascade of reactions result in the formation and accumulation of advanced glycation end products with the release of superoxide radicals, which cross-link proteins and damage vascular and extravascular structures [26]. Hyperglycemia also induces oxidative stress pathways and promotes free radicals that contribute to the pathogenesis of DR [27]. These reactive species concentrate near retinal capillaries, leading to the loss of pericytes and to the formation of micro-aneurysms, finally resulting in the onset of vascular syndromes and DR. Therefore, an antioxidant treatment might be a valid strategy to limit the initial damage and slow down or even prevent the onset of DR.

Studies show that curcumin works through a variety of mechanisms to limit the pathophysiological changes to diabetic rat retina. One study showed that curcumin prevented the degeneration of cellular organelles and increased the capillary basement membrane thickness in the retina. Curcumin acted by decreasing TNF-α, decreasing pro-angiogenic vascular endothelial growth factor (VEGF), and increasing the antioxidant enzymes SOD and catalase in this study [28]. Curcumin also plays a role in extracellular matrix production, which decreases as cells undergo retinopathy. Curcumin increases levels of extracellular matrix production by increasing levels of mammalian excision repair cross-complementing (ERCC) 1 and ERCC4 enzymes [29]. In addition to its anti-apoptotic effects, curcumin also has anti-angiogenic effects on the choroidal vasculature of rat retinas. Diabetic microvasculature treated with curcumin had attenuated tortuosity, shrinkage, narrowing, and micro-aneurysms. Moreover, the choroidal microvasculature regenerated and repaired to near-normal characteristics [30]. Although studies did not compare curcumin against laser therapy or intravitreal injections, these studies did note that rats fed a diet with curcumin were found to have decreased VEGF in their retinas [31].

In summary, several animal studies have shown the benefits of curcumin on normalizing or preventing diabetic-induced changes in retina. These include structural changes in capillaries, endothelial cellular organelles, and extracellular matrix production. Curcumin affects both the toxic neuronal damage and the vasculopathy that both underlie DR. The mechanisms of curcumin's actions are indeed diverse and range from hypoglycemic to anti-inflammatory to anti-angiogenic. Human studies are needed to further investigate these relationships.

Retinitis pigmentosa

Retinitis pigmentosa (RP) is a common inherited retinal dystrophy that preferentially affects the rod photoreceptors, which control dim vision and peripheral vision. The disease process causes misfolding of rhodopsin proteins, which are G-protein-coupled receptors involved in the visual transduction cascade. Conformational shift of proteins, dysregulation of molecular chaperones, and cellular cytotoxicity all disrupt protein folding and increase protein aggregation. Current therapies are focusing on enhancing activities of chaperone proteins that augment folding as well as other targets such as cell apoptosis, mitochondrial dysfunction, and oxidative stress [32]. Free radical formation, decline in retinal oxygenation, and neurochemical changes complement genetic changes to play a role in degeneration of photoreceptors. In addition, retinal blood flow may play a role in the pathogenesis, given the attenuation of retinal blood vessels and atrophy of the choriocapillaris seen in RP [33]. The specific biochemical pathways that lead to cell death in RP are extremely diverse and include genes involved in the phototransduction cascade, vitamin A metabolism, cytoskeletal proteins, cell signaling, intron splicing, intracellular trafficking, and phagocytosis [34]. Retinal cell apoptosis is the final common biochemical pathway seen in RP and is caused by an alteration in the balance of pro- and anti-apoptotic molecules [35].

While the data regarding curcumin's use in inherited retinal dystrophies such as RP are quite limited, the few studies that have been detailed are promising. An animal study found that the number of functional photoreceptors in the central retina after curcumin injection was related to the amount of curcumin injected in a dose-dependent fashion [36]. Another study simulated RP in rats naturally through a mutated P23H rhodopsin. Curcumin led to a number of benefits in these rat retinas—decreased formation of mutant protein aggregates, preservation of photoreceptor morphology, increased levels of expression of photoreceptor marker genes, improvement in retinal physiology on electroretinogram, facilitation of translocation of mutant rhodopsin to the outer segment region, and decrease in the endoplasmic reticulum stress in cells [37]. These studies are impactful because they show that curcumin has a measurable impact on the cellular and biochemical levels. Curcumin's antagonism to cellular mutation and eventual destruction, in addition to its decrease in levels of cellular stress, gives it satisfactory function in other retinal dystrophies as well. Unfortunately, many more studies need to be performed to confirm these findings before clinical studies on humans are underway.

Proliferative vitreoretinopathy

Curcumin can also reduce the incidence of proliferative vitreoretinopathy (PVR) after retinal detachment (RD) surgery. This condition is normally seen in 8–10% of cases of rhegmatogenous RD and is caused by vitreous fluid entering cell layers below the retinal break. Vitreous cytokines such as TNF-α, transforming growth factor-β2 (TGF-β2), platelet-derived growth factor (PDGF), and interleukins release cytokines and ATP that promote retinal ischemia, cell proliferation, and tissue remodeling. The increased distance between retinal layers and choroidal blood supply after detachment results in tissue hypoxia, atrophy, and cell death. At the same time, RPE cells stimulated by the cytokines lay down epiretinal membranes which contract and may pull at the retina, predisposing to a second retinal detachment [38–40].

Several studies have cultured human RPE cells with and without curcumin and used flow cytometry, transmission electron microscopy, and Western blot analysis to study features such as cell cycle progression, apoptosis, and protein expression in PVR. Sun et al. [41] showed that curcumin added to human RPE cells inhibited proliferation in a dose-dependent and time-dependent fashion through cell cycle arrest at the G0/G1 phase and induction of apoptosis. Gong et al. [42] used human fetal RPE cells and found that curcumin was able to inhibit proliferation of those cells through cell cycle arrest at the G2/M phase. Curcumin, in this way, acts analogous to a tumor suppressor gene by providing checkpoints to the pathological cell growth and division. Cell growth, in this case, is driven by growth factors that are a response to the stress and inflammation of RD surgery. Alex et al. noted that curcumin promoted human RPE cell death through organized apoptotic pathways that included both caspase-3/7-dependent and caspase-8-independent mechanisms. This contrasts with other compounds that were likely to induce toxic necrotic

pathways [43]. Lu et al. [44] identified several more pathways through which apoptosis can occur, including the intrinsic pathway, caspase-3-dependent pathways, and caspase-3-independent pathways. These encouraging studies show that curcumin can also effect changes on cells even after pathological changes have happened. It has multiple mechanisms to promote self-destruction of those cells. One study attributed the mechanism of apoptosis of RPE cells to increase in calcium and a decrease in mitochondrial transmembrane potential [45].

Curcumin has several promising effects on PVR, including promoting cell cycle arrest at multiple checkpoints, increasing rates of apoptosis through various pathways, and consistently inhibiting the proliferation of RPE cells. Because currently all the studies have utilized in vitro cultures of human RPE cells, the next step is assessing in vivo cultures. Another major question will be how to get the curcumin in optimal contact with the RPE, whether it be oral, intravenous, or intravitreal.

Retinal and choroidal tumors

While relatively rare in comparison to other neoplasms, cancers that affect the eye are most likely to manifest in the retina. Retinoblastoma is common in children and has an incidence of 1 in 15,000. Retinoblastoma has a strong genetic basis and occurs when the tumor suppressor gene Rb1 is inactivated by a familial mutation. If the second tumor suppressor gene undergoes a sporadic mutation, cell cycle progression proceeds unchecked [46]. Next, ocular metastases have an incidence of approximately 20,000 per year, but rarely present to the ophthalmologist because patients' visual symptoms are often less severe compared to their medical complaints at the given time. In addition, they tend to be a fairly low percentage relative to the incidence of primary cancers—one study showed that 2% of all lung cancers had ocular metastases [47]. A variety of treatments have been used for these cancers, including radiotherapy, chemotherapy, photodynamic therapy, and intravitreal injections. Next, uveal melanomas are the most common primary cancers in adults. They start as pigmented lesions in the eye that may be more likely to exhibit malignant behavior if they have features such as associated fluid, increased tumor thickness, and ultrasonographic hollowness. In uveal melanoma, there is inhibition of apoptosis through various intracellular signaling mechanisms such as inactivation of the p53 pathway, defects in the Bcl-2 pathway, and activation of the pro-survival PI3K-AKT pathway; this one directly related to cellular quiescence, proliferation, cancer, and longevity [48]. Treatment for uveal melanoma chiefly depends on tumor size, with observation, radiotherapy, and enucleation being the three primary treatment paradigms [49, 50].

Many of the pro-apoptotic effects that have made curcumin extremely versatile in systemic cancers also make it useful in ocular malignancies. Mechanisms such as promoting cell cycle checkpoints and apoptosis that led curcumin to be beneficial in PVR also lead it to be beneficial in cancers. However, this relationship is only theoretical at this point, as there are very few supportive studies available at this time. A study that assessed curcumin's effects on the Y79 retinoblastoma cell line found microarray expression pattern that showed that curcumin exerted its anticancer effect through modulation of miRNA expression [51]. Another study assessed curcumin's impact on cancerous cells by looking at its effect on a N18 cell line, made up of retina ganglion cells hybrid with lymphoma cells. The study found that the mechanism of inhibition of cancer cell growth was through DNA damage and inhibition of DNA repair genes [52]. This is particularly useful because it may act in conjunction with other mechanisms of cancer treatment, such as radiation, which also damages DNA [53]. A second study also looked at curcumin's effect on the N18 cell line and found that curcumin inhibited matrix metalloproteinases responsible for metastatic spread of cancer cells [54]. Many more studies are needed to understand how curcumin may affect ocular cancers such as retinoblastoma, uveal melanoma, and ocular metastases.

Future work

There are several strengths of curcumin as a therapeutic compound. As a naturally occurring compound with pharmaceutical potential, curcumin has found itself in the food and drug category of "generally regarded as safe" [55]. Moreover, it is inexpensive, readily available, and natural. It can even be mixed in a

patient's normal diet, making it much easier to be regularly compliant. Consumption of curcumin has the potential to have positive effects on multiple organ systems at once as well (Fig. 1).

However, it is primarily held back by its poor bioavailability. A very small fraction of the curcumin that is consumed actually makes it into the blood stream in its active state. Systemically, possible solutions have included structural modifications to the molecule and administering it with current therapeutic treatments to look for synergistic effects. Novel delivery mechanisms including liposomes and nanoparticles are currently being investigated as alternate mechanisms to deliver curcumin to the target sites [56]. To reach the retina, the particles could theoretically be delivered through the air–cornea interface. However, because they need to have hydrophilic properties in order to do so, studies have looked at micelles and their ability to penetrate the cornea. The results show mild improvement in penetration, at a factor of 1.16 or 1.32 more if they are dispersed with the micelles at a ratio of either 1:1 or 3:1 [57, 58]. Another study showed that drugs given in a lecithinized form showed improvements in retinal pathology, such as DR. There were improvements in diabetic microangiopathy as assessed by venoarteriolar response, improved visual acuity, and improvement in retinal flow [59]. Future research is looking into on-demand release of drugs from liposomes, such as an endogenous or exogenous stimulus controlling the release of the drug [60]. In a 2010 patent, Chaniyilparampu proposed the use of cyclodextrins to aid in the administration of curcumin as a topical ophthalmic drop or eye gel formulation and tested this to find that it was effective in reducing selenite-induced cataracts in rats [61].

There is substantial work needing to be done in moving curcumin from the laboratory to the

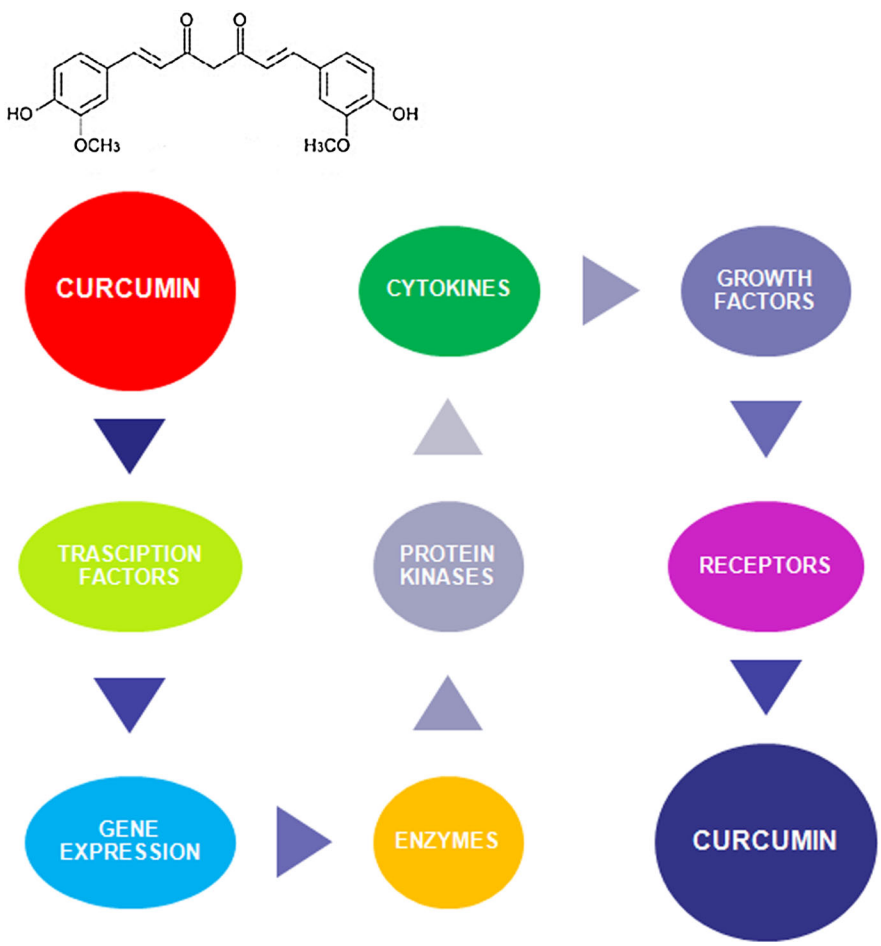

Fig. 1 Chemical structure of curcumin. Curcumin inhibits the expression of nuclear growth factor κB (NF-κB). It also down-regulates tumor necrosis factor-α (TNF-α) and other pro-inflammatory and pro-fibrotic molecules: phorbol ester (PMA), cyclooxygenase-2 gene (COX-2), subunit of NF-κB (IκBα), reactive oxygen species (ROS), prostaglandin E-2 (PGE-2), interleukins-1–6–8 (IL-1, IL-6, IL-8), osteopontin (OPN), and matrix metalloproteinase-9 (MMP-9)

ophthalmology clinic. There are currently no human trials examining the ocular effects of curcumin. This is the next logical step, because curcumin has shown potential in animal studies that have been done so far. After this, there should be prospective studies comparing traditional treatments such as AREDs vitamins to curcumin particles or oral curcumin. Another important question that remains unanswered by the current literature is whether curcumin can help prevent some of these retinal conditions before they develop. This is important to ask, because it is unclear whether curcumin is of benefit in the acute setting for humans, as opposed to being potentially more beneficial when used in preventative circumstances. Overall, curcumin has strong potential in retinal conditions, but much more work remains before it is brought into the clinic as a treatment modality.

Compliance with ethical standards

Conflict of interest The authors have no financial or proprietary interest in any materials or methods described within this manuscript.

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