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Therapeutic potential of curcumin in eye diseases

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Abstract

Curcumin (diferuloylmethane) derived from the rhizome of Curcuma longa L. has been used for thousands of years in traditional Chinese medicine and Ayurvedic medicine in Asian countries to treat liver diseases, rheumatoid diseases, diabetes, atherosclerosis, infectious diseases and cancer. It exhibits a wide range of pharmacological properties, which include antioxidant, anti-inflammatory, antimutagenic, antimicrobial and anticancer activity. Herein the mechanisms of curcumin impact on oxidative stress, angiogenesis and inflammatory processes are described indicating that curcumin use may inhibit those pathological conditions and restore body homeostasis. Its effectiveness was also proved for major eye diseases. In this review, the influence of curcumin on eye diseases, such as glaucoma, cataract, age-related macular degeneration, diabetic retinopathy, corneal neovascularization, corneal wound healing, dry eye disease, conjunctivitis, pterygium, anterior uveitis are reported. The analysis of a number of clinical and preclinical investigations indicates that curcumin may be used as a therapeutic agent in the treatment of various eye disorders.

Key words: *curcumin, angiogenesis, glaucoma, diabetic retinopathy, conjunctivitis, cataract, eye disease, reactive oxygen species (ROS), age-related macular degeneration (AMD).*

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Introduction

Curcumin (diferuloylmethane) derived from the rhizome of *Curcuma longa* L. belongs to polyphenols. It was isolated over 140 years ago by Vogel and was synthesized in 1913 by Lampe [1]. Curcumin has been used for thousands of years in traditional Chinese medicine and Ayurvedic medicine in Asian countries as an active ingredient of herbal remedies to treat liver diseases, rheumatoid diseases, diabetes, atherosclerosis, infectious diseases and cancer [2]. It is characterized by an antioxidant, anti-inflammatory, antimutagenic, antimicrobial and anticancer activity [3-7]. Turmeric rhizome is also known as a spice widely used in cookery, fabric dying and cosmetic industry.

Curcumin was introduced to the Western world in the 14th century and is still in use. Unfortunately, turmeric has poor bioavailability (poor absorption, rapid metabolism, and elimination) and selectivity [8, 9]. Therefore, numerous curcumin analogs were produced and tested in order to improve the pharmacological profile of the natural product [10]. Piperine, a component of black pepper, is among the bioavailability enhancers used for this purpose. This agent, when used together with curcumin, improves it bioavailability by 2000%. Turmeric, despite its poor bioavailability, is well tolerated and is not toxic to animals or humans even at high doses. Chang *et al.* [11] demonstrated in a clinical trial that doses of 8 or even 12 g/day were safe for humans.

Curcumin may be used as a preventive and curative agent in many diseases, such as neurodegenerative diseases (including Alzheimer's disease), diabetes, cancer, rheumatoid diseases, atherosclerosis, pulmonary infective disease, chronic intestinal inflammation, allergy, asthma, autoimmune diseases, AIDS, psoriasis, and others [12]. Its effectiveness was also proved for major eye diseases. We focus on this subject later on in the article.

Reactive oxygen species and antioxidant properties of curcumin

Reactive oxygen species (ROS), a product of normal metabolism of cells, may be either advantageous or damaging for the cell and the body, depending mainly on the concentration. The level of ROS may be influenced by two things: endogenous ROS formation and exposure to exogenous ROS. The main source of endogenous ROS is mitochondrial oxidative process and some enzymatic reactions catalyzed by the oxidoreductase group of enzymes [13,

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14]. Overall, ROS at low concentrations act as intracellular signal transducers and inducers of cell proliferation, transcription, and apoptosis. They activate some transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP-1) [15]. They also contribute to angiogenesis and inflammatory processes. Conversely, high levels of cellular ROS may be cytotoxic and mutagenic for cells leading to the damage of lipids, proteins, DNA, carbohydrates and, finally, inducing cell apoptosis.

Substances present at low concentrations compared to oxidizable compounds that delay or prevent substrate oxidation are known as antioxidants. Antioxidant defense systems of the body are divided into endogenous and exogenous. The endogenous antioxidant defense system consists of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, glutathione peroxidase, heme oxygenase (HO-1), and non-enzymatic antioxidant system composed of low molecular weight scavengers (e.g. glutathione [GSH], uric acid, lipoic acid, ascorbic acid, tocopherol). The exogenous antioxidant defense system consists of antioxidants that may be grouped into natural products and identical to natural ones but synthesized by the industry, such as vitamins and synthetic ones [16, 17].

The imbalance between the production of ROS and antioxidant mechanisms is defined as oxidative stress. Oxidative stress plays a crucial role in the pathogenesis of several serious diseases and aging [18, 19].

Curcumin belongs to a group of natural antioxidants. It exists in the form of strong antioxidant agents, such as vitamin C or E. The effect of curcumin on free radicals is carried out by several different mechanisms. It may scavenge various forms of free radicals, such as ROS and reactive nitrogen species (RNS) [20]. Besides, it may modulate the activity of GSH, catalase, and SOD enzymes active in the neutralization of free radicals [21, 22]. Furthermore, it may inhibit ROS-generating enzymes, such as lipoxygenase/cyclooxygenase and xanthine hydrogenase/oxidase [21]. In addition, curcumin is a lipophilic compound, which makes it an efficient scavenger of peroxyl radicals. Therefore, like vitamin E, curcumin is also considered as a chain-breaking antioxidant [23]. It was proved that curcumin increased the GSH level in normal and cancer cells [24]. Curcumin suppresses nitric oxide synthase (NOS) activity in murine macrophages as well as the synthesis of NOS in mouse spleen in *in vivo* studies. It induces the expression of heme oxygenase in various types of cells [25]. It is an enzyme that catalyzes the degradation of heme to biliverdin, ferrous iron, and carbon monoxide. HO-1 also plays a pivotal role in cell response to oxidative stress [26] and in angiogenesis [15]. Antioxidant properties of curcumin cause oxidative stress inhibition. This allows people to understand the effectiveness of treatment in numerous lifestyle-related diseases.

The response of cells to oxidative stress induces an inflammatory process. Proinflammatory gene expression is enhanced by a number of reactive oxygen/nitrogen species that initiate an intracellular signaling cascade.

Curcumin was proved to block the activation of proinflammatory NF-κB increased by several different inflammatory stimuli [27]. NF-κB is known to regulate tumor necrosis factor α (TNF-α), a major mediator of inflammation in most diseases.

In addition, curcumin suppresses TNF-α synthesis and inhibits the release of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8 and chemokines. Furthermore, it downregulates proinflammatory enzyme expression, i.e. cyclooxygenase 2 (COX-2), the main enzyme engaged in prostaglandin production and 5-lipoxygenase (5-LOX) [21, 22]. Antioxidant properties of curcumin imply the influence on angiogenesis.

Angiogenesis and curcumin angiogenic properties

Studies published last year indicated that ROS are critical regulators of angiogenic homeostasis.

The effect of ROS on the vascular function depends critically on the amount of ROS present. High ROS doses induced oxidative stress and a subsequent death of cells necessary for angiogenesis, thereby inhibiting angiogenesis. Low doses of ROS (mainly H_2O_2) were found to promote angiogenesis *via* sub-lethal cell membrane damage and subsequent FGF-2 release [28-30]. It initiated the intracellular production of ROS through NAD(P)H oxidase (NOX) and SOD activation and subsequent downstream growth factor signaling for proliferation, migration and tube formation.

Angiogenesis, a process that allows new blood vessels to be formed within a host's vasculature, plays an important role in physiology and pathology. Physiologically, it occurs e.g. during the menstrual cycle, embryogenesis and wound healing.

One essential element for angiogenesis to work is the angiogenic switch mediated by angiogenic oncogenes. They upregulate the expression of proangiogenic proteins such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) and diminish the expression of angiogenesis inhibitors. VEGF and bFGF are the most stimulated factors for physiological angiogenesis and basic factors in pathological angiogenesis [15, 31]. VEGF activates receptor tyrosine kinases (mainly VEGFR-1, VEGFR-2) present on endothelial cells, monocytes and cancer cells. VEGFR-2 activates downstream signaling pathways, such as Erk, Akt, eNOS, which are necessary for early angiogenesis [32]. The degradation of the basement membrane of the maternal vessel and surrounding extracellular matrix components mediated by the proteolytic activity of metalloproteinases (MMPs) and

plasmin [33] is necessary for neovascularization. Further steps of a new blood vessel creation process include the proliferation and migration of endothelial cells of the maternal vessels for sprouting and growth of a new capillary. It depends on the ability to alter the arrangement of their adhesion membrane proteins, belonging mainly to the integrin family. The stabilization of new vessels is achieved by the formation of the basement membrane and pericyte recruitment [34].

Mitogens and chemoattractants acting on pericytes are induced by platelet-derived growth factor (PDGF), while pericyte differentiation is assured by transforming growth factor β (TGF-β) and FGF-2. Angiopoietins – endothelial cell growth factors – regulate the maturation and structure of new vessels at the very end of new capillary formation [29, 34].

Extensive research revealed that curcumin inhibits angiogenesis *via* various mechanisms. Chen *et al.* demonstrated the suppression of VEGF (isoforms 165 and 121 of VEGF) secretion in U937 and Raji cells by curcumin treatment [35]. Curcumin inhibited angiogenesis measured as network formation of endothelial cells on Matrigel. It also suppressed angiogenesis in the endothelial cell line – ECV304 cells.

HepG2 cell line (hepatocellular carcinoma cell line) characterized by the overexpression of VEGF and cyclooxygenase-2 (COX-2) was also inhibited by curcumin [36]. In another study, HepG2 cells were inoculated onto the upper layer of the skinfold chamber and curcumin solutions were orally fed to the HepG2 cell-implanted nude mice. Angiogenesis was evaluated as tumor neocapillary density using a digital image analysis [37]. Curcumin (3000 mg/kg BW) treatment inhibited tumor angiogenesis by the reduction of proangiogenic factors such as VEGF and COX-2. Such inhibition also occurred with liposomal curcumin as shown by Li *et al.* [38] through the attenuation of the NF-κB mechanism. Curcumin was also shown to inhibit angiogenesis in bFGF-induced corneal neovascularization, as assessed by measuring vessel length and density in normally avascular cornea. Curcumin reduced the proliferation of primary endothelial cells in the presence and absence of bFGF and also inhibited the proliferation of an immortalized endothelial cell line [39]. Other investigators also described the inhibition of fibroblast growth factor (FGF)-induced neovascularization [39-41]. In addition to the suppression of ligands of VEGF, it was also demonstrated to suppress angiopoietin 1 and 2 [41]. Furthermore, curcumin indirectly modulated angiogenesis through the ability to regulate cell adhesion molecules, such as endothelial leukocyte adhesion molecule-1 (ELAM-1), intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and cell surface proteins involved in angiogenesis and tumor metastasis [42].

A study of Aggarwal and Natarajan [43] showed that curcumins influenced angiogenesis through the inhibition of tube formation in a dose-dependent manner when the cells were treated before or at the time of plating on Matrigel.

It was reported that curcumin decreased the activity of metalloproteinases and serine protease family, the urokinase plasminogen activator system (uPA). uPA interacts with a specific receptor (uPAR) through the epidermal growth factor (EGF)-like domain in the urokinase amino-terminal fragment (ATF). This effect of curcumin causes the inhibition of endothelial cell migration and the stimulation of bFGF, transforming growth factor (TGF), TNF, hepatocyte growth factor (HGF), and VEGF release [44]. It was found that curcuminoids inhibited the expression of MMP-2 acting *via* FGF-2 angiogenic signaling pathways [45]. The inhibitory effect of curcumin was also described for mouse keratinocytes. Turmeric diminished the uPA levels induced by TGF-β1 in transformed keratinocytes and TGF-β-induced synthesis of fibronectin as well as inhibited TGF-β-stimulated cell migration and invasiveness [46].

Disturbances of angiogenesis may result in serious medical consequences. Excessive angiogenesis exists e.g. in AMD, cancer, endometriosis, while insufficient angiogenesis is noted e.g. in neurodegenerative diseases, diabetes mellitus, stroke, atherosclerosis, hypertension, and ischemic heart disease. Numerous antiangiogenic and antioxidant properties of curcumin prove that it may be sufficient in the treatment of angiogenesis-related diseases including eye diseases [47-51].

Diseases of the cornea

Corneal neovascularization

Corneal neovascularization (NV) is characterized by the invasion of new blood vessels into the cornea from the limbus. Immature new blood vessels may lead to lipid exudation, persistent inflammation, and scarring, thus threatening corneal transparency and visual acuity. Advanced stages, in which ingrown blood vessels reach the visual axis, can become permanently vision-threatening and are a leading cause of blindness. They are triggered by a disruption of the balance between angiogenic and antiangiogenic factors, corneal hypoxia and inflammation [52]. Concentrations of two major proangiogenic factors, VEGF and bFGF, are elevated in such conditions and lead to corneal neovascularization. It was shown that curcumin suppressed the proliferation of primary endothelial cells cultured *in vitro* in the presence or absence of bFGF. An *in vivo* study of the same group revealed that curcumin inhibited mouse corneal NV induced by bFGF [52]. The results of the rabbit *in vivo* model of suturing-induced corneal NV demonstrated the efficacy of curcumin in inhibiting angiogenesis through decreasing VEGF mRNA levels and NF-κB phosphorylation [53]. Moreover, curcumin nanoparticles (NPs) inhibit the angiogenic sprouting in mouse aortic ring *in vitro* in a dose- and time-dependent

manner. NF-κB inhibition by curcumin NPs was shown in an *in vitro* study of LPS-induced corneal cells by Pradhan *et al.* [54]. In the same group, curcumin NPs inhibited the level of proangiogenic VEGF, MMPs (MMP2 and MMP-9) as well as proinflammatory IL-1β and TNF-α in an *in vivo* silver nitrate-induced corneal NV study [54].

Curcuminoids inhibit FGF-2-induced rabbit corneal NV *in vivo* through diminishing DNA binding activity from transcription factor activator protein-1 (AP-1) and gelatinase B promoter activity [40].

Corneal wound healing

The risk of corneal diseases is very high in the course of diabetes. Diabetic keratopathy concerns 50% of diabetic patients [55]. Guo *et al.* [56] demonstrated the effectiveness of intranasal nanomicelle curcumin in corneal epithelial/nerve wound healing in STZ-induced model of diabetic mice with corneal epithelium abrasion. In this study curcumin recovered the enhanced accumulation of ROS, decreased free radical scavengers, decreased mRNA expression of neurotrophic factors, and increased mRNA expression of inflammatory cytokines in the cornea. The authors observed trigeminal ganglion neurons in mice with corneal epithelium abrasion suggesting that intranasal curcumin may support the diabetic corneal epithelial or nerve wound healing process [56].

Dry eye disease

Dry eye disease is characterized by a decreased secretion of tears and rapid tear evaporation [57] causing ocular surface damage. The pathogenesis of this process includes elevated tear osmolality and an inflammation of the ocular surface. Proinflammatory cytokines, including IL-6, IL-8, IL-1β, are detected in corneal cell lines and dry eye patients in hyperosmotic environment [58]. Curcumin could exert a protective effect through its anti-inflammatory activity. Notably, curcumin was shown to inhibit the expression of ovalbumin-induced proinflammatory cytokines, such as IL-4 and IL-5, in the conjunctiva in mice [59]. In addition, an *in vitro* study demonstrated that curcumin protected hyperosmoticity-induced IL-1β upregulation in the corneal epithelial cell via p38 mitogen activated protein kinase (MAPK/NF-κB) pathways [60].

Conjunctivitis

Conjunctivitis is an inflammation of the conjunctiva, a thin transparent layer of tissue that lines the inner surface of the eyelid and covers the white part of the eye.

The most common infectious causes are viral, followed by bacterial ones. It may also develop due to an allergic reaction to air irritants, such as pollen and smoke, chlorine in swimming pools, ingredients in cosmetic products, or other products that come in contact with eyes, such as contact lenses. Sexually transmitted diseases, like chlamydia and gonorrhea, are among less common causes of conjunctivitis [61].

Chung *et al.* [59] reported that curcumin had the potential of inhibiting ovalbumin-induced conjunctivitis caused by allergy in a mouse model. Mice developed severe allergic conjunctivitis as a result of challenging with ovalbumin *via* the conjunctival sac of systemic sensitization in aluminum hydroxide. Curcumin administered 1 h before the ovalbumin challenge exerted anti-inflammatory and antiallergic effects. It suppressed the activation levels of inducible nitric oxide synthase (iNOS) production in mouse conjunctiva and inhibited immunoglobulin E (IgE)-mediated and eosinophil-dependent conjunctival inflammation. Furthermore, IL-4 and IL-5 expression in the conjunctiva, cervical lymph nodes, and the spleen were reduced in mice treated with curcuma as compared to the control group [59].

Curcuma longa called haridra in India and in tropical areas is available as Haridra Eye Drops. It has anti-inflammatory properties and antibacterial activity against *Escherichia coli*, *S. aureus, Klebsiella*, and *Pseudomonas* organisms [62]. A clinical study demonstrated the effectiveness of Haridra Eye Drops in treating bacterial conjunctivitis. Another kind of eye drops with curcumin, Ophthacare, is produced by Himalaya Drug Company. Ophthacare, which contains eight different herbs including 1.30% w/v of *Curcuma longa* (rhizome), was reported to be effective in the treatment of conjunctivitis, conjunctival xerosis (dry eye) and safe in various infective and inflammatory conjunctival diseases [63].

Pterygium

A pterygium is a growth of the conjunctiva or mucous membrane forming fibrous tissue in a triangular shape that covers the white part of the eye over the cornea. The first-choice treatment for this inflammatory and degenerative ocular surface disease is surgical excision, but a high rate of re-occurrence renders this method controversial. Zhang *et al.* [64] found that curcumin exerted a therapeutic action against pterygium. An *in vitro* study was conducted using human pterygium fibroblasts. Curcumin at a dose of 20-80 μmol/l increased the expression of spreading cell nuclear antigen, inhibited the proliferation and caused the cellular death of human pterygium fibroblasts in a dose- and time-dependent manner. Ophthacare treatment of pterygium also showed positive effects in a study by Biswas *et al.* [63].

Anterior uveitis

Anterior uveitis is an inflammation of the middle layer of the eye. This layer includes the iris and the adjacent tissue, known as the ciliary body. If untreated, it

can cause permanent damage and loss of vision from the development of glaucoma, cataract or retinal edema. The pathomechanism of uveitis is not clear due to its heterogeneity. The treatment usually involves corticosteroids and NSAIDs, although several side effects (i.e. cataract, secondary glaucoma, anterior and posterior synechiae) may occur as a result. Lal *et al.* [65] reported an improved vision in patients with chronic anterior uveitis who were administered oral capsules with 375 mg/capsule of curcumin t.i.d. along with local cycloplegics (e.g. atropine). Decreased aqueous flare and keratic precipitates were observed after treatment [65].

A beneficial effect of Meriva (Indena, Milano, Italy), curcumin formulated with phosphatidylcholine, which improves bioavailability at least 10-fold as compared to the standard preparation, was observed in the adjunct therapy of recurrent anterior uveitis of various etiologies [66]. Another study of a standardized aqueous extract of *Curcuma longa* applied topically led to the inhibition of *E. coli* lipopolysaccharide-induced anterior uveitis in rats and rabbits by reducing TNF-α activity [67]. Its beneficial effects may stem from their antioxidative, anti-inflammatory, as well as antifibrinolytic properties.

Glaucoma

Glaucoma is a group of eye diseases which result in the damage to the optic nerve and vision loss [68]. The most common type is an open-angle glaucoma with less common types including closed-angle glaucoma and normal-tension glaucoma. The development of the disease involves retinal ganglion cell loss, i.e. thinning of the retinal nerve fiber layer and progressive loss of the vision field [69]. Several causes of glaucoma exist, with ocular hypertension (increased pressure within the eye) being the most significant risk factor in most glaucomas. However, in some populations only 50% of people with primary open-angle glaucoma actually have the ocular pressure elevated. In some cases, even when eye pressure decreased to normal levels, glaucoma progresses anyway. Thus, neuroprotective agents are desired to prevent, limit or even fix the damage to the optic nerve.

You *et al.* [69] indicated that curcumin may possess neuroprotective properties. Pretreatment with curcumin in an *in vivo* rat model of chronic high intraocular pressure, resulted in significantly increased cell viability of BV-2 microglia and the increased presence of ROS and a decrease in the apoptosis of BV-2 microglia. The neuroprotective effect of curcumin may be demonstrated by inhibiting oxidative damage to microglia. Curcumin at low doses (< 50 M) attenuated staurosporine-induced ganglion cell death in *in vitro* and *in vivo* studies [70].

One of the animal models for open-angle glaucoma is acute retinal ischemia induced by high intraocular pressure followed by reperfusion (I/R). The neuroprotective effect of retinal I/R injury was seen in case of dietary curcumin. Curcumin decreased mitofusin 2 (mfn2), a mitochondrial fusion protein, after retinal I/R injury. Nuclear factor erythroid 2-related factor 2 (Nrf2) exerts a protective effect against oxidative stress and is increased after retinal I/R injury. Mfn2 suppression and Nrf2 elevation were observed after pretreatment with curcumin indicating that curcumin may alleviate retinal I/R injury by regulating the antioxidant system and may restore normal mitochondrial function [71].

Cataract

A cataract is a clouding of the lens in the eye which leads to a decrease in vision. Cataracts often develop slowly and may affect one or both eyes. The mainstream treatment for this disease is cataract extraction surgery. The anti-cataract effect of curcumin may originate from its antioxidant properties. Chhunchha *et al.* [72] showed in an *in vitro* study that curcumin inhibited a pleiotropic oxidative stress-response protein (peroxiredoxin 6) in cultured human lens epithelial cells (hLECs). Curcumin was examined in various cataract models. It suppressed selenium-induced oxidative stress in rat organ cultured lens and delayed the formation of cataracts by inhibiting the non-enzymatic antioxidant depletion [73]. Decreased vitamin C levels observed in selenite-induced rat cataracts suggests that weakened non-enzymatic antioxidant defenses may play a role in selenite-induced rat cataracts. The administration of curcumin was found to increase vitamin C levels [74]. Padmaja and Raju [75] observed an increase in superoxide dismutase and catalase enzyme activity in Wistar rats after pretreatment with curcumin, which may prevent oxidative damage and delay the development of cataracts. Curcumin was shown to delay the progression of diabetic cataract by preventing hyperglycemia-mediated lenticular oxidative stress in rats. It significantly decreased GSH levels and prevented the alteration of protein carbonyls, antioxidant enzymes glutathione peroxidase (GPx), glucose-6-phosphate dehydrogenase (G6PD) [76].

GSH is known to protect cells against lipid peroxidation. Manikandan *et al.* [77] demonstrated an elevation of lipid peroxidation in rat lens by selenite leading to the downregulation of GSH in the lens. Curcumin administration caused the normalization of GSH levels that was detected in tissues and sera in selenite-treated lenses *in vivo*. It confirms the protective role of curcumin against oxidative stress [78].

Age-related macular degeneration

Age-related macular degeneration (AMD) is a condition of the central part of the macula and results in visual loss at its advanced stages. The early stages of age-related maculopathy are distinguished by the occurrence of drusen

in the eyeground and abnormalities of retinal pigment epithelium. Geographical atrophy and choroidal neovascularization are observed at late atrophic and exudative stages of the AMD [79]. Neovascular AMD is characterized by choroidal neovascularization that invades the subretinal space, often leading to exudation and hemorrhage [79]. This type of AMD is caused by abnormally high pathological angiogenesis [50, 51]. The neovascular form of the disease represents approximately 10% of the overall disease prevalence, but it is responsible for 90% of severe vision loss. If the condition is left untreated, damage to photoreceptors and loss of central vision usually occur, and after several months to years, the vessels are largely replaced by a fibrovascular scar. The main risk factors for the disease include age, sex, ethnicity, genetic predisposition, visible light, arterial hypertension, atherosclerosis, smoking and antioxidant deficiency.

Curcumin was found to prevent cell death across different cellular models of AMD. The mechanisms of action include decreasing apoptotic rates of retinal pigment epithelial (RPE) cells and decreasing overall inflammation. Zhu *et al.* [80] used the model of AMD based on pulsed H_2O_2 induction of retinal pigment cell aging. They demonstrated that curcumin reduced free radicals as well as gene expression of the oxidative biomarkers, including superoxide dismutase, maleic dialdehyde, and GSH. Curcumin suppressed apoptosis and thus increased cell viability. Specific microRNAs (miRNAs) that regulate the antioxidant system were reported to be regulated by curcumin [81]. Besides, HO-1, an enzyme that serves cellular defense mechanisms in AMD, was increased due to curcumin effects. The results of the light-induced retinal degeneration model of AMD indicated that curcumin inhibits nuclear factor jB (NfjB) and downregulates cellular inflammatory genes [82].

Diabetic retinopathy

Diabetic retinopathy (DR) is a metabolic disorder and a chronic inflammatory state that leads to damage to both photoreceptors and blood vessels of the retina. In the course of diabetes mellitus, the vasculature shows signs of local hypertension that includes basement membrane thickening that disrupts tight connections between the pericytes. It results in pericyte apoptosis and the release of cellular mediators that promote angiogenesis [83]. The accumulation of advanced glycation end products causes a release of ROS which cross-links proteins and damages vascular and extravascular structures. Oxidative stress induced by hyperglycemia and pathological neovascularization contributes to the pathogenesis of DR. ROS may cause the loss of pericytes and formation of micro-aneurysms that leads to the vascular syndrome of DR [84, 85].

Gupta *et al.* [86] found that curcumin prevented the degeneration of cellular organelles and increased the capillary basement membrane thickness in the retina. The mechanism of curcumin action involved decreasing TNF-α, decreasing proangiogenic vascular endothelial growth factor (VEGF), and increasing the levels of antioxidant enzymes SOD and catalase. Extracellular matrix production decreases as cells are affected by retinopathy in the course of DR. Curcumin enhances extracellular matrix production by increasing levels of mammalian excision repair cross-complementing (ERCC) 1 and ERCC4 enzymes [87]. Furthermore, curcumin exerts the antiangiogenic action of the choroidal vasculature of rat retina. Curcumin normalizes diabetic microvasculature, attenuates its tortuosity, shrinkage, narrowing and micro-aneurysms. The processes of regeneration and repair are observed in choroidal microvasculature after curcumin treatment [88].

Conclusions

Curcumin, a natural polyphenol agent isolated from C*urcuma longa* L. exhibits a wide range of pharmacological properties including antioxidant, anti-inflammatory, antimutagenic, antimicrobial and anticancer activity. The influence of curcumin on oxidative stress, angiogenesis and inflammatory processes indicates that it may inhibit these pathological conditions and restore homeostasis. The analysis of a number of clinical and preclinical investigations shows that curcumin may be used as a therapeutic agent in the treatment of various eye diseases such glaucoma, cataract, age-related macular degeneration, diabetic retinopathy, corneal neovascularization, corneal wound healing, dry eye disease, conjunctivitis, pterygium, and anterior uveitis.

The authors declare no conflict of interest.

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