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Therapeutic Role of Curcumin, a Traditional Indian Remedy in Various Ocular Disorders

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Abstract

Curcumin (diferuloylmethane) derived from the rhizome of *Curcuma longa L*. has been an active ingredient of traditional Chinese medicine and Ayurvedic medicine for thousands of years to treat liver diseases, rheumatoid diseases, diabetes, atherosclerosis, infectious diseases and cancer. Curcumin has multiple essential pharmacological properties namely, antioxidant, anti-inflammatory, antimutagenic, antimicrobial and anticancer activity. Curcumin inhibits oxidative stress, angiogenesis and inflammatory processes and restore body homeostasis. Its effectiveness was also proved for major eye diseases. In this article, the influence of curcumin on various eye diseases such as dry eye disease, conjunctivitis, pterygium, anterior uveitis, glaucoma, cataract, age-related macular degeneration, diabetic retinopathy, corneal neovascularization, corneal wound healing are reported. Data analysis from several clinical and preclinical investigations indicate that curcumin is highly effective as a therapeutic agent in the treatment of various eye disorders.

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Introduction

Turmeric rhizome is popular worldwide as a spice and widely used in cookery, fabric dying and the cosmetic industry. Curcumin (diferuloylmethane) derived from the rhizome of turmeric 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 as an active ingredient to treat liver diseases, rheumatoid diseases, diabetes, atherosclerosis, infectious diseases and cancer.[2] It is credited to have antioxidant, anti-inflammatory, antimutagenic, antimicrobial and anticancer activity.[3-7]

Unfortunately, turmeric has poor bioavailability (poor absorption, rapid metabolism, and elimination) and selectivity.[8,9] Therefore, numerous curcumin analogs were artificially developed and tested to improve curcumin's pharmacological profile.[10] Piperine, a component of black pepper, enhances the bioavailability of curcumin by 2000%. Turmeric 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 role in numerous pathologies including, 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.

Reactive Oxygen Species and Antioxidant Properties of Curcumin

Reactive oxygen species (ROS), a product of cellular metabolism, may be either advantageous or damaging for the cell and the body, depending on the concentration. The main source of ROS is a mitochondrial oxidative process and enzymatic reactions catalyzed by the oxidoreductase group of enzymes.[13, 14] Overall, ROS at low concentrations act as intracellular signal transducers and inducers of cell proliferation, transcription, and apoptosis.[15] They also contribute to angiogenesis and inflammatory processes. High levels of cellular ROS may be cytotoxic and mutagenic, leading to the damage of lipids, proteins, DNA, carbohydrates and, finally, inducing cell apoptosis.

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], ascorbic acid). The exogenous antioxidant defense system consists of antioxidants 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.[8,19]

Curcumin belongs to a group of natural antioxidants. It exists in the form of strong antioxidant agents, such as vitamin C or E. 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.[23] It was proved that curcumin increased the GSH level in normal and cancer cells.[24] Curcumin suppresses nitric oxide synthase (NOS) activity. It induces the expression of heme oxygenase,[25] which plays a pivotal role in cell response to oxidative stress[26] and in angiogenesis.[15]

Oxidative stress induces inflammatory process and expression of proinflammatory gene that initiate an intracellular signaling cascade.

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

In addition, curcumin inhibits the release of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8 and chemokines. Furthermore, it downregulates cyclooxygenase 2 (COX-2) a pivotal proinflammatory enzyme.[21,22]

Angiogenesis and Curcumin Angiogenic Properties

Studies indicate ROS are critical regulators of angiogenesis.

The effect of ROS on vascular function depends critically on the concentration. High ROS doses induced oxidative stress and subsequent death of cells, thereby inhibiting angiogenesis. Low doses of ROS were found to promote angiogenesis via sub-lethal cell membrane damage and subsequent FGF-2 release.[28-30]

Upregulation of proangiogenic proteins such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are vital for angiogenesis.[15, 31, 32]

The degradation of the basement membrane of the maternal vessel and surrounding extracellular matrix components mediated by 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. Finally, 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 a (TGF-a) and FGF-2.[29,34]

Curcumin inhibits angiogenesis via various mechanisms. Chen et al. demonstrated the suppression of VEGF and COX-2 *in-vitro* by curcumin.[35]

HepG2 cell line (hepatocellular carcinoma cell line) characterized by the overexpression of VEGF and cyclooxygenase-2 (COX-2) was also inhibited by curcumin.[36,37]

Such inhibition also occurred with liposomal curcumin as shown by Li et al.[38] through the attenuation of the NF-IB mechanism. Curcumin was also shown to inhibit angiogenesis in bFGF-induced corneal 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.

It was reported that curcumin decreased the activity of metalloproteinases and urokinase plasminogen activator system (uPA).[44] It was found that curcuminoids inhibited the expression of MMP-2 acting via FGF-2 angiogenic signaling pathways.[45,46]

Numerous antiangiogenic and antioxidant properties of curcumin prove that it may be sufficient in the treatment of angiogenesis-related eye diseases such as AMD and diabetic retinopathy.[47-51]

Corneal Neovascularization and Wound Healing

Corneal neovascularization (NV) is characterized by the invasion of new blood vessels into the cornea from the limbus. Persistent inflammation, exudation and scaring from the immature new blood vessels threatens corneal transparency and visual acuity. Persistent inflammation, corneal hypoxia and excessive pro angiogenic factors like VEGF and bFGF triggers angiogenesis.[52] Animal studies have shown that curcumin inhibits the proliferation of endothelial cells even in the presence of bFGF and VEGF as well as reduces the levels of MMP and proinflammatory IL-1ß and TNF-α in a corneal neovascularization study.[53,54]

Guo et al. demonstrated the effectiveness of curcumin in corneal epithelial/nerve wound healing in corneal abrasion. In this study, curcumin inhibits the accumulation of ROS, decreased neurotrophic factors, and increases inflammatory cytokines in the cornea.[55,56]

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 includes elevated tear osmolality and inflammation of the ocular surface. Proinflammatory cytokines, including IL-6, IL-8, IL-1ß, are detected in corneal cell lines in dry eye patients.[58] Curcumin could exert a protective effect through its anti-inflammatory activity by inhibiting the expression of proinflammatory cytokines, such as IL-4 and IL-5.[59] In addition, curcumin reduced the hyperosmoticity-induced IL-1ß upregulation in the corneal epithelial cell.[60]

Conjunctivitis

Conjunctivitis is an inflammation of the conjunctiva. The most common causes are viral, bacterial or allergic (pollen and smoke, chlorine in swimming pools).[61]

Curcumin has the potential of inhibiting allergic conjunctivitis induced by ovalbumin. It suppressed inducible nitric oxide synthase (iNOS) production and inhibited immunoglobulin E (IgE)-mediated and eosinophil-dependent conjunctival inflammation. IL-4 and IL-5 expression in the conjunctiva, cervical lymph nodes, and the spleen were also reduced.[59]

Curcumin has antibacterial activity against *Escherichia coli, S. aureus, Klebsiella, and Pseudomonas organisms*.[62] A clinical study

demonstrated the effectiveness of ayurvedic eye drops containing curcumin in treating bacterial conjunctivitis.[63]

Pterygium

A pterygium is a degenerative growth of a conjunctival fold in a triangular shape that encroaches upon the cornea. Zhang et al.[64] found that curcumin exerted a therapeutic action against human pterygium fibroblasts. It inhibited proliferation and caused death of human pterygium fibroblasts in a dose- and time-dependent manner.[63]

Anterior uveitis

Uveitis is an inflammation of the middle layer of the eye. If untreated, it can cause permanent damage and loss of vision from the development of glaucoma, cataract or retinal edema. The treatment usually involves corticosteroids and cycloplegics, although several side effects may occur as a result. Lal et al. 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]

Curcumin combined 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 using topical curcumin led to the inhibition of *E. coli* lipopolysaccharide-induced anterior uveitis in animal models by reducing TNF-a activity.[67]

Glaucoma

Glaucoma is a group of eye diseases that damage the optic nerve and vision loss.[68] The most common type is open-angle glaucoma with less common types including closed-angle glaucoma and normal-tension glaucoma. The disease is characterized by retinal ganglion cell loss, i.e., thinning of the retinal nerve fiber layer and progressive loss of the vision field.[69] Thus, neuroprotective agents are desired to prevent and limit the damage to the ganglionic cells. You et al.[69] indicated that curcumin may possess neuroprotective properties. Pretreatment with curcumin in rat model of chronic high intraocular pressure, resulted in significantly increased cell viability and decreased apoptosis of BV-2 microglia. The neuroprotective effect of curcumin may be demonstrated by inhibiting oxidative damage to microglia.[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 dietary curcumin is exhibited through suppression of mitofusin 2 (mfn2), causing retinal I/R injury and elevation of Nuclear factor erythroid 2-related factor 2 (Nrf2) which exerts a protective effect after retinal I/R injury.[71]

Cataract

Cataracts often develop slowly and may affect one or both eyes. The anti-cataract effect of curcumin is due to its antioxidant properties. Chhunchha et al.[72] showed in an *in-vitro* study that curcumin inhibited peroxiredoxin 6 in cultured human lens epithelial cells (hLECs). It suppressed selenium-induced formation of cataracts by inhibiting the non-enzymatic antioxidant depletion.[73] The administration of curcumin was found to increase vitamin C levels (a potent anti oxidant)[74] and increase superoxide dismutase and catalase enzyme activity, which may prevent oxidative damage and delay cataract. Curcumin was also shown to delay the progression of diabetic cataracts by preventing hyperglycemia-mediated lenticular oxidative stress. It increased GSH levels and prevented the alteration of lens protein.[76-78]

Age-related Macular Degeneration

Age-related macular degeneration (AMD) is scaring in central part of the macula and results in visual loss.[79] Neovascular AMD is characterized by choroidal neovascularization 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 formation of fibrovascular scar and loss of central vision.

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 inflammation. Zhu et al.[80] 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.[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. The vasculature shows signs like 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 increases ROS which cross-links proteins and damages vascular and extravascular structures. ROS may cause the loss of pericytes and formation of micro-aneurysms that leads to the vascular syndrome of DR. Gupta et al.[84-86] 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-a, vascular endothelial growth factor (VEGF), and increasing the levels of antioxidant enzymes SOD and catalase.[87] Curcumin stabilizes 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]

Conclusion

Curcumin, a natural polyphenol agent isolated from *Curcuma 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 studies 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.

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