



Role of Curcumin in Retinal Diseases—A review

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Abstract

Purpose To review the role of curcumin in retinal diseases, COVID era, modification of the molecule to improve bioavailability and its future scope.

Methods PubMed and MEDLINE searches were pertaining to curcumin, properties of curcumin, curcumin in retinal diseases, curcumin in diabetic retinopathy, curcumin in age-related macular degeneration, curcumin in retinal and choroidal diseases, curcumin in retinitis pigmentosa, curcumin in retinal ischemia reperfusion injury, curcumin in proliferative vitreoretinopathy and curcumin in current COVID era.

Results In experimental models, curcumin showed its pleiotropic effects in retinal diseases like diabetic retinopathy by increasing anti-oxidant enzymes, upregulating HO-1, nrf2 and reducing or inhibiting inflammatory mediators, growth factors and by inhibiting proliferation and migration of retinal endothelial cells in a dose-dependent manner in HRPC, HREC and ARPE-19 cells. In age-related macular degeneration, curcumin acts by reducing ROS and inhibiting apoptosis inducing proteins and cellular inflammatory genes and upregulating HO-1, thioredoxin and NQO1. In retinitis pigmentosa, curcumin has been shown to delay structural defects of P23H gene in P23H-rhodopsin transgenic rats. In proliferative vitreoretinopathy, curcumin inhibited the action of EGF in a dose- and time-dependent manner. In retinal ischemia reperfusion injury, curcumin downregulates IL-17, IL-23, NF κ B, STAT-3, MCP-1 and JNK. In retinoblastoma, curcumin inhibits proliferation, migration and apoptosis of RBY79 and SO-RB50. Curcumin has already proven its efficacy in inhibiting viral replication, coagulation and cytokine storm in COVID era.

Conclusion Curcumin is an easily available spice used traditionally in Indian cooking. The benefits of curcumin are manifold, and large randomized controlled trials are required to study its effects not only in treating retinal diseases in humans but in their prevention too.

Key messages

- Curcumin—Its pleiotropic effect in Gastrointestinal disorders, Cardiovascular disorders, Neurodegenerative disorders, Rheumatological disorders, Anti-cancer drug are known.
- Curcumin—COVID era –Anti-viral, Immunomodulatory, Anti-inflammatory, Anti-Coagulatory effect
- Curcumin –Its role and mechanism in Diabetic Retinopathy, Age Related Macular Degeneration, Retinitis Pigmentosa and Proliferative Vitreoretinopathy.
- Curcumin –Its role and mechanism in Retinal Ischemia and Reperfusion Injury, Retinoblastoma, Methyl alcohol poisoning and Best Dystrophy.
- Curcumin-Improving bioavailability.

Keywords Curcumin · Diabetic Retinopathy · Age-Related Macular Degeneration · Retinitis Pigmentosa · Retinal Ischemia Reperfusion Injury

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Introduction

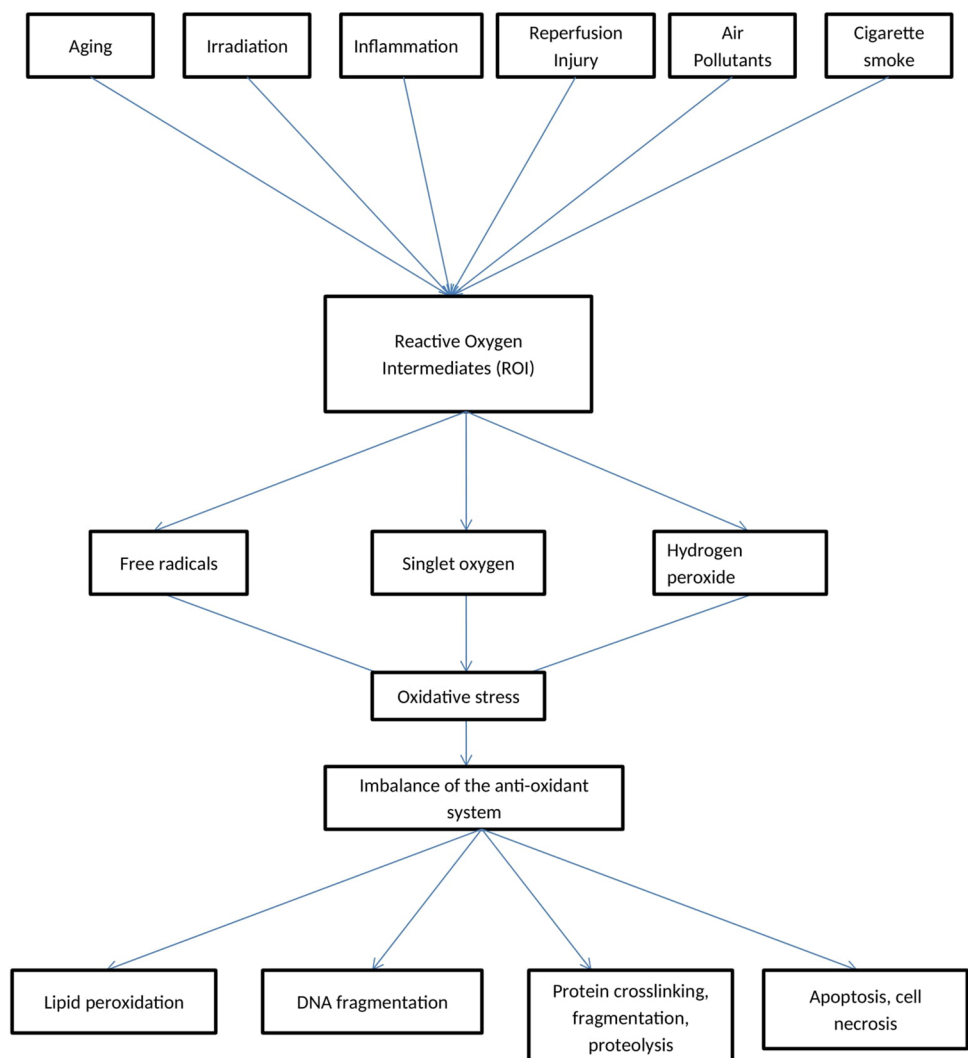
Retinal ganglion cells (RGCs) and photoreceptors in retina are vulnerable to oxidative stress leading to reactive oxygen intermediates (ROI) production. Aging, irradiation, inflammation, air pollutants, cigarette smoke, etc., produce ROI. ROI includes free radicals, singlet oxygen and hydrogen peroxide. Free radicals include superoxide anion, hydroxyl free radicals, hydroperoxyl radicals and lipid peroxyl radicals. All these add to oxidative stress, which causes the imbalance of the anti-oxidant system (Vitamins A, C, E, beta carotene, superoxide dismutase, glutathione peroxidase, catalase, zinc and selenium), which leads to lipid peroxidation, DNA fragmentation, protein cross-linking, fragmentation, proteolysis and cell necrosis and apoptosis. Anti-oxidant enzymes are present in photoreceptors and retinal pigment epithelium (RPE) [1].

Reasons for retina being vulnerable to oxidative stress and thereby generate ROI stem from the fact that retina consumes much more oxygen than any other tissue, poly unsaturated fatty acid-rich photoreceptor outer segments can get oxidized and initiate the cytotoxic cycle, RPE and neuro sensory retina have photosensitizers (melanin, rhodopsin, lipofuscin and cytochrome C oxidase and blood-borne sensitizers like protoporphyrin IX), oxidative stress induced by phagocytosis by the RPE and lastly, retina being subjected to cumulative radiation [1].

Pathway for cellular damage following oxidative stress is depicted in Fig. 1.

Lot of natural products like carotenoids (lutein and zeaxanthin [2]), catechin [3], saffron [4] and ginkgo biloba [5] products have shown greater potential in normalizing diabetes-induced histological, biochemical and functional changes in diabetic rats and neuroprotective effect in retinal degenerative diseases in animal models. Curcumin is a spice that has established its effects in rheumatological

Fig. 1 Pathway for cellular damage following oxidative stress



disorders, rhinitis, gastrointestinal disorders [6], cardiovascular disorders [7], stroke, Parkinson's disease, Alzheimer's disease [8] and certain cancers (brain, lung, breast and colon cancer) [9]. Lately, curcumin has captivated the attention of researchers in retinal disorders owing to its already established therapeutic effects in other systemic diseases.

This review article showcases the biochemical properties, pharmacological properties of curcumin and their possible beneficial role in treating retinal disorders.

Methods

PubMed and MEDLINE searches were pertaining to curcumin, properties of curcumin, curcumin in retinal diseases, curcumin in diabetic retinopathy, curcumin in age-related macular degeneration, curcumin in retinal and choroidal diseases, curcumin in retinitis pigmentosa, curcumin in retinal ischemia reperfusion injury, curcumin in proliferative vitreoretinopathy and curcumin in current COVID era.

Structure and chemical properties of curcumin

Curcumin is a curcuminoid obtained from turmeric (*Curcuma longa*) that belongs to the Zingiberaceae family. They belong to the group of phytochemicals that are biologically active molecules obtained from plants with positive effects on health. Curcumin is a bis- α,β -unsaturated β -diketone with the chemical name 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione and commonly called diferuloylmethane, E100 (European code of food additives) or Natural Yellow 3. Its chemical formula is $C_{21}H_{20}O_6$ and molecular weight is 368.38 gm/mol. It has two aromatic ring systems containing *o*-methoxy phenolic groups that are linked with a seven-carbon linker consisting of α,β -unsaturated β -diketone moiety. It also exists in two tautomeric forms, keto-enol and diketo tautomers. It is present in keto-enol form in polar organic solvents, which is the predominant form of tautomer. Curcumin is hydrophobic, insoluble in water but soluble in methanol, ethanol, chloroform, dimethyl sulfoxide, ethyl acetate and acetonitrile [10–15].

The other curcuminoids include demethoxycurcumin and bis-demethoxycurcumin that have properties similar to curcumin. The most edible part of the plant is its root (rhizome), which is dried and crushed and used as a spice powder, and this powder contains curcumin [10–15].

The anti-inflammatory property of curcumin is by inhibition of TNF-dependent $NF_{\kappa}B$ (tumour necrosis factor-dependent transcriptional nuclear factor kappa B) and pathways that produce reactive oxygen intermediates. Curcumin

downregulates COX-2 (cyclooxygenase-2) that are predominantly seen at the sites of inflammation that mediate pain and inflammatory process. Curcumin inhibits pro-inflammatory enzyme 5-LOX (5-lipoxygenase) that are involved in the biosynthesis of leukotrienes and lipid mediators of inflammation. It also downregulates inflammatory cytokines like TNF, IL-1 (interleukin-1), IL-6, IL-8, iNOS (inducible nitric oxide synthase) and interferon- γ . Curcumin at a dose of 360 mg/dose for 3–4 months in humans reduced clinical relapse in those with quiescent inflammatory bowel disease and decreased the use of concomitant medications [10–16].

The anti-oxidative action of curcumin is mediated through inhibition of stress-induced elevated levels of 8-hydroxydeoxyguanosine and 8-nitroguanine, regulating the activity of mitochondrial respiratory complexes and upregulation of Nrf2 (nuclear factor erythroid-derived 2-related factor 2) that induces haemoxygenase-1 (HO-1). The anti-oxidant activity of curcumin is predominantly due to the hydroxyl group [17–19]. Rats that were pre-treated with daily dose of intragastric curcumin (200 mg/kg for 7 days) prior to induced ischemia and reperfusion showed attenuation of mitochondrial lipid peroxidation and alterations in oxygen consumption along with prevention of decrease in GSH, SOD and GR (glutathione reductase) activity [17]. Curcumin (5, 10, 20 and 30 μ M) stimulates the expression of Nrf2 in a concentration- and time-dependent manner, which in turn increases HO-1 expression and HO-1 activity, which is a redox-sensitive inducible protein that protects from various forms of stress in cultured renal epithelial cells from rats. It stimulates ARE (antioxidant responsive elements) binding activity in NRK cells from rat kidney [19]. Sreejayan et al. showed that curcumin at a dose of 25 μ M reduced nitrite production from incubated solution of sodium nitroprusside in phosphate-buffered saline. The scavenging of nitric oxide (NO) by curcumin was concentration-dependent (50% at 20.4 and 100% at 50 μ M). Curcumin was shown not to interact with nitrite detection assay or directly interact with nitrite. All forms of curcumin—demethoxy curcumin, bisdemethoxy curcumin and diacetyl curcumin—had NO scavenging property irrespective of the methoxy or the phenolic group [20].

Histone acetyltransferases (HAT) and p300/CBP (cyclic adenosine monophosphate response element binding protein) have been linked to degenerative diseases, diabetes and certain cancers. Curcumin (up to 30 μ M for 8 h) reduces the levels of p300/CBP in a dose-dependent manner in vivo. At concentrations 10–100 μ M, curcumin inhibits histone acetylation by causing proteasome-dependent degradation of p300 and CBP in vitro [21].

The anti-tumour activity of curcumin is mediated via anti-inflammatory, apoptosis-inducing, anti-oxidative and anti-angiogenic activities. In colon cancers, the anti-tumour activity of curcumin was mediated via inhibition

of COX-2. P53 (apoptosis-inducing in stressful situations) has been shown to have a varied response to curcumin administration; overexpression in human hepatoblastoma, human breast cancer cells and human basal cell carcinoma and downregulation in colorectal carcinoma reveal that it may be tissue-specific [10]. Its anti-angiogenic effect is by inhibition of angiogenic factors like fibroblast growth factor (FGF), ligands of VEGF and angiopoietin 1 and 2 and regulation of cell adhesion molecules like endothelial adhesion molecule-1 (ELAM-1), intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and cell surface proteins that are involved in tumour metastasis [22].

Limitations of curcumin

Curcumin has been described as PAINS (Pan-assay interference compounds) and IMPS (invalid metabolic panaceas) for producing disproportionate amount of hits and mostly false positives. These questions were raised based on the suspicion regarding its properties [23, 24]. Curcumin had low solubility in aqueous medium and disintegrated into different compounds in physiological conditions raising questions about the actual bioactive form responsible for its actions. There were products in the name of turmeric, turmeric extract, curcuminoid-enriched turmeric extract, curcumin-enriched materials and curcumin itself. Curcuminoid-enriched turmeric extract showed key materials like purcumin (purified curcumin), purcuminoids (purified demethoxycurcumin, bisdemethoxycurcumin), lipophilic metabolites and hydrophilic metabolites. There were concerns regarding the purity of the compound that were used in clinical trials. The need for high levels of this compound (> 3.6 gm/day in humans) to achieve therapeutic benefits was another concern [13].

Modifications of the molecule to overcome the limitations

1. Encapsulation

Curcumin carriers like nanoparticles [25] and liposomes [26] were able to make bioavailability, solubility and stability better in an aqueous medium. Another delivery form of curcumin was the amphiphilic polymer (Soluplus), which had both hydrophilic and lipophilic component [25, 27]. A bio-degradable form of curcumin-loaded scleral plug showed promising results in posterior segment diseases in rabbit eyes both in vitro and in vivo [28]. Curcumin–phospholipid lecithin formulation in the name of Meriva has shown improvement

in visual acuity and macular oedema in DR patients when administered twice daily [29].

Granata et al. used micellar nano-aggregate calix[4]arene as a nano-carrier for ocular use and reported that the solubility of curcumin increased by 9000-fold, stability by 7.5 times and efficacy better than curcumin in reducing ocular inflammation [30]. Davis et al. used a nano-carrier containing TPGS (d- α -tocopheryl polyethylene glycol 1000 succinate) and Pluronic acid F127 for topical in eye diseases and reported that the solubility of curcumin increased by a factor of 4,00,000 and greater neuroprotective effect against glutamate and preservation of RGC in murine models [31]. Another carrier for curcumin was a thermosensitive chitosan gelatin-based hydrogel formulation in combination with latanoprost increased bioavailability for glaucoma [32]. Kim et al. used albumin-based nano-formulation to increase the solubility [33]. Another formulation in the form of tetrahydrocurcumin (THC) and cyclodextrin form showed excellent bioavailability and greater anti-oxidant activity in rabbit corneas and retinas [34].

2. Curcumin analogues

The stability and bioavailability of curcumin can be enhanced by using its pro-drug dephosphorylated curcumin (Cur-2p) and curcumin diethyl disuccinate (Cur-DD). Cur-2p showed greater stability and lower aggregation in aqueous media. Cur-DD had the same effect as curcumin in inhibiting apoptosis but with greater safety and protection [35, 36]. Other analogues like nitric oxide-releasing curcumin (VP10/12) and caffeic acid phenethyl ester (CAPE; VP10/39) decreased reactive oxygen species in a dose-dependent manner in ARPE-19 cells (Retinal Pigment Epithelial immortalized cell line from Amy Aotaki-keen eyes) [37]. Bioavailability enhancer like curcumin–piperine considerably increased the curcumin blood levels [38].

Curcumin in retinal diseases

1. Diabetic retinopathy (DR)

Retina, because of its high content of polyunsaturated fatty acids (PUFA), high oxygen and glucose uptake is, vulnerable to oxidative stress. Inflammation is another underlying factor in the pathogenesis of DR. Oxidative stress leads to formation of ROS, which is hypothesized to cause the development of neuropathy, nephropathy, myocardial infarction and retinopathy. Autooxidation of glucose, shift in redox balance, decrease in the concentration of reduced glutathione (GSH–ROS scavenger), vitamin C, Beta carotene and vitamin E and impairment of antioxidant enzymes like superoxide dismutase (SOD), glutathione reductase,

glutathione peroxidase and catalase are considered as the possible sources of oxidative stress in diabetes. Retina of diabetic rats shows elevated superoxide and hydrogen peroxide (H₂O₂) levels along with lipid peroxidation and oxidative damage to DNA because of ROS. The other pathways that lead to DR are polyol pathway that depletes nicotinamide adenine dinucleotide phosphate (NADPH) essential for regeneration of GSH, advanced glycosylation end product (AGE) and its receptor RAGE that get deposited in the retinal capillary cells leading to more ROS and activation of NF_κB and caspase-3-induced apoptosis and damage to cellular constituents, protein kinase C (PKC) pathway, which gets activated by increased ROS and diacylglycerol as a result of hyperglycaemia that increase vessel permeability and blood flow, stimulate neovascularization, endothelial proliferation and apoptosis by regulating the action of vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β). ROS also activates hexosamine pathway by inhibiting glycerol-

dehyde-3-phosphate dehydrogenase (GAPDH), which further activates AGE pathway and the damage thereafter. ROS causes dysfunction of mitochondria, which leads to superoxide production and free radical damage and mutations in mitochondrial DNA that leads to mitochondrial DNA damage in retina in diabetes. Also, ROS-induced damage to mitochondria suppresses antioxidant-mediated effective scavenging of ROS. Exposure of pericytes and endothelial cells shows an increase in caspase-3 activity, oxidative stress and transcription factors that leads to capillary cell death. Photoreceptors, Muller cells, ganglion cells and astrocytes are affected and are involved in the pathogenesis of DR [39].

Figure 2 shows various pathways leading to pathogenesis in DR.

Chiu et al. reported that chronically elevated blood glucose levels lead to oxidative stress and activation of poly (ADP-ribose) polymerase (PARP), a nuclear enzyme activated by DNA strand, which in turn upregulates the levels of endothelin-1 in target organs like

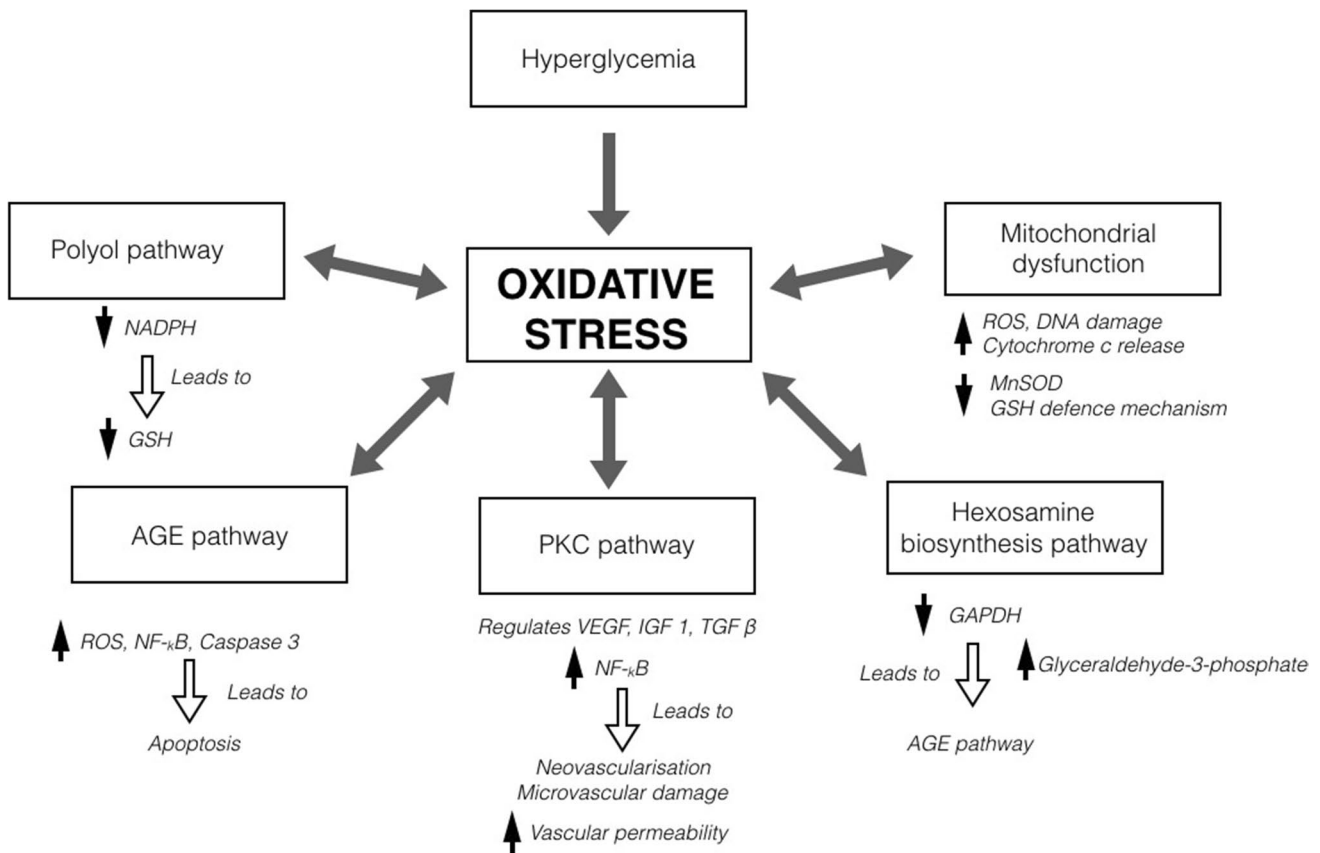


Fig. 2 Various pathways leading to pathogenesis in DR (NADPH—nicotinamide adenine dinucleotide phosphate, GSH—Glutathione, AGE—advanced glycosylation products, ROS—reactive oxygen species, NF_κB—nuclear factor kappa-light chain enhancer of activated

B cells, PKC—protein kinase C, VEGF—vascular endothelial growth factor, IGF-1—insulin-like growth factor-1, TGF-β—transforming growth factor-β, MnSOD—manganese superoxide dismutase, GAPDH—glyceraldehyde-3-phosphate dehydrogenase

retina, kidney and heart, and increased extracellular matrix protein production like fibronectin and diabetic complications. This was averted in streptozotocin-induced rats by using PARP inhibitor, which not only reduced oxidative stress and its damage but also prevented PARP-induced activation of endothelin-1 and fibronectin [40].

Table 1 gives the effect of curcumin in various *in vitro* and *in vivo* studies at various stages of DR.

ARPE-19 cells—spontaneously arising human RPE cell line derived from Ami-Aotaki keen from normal eyes—have structural and functional properties characteristic of RPE cells *in vivo* and are used to study retinal cell biology, pathological conditions and pharmacology *in vitro*.

HREC—Human retinal endothelial cells are isolated from human healthy retina, negative for HIV, HCV, mycobacteria and fungi and can be used only for research *in vitro* and not for animal or human use or for diagnostic procedures *in vitro*.

Thus, curcumin shows its effects in a dose-dependent manner through various mechanisms at various levels both *in vitro* and *in vivo*.

2. Age-related macular degeneration (AMD)

Mandal et al. evaluated curcumin for the management of light-induced retinal degeneration (LIRD) in rats that were reared using 5 lx dim light. These rats were fed with purified and crystalline curcumin 0.2% (2000 ppm) for 2 weeks. Rats were exposed to 1000 lx light (white cool light) for 3 h only in the left when right eye served as control. ERG was performed 5–7 days later, which showed preservation of scotopic a wave, b wave and photopic b wave amplitudes which was reduced (40%) in controls. Superior and inferior outer nuclear layer thickness (ONL) was grossly reduced (37% vs 27%) in uncovered eyes and covered eyes in controls, while curcumin-treated uncovered eyes showed 21% and 19%, respectively. Curcumin reduced the expression of pro-inflammatory, proapoptotic and oxidative stress-related genes in the retina. Curcumin reduced the levels of nitrotyrosine, a strong oxidant. Curcumin causes inhibition of NF- κ B whose activation induces the apoptotic degenerative process and downregulation of cellular inflammatory genes. Pre-treatment with curcumin on retina-derived cell lines (661 W and ARPE-19) showed that curcumin protected these cells from hydrogen peroxide (H₂O₂)-induced cell death by upregulation of cellular protective enzymes like thioredoxin and HO-1 and decreased expression of early growth response protein 1 (EGR-1) and intercellular adhesion molecule-1 (ICAM-1) [49].

Chang et al. used patient-derived RPEs from induced pluripotent-induced cells with AMD-associated background and found them to have reduced anti-oxidant ability when compared to normal RPE cells. Pre-treatment with curcumin (0.1–200 μ M) for 24 h was given, and cell viability was assessed using methyl thiazyl tetrazolium (MTT) assay. This showed that concentrations above 10 μ M increased the proliferation of cells and 150 and 200 μ M reduced cell viability. Curcumin protected against H₂O₂-induced cell death in a concentration of 10 μ M when pre-treatment time was less than 8–12 h. Curcumin reduced and maintained intracellular ROS levels in AMD-RPE cells at varied concentrations (0.1, 1, 10 μ M) for 12 h in H₂O₂-exposed cells. Treatment with curcumin showed increase of anti-oxidant genes HO-1, SOD2 (superoxide dismutase 2) and GPX1 (glutathione peroxidase 1) and reduces the expression of VEGF, PDGF (platelet-derived growth factor) and IGFBP 2 (insulin-like growth factor binding protein 2) using RTPCR in RPE-AMD cells. Pre-treatment with curcumin inhibited JNK pathway that involves a series of inflammatory pathways leading to cell death in RPE-AMD cells. Thus, curcumin may potentially be an ideal drug in restoring the function in AMD patient-derived RPE cells [50].

Park et al. studied the protective effects of curcumin in A2E-accumulated ARPE-19 cells that were exposed to blue light to induce cytotoxicity. A2E and iso-A2E are main pigments of lipofuscin that accumulate in RPE and cause RPE cell death in AMD. Exposure to blue light on A2E-accumulated RPE causes upregulation of transcription factors such as P53, c-Abl, which in turn causes antiapoptotic effect by upregulating JNK (c-Jun N-terminal kinases). Curcumin and curcuminoids extract contained 72.53% of curcumin, 17.56% of dimethoxy curcumin and 9.45% of bisdemethoxy curcumin. Protective effects of curcumin and curcuminoids were observed in a dose-dependent manner with curcumin being 10.46%, 24.89% for 10 and 15 μ M concentrations, demethoxycurcumin being 11.92%, 28.80% and 34.10% for 10, 15 and 20 μ M concentration and bisdemethoxycurcumin being 12.53% and 32.56% for 15 and 20 μ M concentration. Protective effect was seen at 15 μ M in all three forms, and at doses more than 20 μ M, the protective effect was lost and cell viability decreased showing the toxic nature of curcumin at higher doses. All three of them significantly lowered the mRNA expression of c-Abl and p53 and more with dimethoxy curcumin [51].

Bhattacharjee et al. described similar pathogenesis in AMD and certain neurological disorders which demonstrated that accumulation of β amyloid peptide 42 (A β 42) and the inability to clear these self-aggregating

Table 1 The effect of curcumin in various in vitro and in vivo studies at various stages of DR

Study	Type of research	Dose of curcumin	Outcome
Kowluru et al. [41] (2007)	Streptozotocin-induced diabetic rats	0.5 gm/kg for 6 weeks	-Prevents increase of OHdG (oxidatively modified DNA) -Prevents increase of nitrotyrosine levels -Partly restores GSH -Inhibits increase in IL-1 β , VEGF, NF κ B -HbA1C significantly lower than in the diabetic group -Decreases retinal vessel diameter and tortuosity than in the diabetic group -Restoration of antioxidant enzymes SOD and catalase -Decreases VEGF and TNF- α -Prevents thickening of basement membrane with clearly visible capillary lumen and no structural degeneration of pericytes and their cytoplasm
Gupta et al. [42] (2011)	Streptozotocin-induced diabetic rats	1 gm/kg body weight of rat for 16 weeks	-Repair and regeneration of shrinkage, constriction, microaneurysm and blind ending in choroidal vasculature -Reduces ERCC1 and ERCC4 (excision repair cross complementing 1 and 4) that in turn leads to decreased fibronectin production via p300-dependent pathway -Inhibits stromal cell-derived factor -1 α (SDF-1 α) induced HREC migration by blocking calcium influx and reduction of phosphor-phosphatidylinositol-3-kinase/ protein kinase B (P13-K/AKT) signals and reduced expression of CXCR4 (chemokine receptor)
Khimraktong et al. [43] (2014)	Streptozotocin-induced diabetic rats	200 mg/kg/body weight for 8 weeks	Inhibits P13-K/AKT signaling pathway, reduces NF κ B transcription and TNF- α expression
Wang et al. [44] (2012)	Human umbilical vein endothelial cells Streptozotocin-induced diabetic rats	20 μ mol/L	Significantly decreased ROS in ARPE-19 cells and TNF- α release in retinal pigment epithelial cells and retinal endothelial cells Among various formulations, the hydrophilic carrier produced satisfactory therapeutic levels
Sameer mahmoos et al. [45] (2008)	Primary HREC (human retinal endothelial cell) culture	Pre-treated with curcumin (10 and 30 μ M)	Reduces basal cell proliferation of HREC cells, increases the number of apoptotic bodies, increases the expression of caspase-, reduces VEGF levels and PKC signalling pathway
Platania et al. [46] (2018)	In silico study In vitro study – ARPE-19 cells exposed to oxidative stress and HRPC cells cultured with high glucose In vivo study—White rabbits (ARPE-19-Human retinal pigment epithelial immortalized cell line derived from Amy Aotaki Keen eyes and HRPC-Human retinal pericytes)	1,10,20,100 μ M in ARPE-19 cells and 10 μ M in HRPC cells (In Vitro) 5 mg/kg (In Vivo)	Reduces high glucose-induced reduction of cell viability, reduces DNA damage caused by high glucose, upregulates nrf2 and HO-1 through ERK (extracellular-signal-regulated kinase) pathway, reduces caspase-3-mediated apoptosis
Premanand et al. [47] (2006)	HREC cells (Human retinal endothelial cells)	1,3,10 and 30 μ M	
Bucolo et al. [48] (2019)	ARPE-19 cells exposed to high glucose	5,10,15,20 μ M	

peptides in part form the basis of drusen and AMD pathogenesis. TREM-2 (triggering receptor expressed on myeloid cells/microglial cells-2) is responsible for clearing A β 42 peptides in AMD retina and oxidatively stressed microglial cells in central nervous system. This was mediated via upregulation of NF κ B-sensitive miRNA34a (micro-RNA34a) that downregulated TREM-2 which compromised the phagocytic process. Human post-mortem retinal tissues and cultured C8B4 microglial cells (one week old) in which ROS was induced using H₂O₂. These were further treated with phenyl butyl nitron (PBN), resveratrol analogue, caffeic acid ester and curcumin, before adding NF κ B containing miRNA34a, and observed that all of them lowered ROS-induced IL-1 β and TNF- α mediated induction of miRNA34a and restored TREM-2. This formed the basis of anti-NF κ B and anti- miRNA34a therapeutic strategy for upregulating TREM-2 [52].

Kakouri et al. used 200 mg of resveratrol, 240 mg for quercetin and 2000 mg of curcumin per day for 12 months in patients with advanced (9 patients—hyperfluorescent area of macular atrophy greater than 0.15 mm² and hyperreflectivity in the choroidal region by OCT) and nascent (3 patients—area of macular atrophy not greater than 0.015 mm²) geographic atrophy (GA). Fundus autofluorescence and Spectralis OCT were performed at 3 monthly intervals, and growth rate was measured in mm²/year and square-root-transformed mm/year. For advanced GA, the annual growth rate was 0.35 ± 0.66 mm²/year (square-root-transformed 0.10 ± 0.11 mm/year) and that of nascent GA was 0.01 ± 0.02 mm²/year (square-root-transformed 0.02 ± 0.03 mm/year) which were significantly less when compared to the results published by Yehoshua et al., which was 1.20 ± 0.9 mm²/year (square-root-transformed 0.18 mm/year) with curcumin ($P=0.003$) [53].

Barry et al. used curcumin (diaryl heptanoid -1330 mg twice daily for 6 months) as a naturally fluorescent probe for in vivo visualization of β -amyloid (present in macular drusen in AMD patients) and determine and quantitate the time course of curcumin fluorescent labelling of drusen. Using an interactive cursor outline and spot analysis (to determine fluorescence), individual drusen was identified, segmented, thresholded and analysed. Patients demonstrated increased curcumin fluorescence at 2, 4 and 6 months at the fovea, thereby demonstrating drusen fluorescence over time. Absence of fluorescence indicated disappearance of β -amyloid in drusen. Thus, progression of drusen and progression to late forms of AMD might be monitored using curcumin-labelled β -amyloid [54].

Bielskus et al. used oral curcumin (1330 mg twice daily for 6 months) to evaluate its effect on drusen size in dry AMD and took retinal images at 0, 2, 4 and 6 months after dividing into 2 groups (14/20 in group 1 and 6/20 in group 2). Nineteen belonged to intermediate and 1 was advanced AMD. Change in total drusen volume, total drusen volume threshold of 0.03 mm³ for increased risk of developing late AMD and change of staging. Drusen volume decreased in 11 subjects (0.110 ± 0.106 — 0.055 ± 0.060 , $p=0.004$), remained stable in 3 (0.265 ± 0.127 — 0.260 ± 0.168 , $p=0.18$) and increased in 4 (0.112 ± 0.219 — 0.154 ± 0.206 , $p=0.04$). Mean foveal volume significantly decreased at 6 months (-14.0%, $p<0.0001$). Staging decreased from intermediate to early AMD in 1; volume decreased below the threshold risk volume of 0.03 mm³ and increased above 0.03 mm³ in 2. The same researchers used oral curcumin 2660 mg/day for 1 year in 18 patients with pre-advanced AMD (drusen ≥ 63 μ m without CNV or GA). The total mean drusen volume reduced from 0.0204 to 0.0184 mm³ ($p=0.009$), foveal drusen volume reduced from 0.0092 to 0.0079 mm³ ($p=0.030$), parafoveal volume decreased from 0.0086 to 0.0078 mm³ ($p=0.10$) and perifoveal volume increased (30.9%, $p=0.08$) after 1 year with responders and non-responders being 56% and 19%, respectively, and no cases of CNV or GA after 1 year [55, 56].

3. Retinitis pigmentosa (RP)

In the autosomal dominant form, the mutation in the P23H gene is associated with the misfolding of the rhodopsin gene which retains this gene within the endoplasmic reticulum and causes subsequent formation of insoluble aggregates which consequentially causes photoreceptor cell death in RP [57]. Vasireddy et al. used COS-7 cells expressing wild type or mutant (P23HR) rhodopsin with V5 tag for analysing the presence of protein aggregates using immunocytochemistry and fluorescent microscopy. Co-expression of wild type and P23H-R showed that mutant rhodopsin interacts with wild type to form cytoplasmic inclusions. Treatment with curcumin (5 μ M) showed reduction of formation of mutant protein aggregates. The bioavailability of curcumin in brain and ocular tissues was assessed using 100 mg/kg body weight of Sprague–Dawley rats, which showed that oral curcumin crosses blood–brain and blood–retina barriers after 2 h of oral administration, and the highest amount of curcumin was found in sclera, RPE and optic nerve (0.076–0.079 ng/mg tissue weight) and the lowest was found in lens and vitreous (0.003–0.004 ng/mg tissue weight). Transgenic rats that were treated with curcumin from P30–P60 showed preservation of 6–7 rows

of photoreceptor nuclei, preservation of photoreceptor outer segments and increase in thickness of outer nuclear layer and inner nuclear layer when compared to untreated rats which showed shorter photoreceptor outer and inner segments, thin outer nuclear layer with 2–3 rows of nuclei. Curcumin-treated transgenic rats showed increase in expression of rod-specific photoreceptor markers like rhodopsin and rod outer segment membrane protein (ROM-1) and cone-specific photoreceptor markers like S-Opsin Short wavelength and M-Opsin (medium wavelength) when compared to untreated rats. Electroretinography of transgenic rats treated with curcumin from P30–P70 showed the mean maximum scotopic a-wave amplitude in treated and untreated rats (60.09 μ V vs 28.96 μ V), mean maximum scotopic b-wave amplitude in treated and untreated rats (264.8 μ V vs 96.39 μ V), mean maximum photopic b-wave amplitude in treated and untreated rats (61.3 μ V vs 32.95 μ V), while the implicit time was unchanged in both the groups. Cryo sections of curcumin-treated P23H-R transgenic rats showed that curcumin can translocate rhodopsin to outer segment region when compared to untreated rats where it was located adjacent to few rows of nuclei in the outer nuclear layer. Curcumin-treated mutant rhodopsin-expressed cells showed decrease in expression endoplasmic reticulum stress proteins like CHOP and Grp78/Bip. Treatment of curcumin in retina of P23H-R transgenic rats showed that both the endoplasmic reticulum stress genes showed reduced expression as the concentration increased to P30 [58].

Emoto et al. showed that 100 mg/kg and 200 mg/kg of curcumin, when administered to N-methyl N-nitrosourea (MNU)-induced photoreceptor cell apoptosis in rats, showed betterment in the loss of outer nuclear layer and photoreceptor cell layer in central retina in a dose-dependent manner. Curcumin at a dose of 200 mg/kg also improved photoreceptor cell survival when compared to 100 mg/kg and untreated group. The same dosage prevented retinal damage from central to peripheral retina 7 days after exposure to MNU in rats. A marker of retinal oxidative DNA damage 8-hydroxydeoxyguanosine (8-OHdG) measured by ELISA was significantly reduced in those treated with 200 mg/kg of curcumin in MNU-exposed rats at 12 h. 200 mg/kg of curcumin reduced the apoptotic cell ratio in the central retina at 12 h at which point the oxidative stress peaked [59].

Scott et al. studied the neuroprotective effect of curcumin by administering 100 mg/kg body weight/day to embryonic transgenic mini swine and showed that curcumin prevented central-to-peripheral retinal pattern of thinning of outer nuclear layer and photo-

receptor layer, abnormal changes to rod photoreceptor morphology and mislocalization of rhodopsin in rod photoreceptors when compared to untreated embryonic transgenic mini swine that showed significant thinning of outer retina, abnormal rod photoreceptor morphology and mislocalization of rhodopsin to outer nuclear layer [60].

4. Proliferative vitreoretinopathy (PVR)

The pathogenesis of PVR includes cell migration phase, wherein there is migration of RPE cells through the break, and contraction phase, wherein damage to blood–retinal barrier leads to exudation of fibrin, elastin, fibronectin, growth factors and cytokines and cell proliferation phase, which is evidenced by the formation of collagen which further pulls the retina by exerting traction. Growth factors like epidermal growth factor (EGF), transforming growth factor- β (TGF- β), PDGF, hepatocyte growth factor, TNF- α and β and cytokines like IL-1, IL-6, IL-8, interferon- γ (INF- γ) have been raised in patients with PVR [61].

Sun et al. evaluated the role of curcumin in human RPE cell proliferation obtained by in vitro culture. These cells were treated with 15 μ g/ml of curcumin and studied after 24, 48 and 72 h. Curcumin inhibited hRPE cell proliferation in a dose- and time-dependent manner showing greater effects at 15 μ g/ml than lower concentrations (5 μ g/ml or 10 μ g/ml) in the form of cell cycle arrest at G0/G1 phase, induction of apoptosis at early, mid- and late phases, increasing expression of P21 and P53 proteins but decreasing the levels of proliferating cell nuclear antigen (PCNA) protein levels [62]. Zhu et al. evaluated the role of various doses of curcumin (10 μ M, 20 μ M, 40 μ M, 60 μ M, 100 μ M) in aging ARPE19 cells (pulsed H₂O₂ exposure aging model) in vitro. Aging cells had lower cell viability, higher apoptosis rates and more severe oxidative stress when compared to normal cells. Curcumin significantly improved cell viability, reduction of early and late apoptosis, upregulation of Bcl-2 (anti-apoptotic) and downregulation of Bax and caspase-3 (apoptotic), reduction of reactive oxygen species malondialdehyde (MDA) and upregulation of superoxide dismutase (SOD) and glutathione (GSH) in a dose- and time-dependent manner [63].

Ren et al. used cultured rabbit RPE cells and detected EGF expression by immunocytochemistry and RPE cell proliferation by EGF in vitro at an optimal concentration of 9 ng/ml using 3-(4,5-dimethylthiazol-2-yl)-2,5-biphenyl tetrazolium bromide (MTT) assay in a time-dependent manner. Immunocytochemistry also revealed EGF expression in the cytoplasm, which was significantly lower in the curcumin-treated group than in the control group. EGF expression decreased

with increasing curcumin dose and increasing incubation time, and the optimal dosage of curcumin causing decrease in EGF was 15 µg/ml. The EGF mRNA content by RT-PCR decreased by this dosage of curcumin over time. EGF protein expression in RPE cells by western blot analysis in the curcumin group decreased with time. Vitreous clouding seen by slit-lamp biomicroscopy and indirect ophthalmoscopy reduced in the curcumin group on day 7 and PVR membrane, which was graded using colour fundus photography, ultrasound B scan and indirect ophthalmoscopy, showed lower grading, being thin and lower incidence of retinal detachment (11% vs 61%, 16% vs 75% and 16% vs 83%) on days 14, 21 and 28 post-treatment with curcumin [64].

5. Retinal Ischemia–Reperfusion Injury (RIRI)

This happens due to ocular hypertension or as a consequence of stroke in hypertension. The retinal ganglion cells are vulnerable to ischemia due to any cause and can lead to irreversible vision loss [13]. Liu et al. showed that heat shock transcription factor 1 (HSTF1) has been shown to play a vital role in promoting survival of cells under stressful circumstances that negated RIRI-induced neuronal apoptosis and necrosis 12 h after RIRI in HSTF 1 transgenic mice. It gets upregulated in acute stages as a self-protective mechanism to prevent retinal damage [65]. Zhang et al. showed that in RIRI, there is increased expression of inflammatory mediators, interleukins IL-17 (peaked at 72 h) and IL-23 (peaked at 24 h) aggravating retinal injury in rat models. Curcumin at doses of 20 mg/kg/day and 100 mg/kg/day reduced the expression of IL-17 and IL-23 in a dose-dependent manner, thereby reducing RIRI-induced damage to retina [66]. RIRI induces increased NF-κB and signal transducer and activator of transcription 3 (STAT 3) in response to stress, which increases monocyte chemoattractant protein 1 (MCP-1) in rats. MCP-1 in turn causes retinal damage by recruiting inflammatory cells to the site of injury. Curcumin (oral curcumin in a dose of 0.05% and 0.25%) before RIRI reduces vascular damage by nearly 40% which extends its action even 2 days after RIRI. Oral administration of curcumin (0.01%, 0.05% and 0.25%—all 3 doses) inhibited RIRI-induced cell loss in ganglion cells 2 days after RIRI. Curcumin downregulates NF-κB and STAT 3 and MCP-1 consequentially and protects both retinal neurons and microvasculature as per Wang et al. [67].

Wang et al. evaluated the role of curcumin in retinal injury in stroke spontaneously hypertensive rats (SHR). This was obtained by electrocoagulation of bilateral vertebral artery along with transient common carotid artery ligation. In SHR rats, stroke caused

apoptosis of retinal neurons and capillary cells due to the increased expression of c-Jun N-terminal kinase (JNK) and JNK-mediated activation of BAX (Bcl-2-associated X protein) and altering the stability of P53 protein. Curcumin when administered at 100 mg/kg intraperitoneally 1 h before RIRI showed that it can prevent apoptosis in retinal capillary cells and subsequently hypertensive retinopathy after RIRI by inhibiting phosphorylated JNK-mediated actions [68].

The literature evidence, however, is not enough to support the action of curcumin and hence applied with caution.

6. Retinal and choroidal tumours

Retinoblastoma (RB) is due to mutation of RB1 gene which is a tumour-suppressor gene. Yu et al. showed that curcumin reduced viability of retinoblastoma (RB Y79) cells at 40 µM (range 0–80 µM for 24 h) and caused G1 phase arrest (0–80 µM for 24 h). It induced apoptosis of RBY79 cells through activation of caspase-9 and caspase-3 and mitochondrial membrane potential collapse in RBY79 cells (dose of 0–80 µM for 24 h). It induces the phosphorylation of JNK (c-Jun N-terminal kinase) and P38 MAPK (mitogen-activated protein kinase) which further enhanced the apoptosis of RBY79 cells (dose of 80 µM for 24 h) [69]. Li et al. showed that curcumin inhibited proliferation, migration, invasion and apoptosis of Rb cell lines RBY79 and SO-RB 50 through upregulation of mir-99a (micro-RNA-99a), which in turn inhibits the JAK/STAT (Janus kinases and signal transducer and activation of transcription proteins) pathway, which are a series of events involved in tumour formation (0–50 µM in a dose-dependent manner) [70]. Mukhopadhyay et al. showed that curcumin downregulates the activity of cyclin D1-dependent kinase 4 (CDK4), which is responsible for phosphorylation of RB protein, cyclin D1 m-RNA, which is responsible for the synthesis of cyclin D1 and cyclin D1 promoter-dependent reporter gene expression, thereby substantiating its anti-proliferative effects in RB and other cancers. The dosage has been different for different cancers [71].

The above paragraph describes only cell lines and no animal models, and these various dosages for different cancers cannot give us strong evidence in favour of curcumin and hence have to be used with caution.

7. Best Vitelliform Macular Dystrophy (BVMD)

The mutation of human bestrophin-1 (BEST-1) gene is responsible for causing bilateral macular disease in both adolescents and adults. This gene encodes a protein called human bestrophin-1 that acts as a calcium-activated chloride channel that is greatly expressed in RPE. Mutation of BEST-1 gene causes reduced expression of its encoded protein that leads

to protein structure impairment and downregulation of calcium-activated chloride channel expression, which in turn caused disturbance of intracellular calcium homeostasis, loss of tight junction protein ZO-1 and decreased phagocytic ability of RPE. There was always a question regarding the mechanism of the disease and a model to solve the questions regarding the pathogenesis, and drug screening was warranted. Patient-specific human-induced pluripotent stem cell (BVMD-iPSC) was developed from BVMD patient-derived dental pulp stromal cells, which was then differentiated into BVMD-RPE cells. BVMD-RPE cells were used for in vitro candidate drug screening, and it replicated multiple pathogenetic mechanisms in BVMD. BVMD-RPE cells exhibited specific markers in the form of reduced expression of BEST-1 and ZO-1 and poor phagocytic potential when compared to unaffected sibling-derived iPSC-derived RPE cells. Curcumin-loaded nanoparticles (Cu-NP—10 μM for 72 h) increased the expression of ZO-1, BEST-1, and suppressed hydrogen peroxide-induced ROS production and increased ROS scavenging, thereby promoting phagocytosis and increased expression of anti-oxidant enzymes providing a cytoprotective effect [72].

8. Methyl alcohol intoxication of retina

Seme et al. have demonstrated that in rats intoxicated with methanol in the presence of $\text{N}_2\text{O}/\text{O}_2$, histopathological changes showed photoreceptor inner segment swelling and mitochondrial disruption and increased oxidative stress. This was hypothesized to be due to the toxic metabolite of methanol, i.e. formate. During recovery, there was partial improvement of rod-dominated responses but no improvement of UV cone-mediated responses [73]. Oral curcumin when administered for 4 weeks at a dosage of 2.5 mg/kg/day in rats caused reversal of methanol-induced vacuolations in the photoreceptor inner segments and disaggregation of cells in the inner and outer nuclear retinal layers [15, 74].

9. Central serous retinopathy (CSR)

Curcumin when given in the form of oral phosphatidylcholine formulation had good oral availability. These Norflo tablets when given twice daily for a 6-month period in acute and chronic CSR in a pilot study of 18 eyes of 12 patients showed improvement in visual acuity in 61% of eyes and decreased detachment of retinal pigment epithelium in 78% of eyes. More randomized trials are, however, required to substantiate this [75].

10. Cystoid macular oedema (CME)

Allegrì et al. studied the role of hydrophilic carrier of curcumin (Diabec) as an add-on treatment in recent onset non-infectious inflammatory CME. Curcumin was administered

twice daily for 6 months with oral prednisolone 15 mg/day \pm 15 mg methotrexate once a week and a control group without curcumin and only standard therapy. Out of 48, 25 eyes in curcumin-treated group showed reduction in central foveal thickness from 320 (\pm 96.7) μm to 283 (\pm 46.3) μm and control group showed no variations. Mean improvement in BCVA was 5.8 ETDRS letters in the curcumin group with no difference in the control group. These were preliminary results which will be assessed at 12 months [76].

Figure 3 shows the possible role of curcumin in treating retinal disorders.

Curcumin in COVID era

Liu et al. in their review have shown that pre-treatment with curcumin at various dosages of 5 mg/kg/day, 150 mg/kg for 15 days and 50 mg/kg/day have reduced inflammation, acute lung injury-induced pneumonia and subsequent fibrosis in paraquat-induced lung inflammation, Klebsiella and reo virus-induced lung damage, respectively, in animal models. This has been attributed to the downregulation of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-8, TNF- α and upregulation of anti-inflammatory cytokines like IL-10. Curcumin directly scavenges ROS through indirect enzymatic regulation of SOD2, which plays an important role in maintaining oxidant–anti-oxidant balance [77]. Studies have shown that curcumin has strong affinity for S-protein and angiotensin-converting enzyme-2 (ACE-2) receptor and its complex, thereby directly targeting viral proteins inhibiting particle production and gene expression, blocking the entry of the virus, its replication and budding. This computational study showed the binding affinity of catechin and curcumin for S-protein, ACE-2 receptor and its complex to be -10.5 and -7.9 kcal/mol, -8.9 and -7.8 kcal/mol and -9.1 and 7.6 kcal/mol, respectively [78]. Investigators studied the extenuating effect of curcumin on thrombosis by its anti-coagulant and anti-platelet activity both in vitro and in vivo. Pre-treatment with 45 mg/kg of curcumin or 200 μl of vehicle alone 1 h before in diesel exhaust particle (DEP)-induced mice prevented the increase of D-dimer and plasminogen activator inhibitor-1 (PAI-1) along with prevention of increase of CRP, TNF- α and systolic blood pressure. This was further supported by Kim et al. who demonstrated that curcumin and bisdemethoxycurcumin prolonged activated partial thromboplastin time (APTT) and prothrombin time (PT) and inhibited thrombin and activated factor x both in vitro and in vivo at or concentration greater than 5 μM [79–81]. Lot of evidence has already emerged regarding the action of curcumin in SARS-associated corona virus (SARS CO-V) by directly interacting with viral

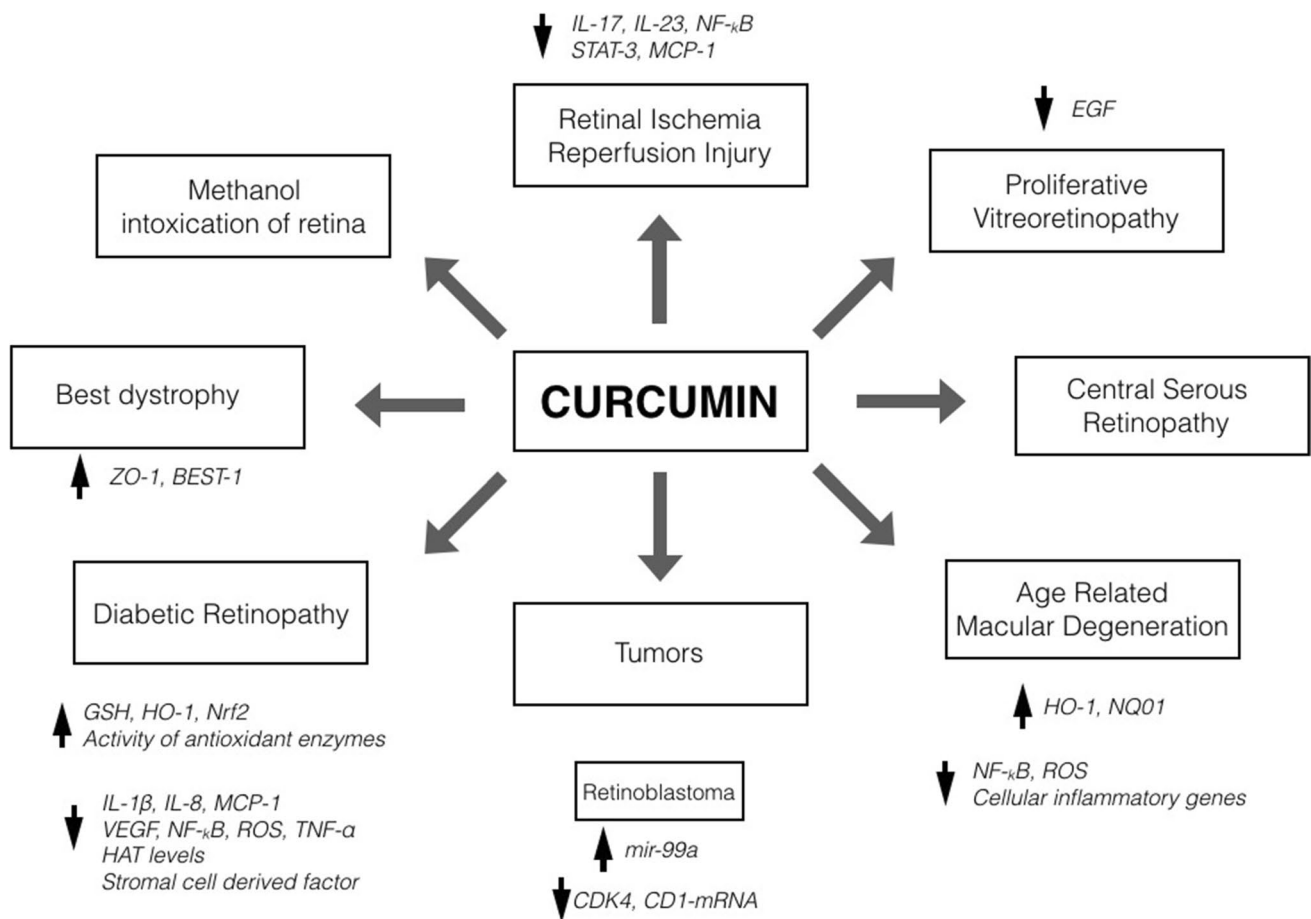


Fig. 3 Possible mechanism of curcumin in various retinal diseases. (IL- 8, IL-17, IL-23, IL-1 β Interleukin—8, Interleukin – 17, Interleukin – 23, Interleukin 1 β , NF κ B – Nuclear Factor Kappa B, STAT 3 – Signal Transducer and Activation of Transcription 3, MCP-1 – Monocyte Chemoattractant Protein- 1, EGF – Epidermal Growth Factor, HO-1 – Haemoxygenase -1, NQO-1- NADPH Quinone Dehydrogenase – 1, ROS – Reactive Oxygen Species, BAX – Bcl-2 associ-

ated X-Protein, Bcl-2 – B-Cell Lymphoma- 2, mir -99a – microRNA 99a, CDK4 – Cycline D1 dependent Kinase 4, CD1 mRNA – Cycline D1 mRNA, VEGF- Vascular Endothelial Growth Factor, TNF – α – Tumour Necrosis Factor – α , HAT – Histone Acetyl Transferase, GSH – Glutathione, Nrf2—Nuclear factor erythroid-2 related factor-2, ZO-1 – Zonula Occludens -1)

proteins, disrupting the viral envelope, inhibiting viral proteases and modulating NF κ B, Nrf2 and high mobility group box 1(HMGB1) pathways in vitro. SARS-CoV-2 (COVID-19) has nearly 79% resemblance to SARS CO-V and hence the postulation [82].

The above-mentioned studies show the possible mechanisms and pleiotropic effects of curcumin in animal models. We should also look for reproducibility of its effects in humans and the right dosage that can be used as a therapeutic option in humans. It should be clearly understood that curcumin can never be a replacement for the vaccine and can be tried as an adjunct therapeutic agent or as a natural medicine.

The following figure shows the possible mechanisms of curcumin in combating the COVID virus at various stages of the disease (Fig. 4).

Retinal distribution of curcumin

Platania et al. studied the retinal distribution of three commercial products of curcumin—curcumin with a polyvinyl pyrrolidone-hydrophilic carrier (CHC), with phosphatidyl complex (CPC) and with piperine (CPI) in vivo in white rabbits that were given curcumin orally. Rabbits received single dose of 5 mg/kg by oral lavage after sedation. Retinal distribution of curcumin was assessed at various time points (0, 2, 6, 12 and 24 h) after oral administration. Only the hydrophilic carrier form reached rabbit retina, the maximum serum concentration (C_{max}) of CHC was 0.036 ± 0.002 , time taken for the drug to reach its maximum concentration (T_{max}) for CHC was 6 h, and area under the curve (AUC—the definite integral of a curve that

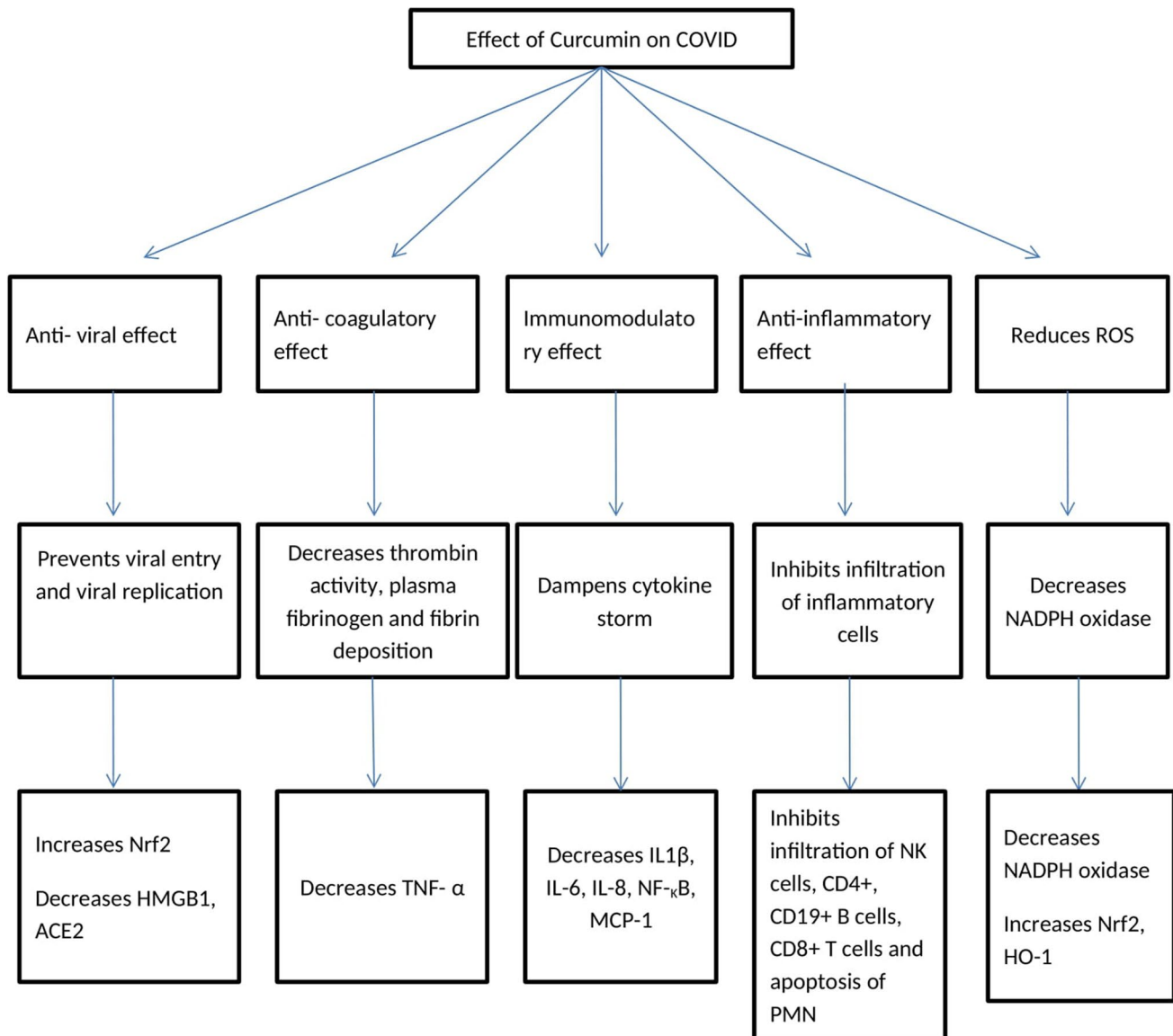


Fig. 4 Mechanism of curcumin in reducing viral replication, cytokine storm and its immunomodulatory effect and anti-coagulant effect. (NADPH oxidase – Nicotinamide Adenine Dinucleotide Phosphate

oxidase, HMGB1 – High Mobility Group Protein B1, ACE2 – Angiotensin Converting Enzyme 2, NK cells – Natural Killer cells, CD – Cluster of Differentiation, PMN- Polymorphonuclear leucocytes)

describes the variation of the drug concentration in plasma as a function of time) was 15.48 ± 0.05 ng*/min/mg. Curcumin significantly stopped ROS production ($p < 0.05$) in ARPE-19 cells that were exposed to oxidative stress (hydrogen peroxide-induced) at lower concentration of 1 μ M and reduced TNF- α in HREC cells that were exposed to high glucose at a dose of 10 μ M [46, 83].

Safety profile of curcumin in humans

Cheng et al. studied the pharmacokinetics, toxicology and biologically effective dose of curcumin in humans with high risk or premalignant lesions. An initial dose of 500 mg once a day in empty stomach in 25 patients and the

dose was increased to 1000, 2000, 4000, 8000 and 12,000 mg if there was no toxicity \geq grade 2 in at least 3 successive patients. No toxicity was seen in doses up to 8000 mg. However, 12,000 mg was not acceptable by patients because of the bulky nature of the tablet. The serum concentration peaked at 1–2 h of intake but declined gradually within 24 h with barely detectable serum concentration up to 2000 mg, and urinary excretion was undetectable. The C_{\max} of 4000, 6000 and 8000 mg was $0.51 \pm 0.11 \mu\text{M}$, $0.63 \pm 0.06 \mu\text{M}$ and $1.77 \pm 1.87 \mu\text{M}$, respectively. Curcumin showed no toxicity up to 8000 mg when taken for 3 months. Though 1 patient each with CIN and leucoplakia developed frank malignancies, there was histological improvement in some of them [84].

To study the maximum-tolerated dose and safety of curcumin, Lao conducted a study in eligible study participants (24 subjects) who were 18 years or older and who had not consumed curcumin-rich food in the last 14 days. A dose escalation of 500–12,000 mg of standardized curcumin was administered, and safety was assessed for 72 h, which showed 7 adverse events that were grade 1 (diarrhoea, rash, headache and yellow stool) according to National cancer institute, common toxicity criteria version 2.0. There was no dose-related toxicity. Only curcumin at doses of 10,000 and 12,000 mg in 2 subjects showed serum concentration. This low-serum concentration partly might be due to extensive intestinal and hepatic metabolic biotransformation [85].

Summary

Curcumin is a spice that is available easily and is affordable. It is edible and can be consumed in large quantities in food. There are only a few literature evidence that exists for few retinal diseases, and hence, the reproducibility of such observations remains a question. It is imperative to establish a proper dosage that will produce the desired effects in humans akin to animal models. It would be a challenge to investigate whether large quantities that are consumed are enough to produce the required amount of serum concentration to treat retinal diseases. The dosage may be different for different retinal diseases though. The solubility, bioavailability and stability of curcumin can be improved by using carriers and newer formulations of curcumin. Curcumin also seems to have favourable safety profile, but this small evidence may not be enough to translate into humans particularly for retinal diseases. However, it should be clearly understood that curcumin can never replace the vaccine and can only be considered as an alternative therapeutic agent, provided the results are reproducible in humans or human concentrations in cell culture experiments. Results of its actions and efficacy in retinal diseases in humans are at the experimental level with a lot of scope for future research.

More randomized controlled clinical trials with a large cohort are required to establish its efficacy and safety in humans, but there is still a long way to go before establishing its true therapeutic role in retinal diseases.

Declarations

Presentation at a conference No.

Conflict of interest Nil.

Financial Disclosure Nil.

Research involving human participants and/or animals Nil.

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