Curcumin and Wnt/β-catenin signaling in exudative age-related macular degeneration (Review)

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Abstract. Curcumin is a natural product widely used due to its pharmacological effects. Nevertheless, only a limited number of studies concerning the effects of curcumin on exudative age-related macular degeneration (AMD) is currently available. Since ophthalmic diseases, including exudative AMD, have a marked impact on public health, the prevention and therapy of ophthalmic disorders remain of increasing concern. Exudative AMD is characterized by choroidal neovascularization (CNV) invading the subretinal space, ultimately enhancing exudation and hemorrhaging. The exudative AMD subtype corresponds to 10 to 15% of cases of macular degeneration; however, the occurrence of this subtype has been reported as the major cause of vision loss and blindness, with the occurrence of CNV being responsible for 80% of the cases with vision loss. In CNV increased expression of VEGF has been observed, stimulated by the overactivation of Wnt/β-catenin signaling pathway. The stimulation of the Wnt/β-catenin signaling pathway is responsible for the activation of several cellular mechanisms, simultaneously enhancing inflammation, oxidative stress and angiogenesis in numerous diseases, including ophthalmic disorders. Some studies have previously demonstrated the possible advantage of the use of curcumin for the inhibition of Wnt/β-catenin signaling. In the present review article, the different mechanisms of curcumin are described concerning its effects on oxidative stress, inflammation and angiogenesis in exudative AMD, by interacting with Wnt/β-catenin signaling.

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Abbreviations: COX-2, cyclooxygenase 2; TNF-α, tumor necrosis factor-α; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; IL, interleukin; AMD, age-related macular degeneration; CNV, choroidal neovascularization; VEGF, vascular endothelial growth factor; SOD, superoxide dismutase; SIRT1, sirtuin-1; HIF, hypoxic inducible factor; HO-1, heme oxygenase 1

Key words: age-related macular degeneration, Wnt, VEGF, curcumin, oxidative stress, inflammation, angiogenesis

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1. Introduction

Age-related macular degeneration (AMD) is a widely reported cause of blindness in elderly adults worldwide (1). The progression of AMD is initially marked by the accumulation of debris during the early stages, while later stages are characterized by the accumulation of retinal epithelial dysregulations. AMD is classified into two distinct subtypes, known as 'non-exudative' and 'exudative' AMD.

The early stages of AMD are characterized by the presence of drusen in the retina eyeground and the dysregulation of the retinal pigment epithelium (RPE). Geographical atrophy and choroidal neovascularization occur during the late atrophic and exudative phases. Exudative AMD is characterized by choroidal neovascularization (CNV) invading the subretinal space, concurrently enhancing the appearance of exudation and hemorrhaging, and it has been reported to be caused by angiogenesis (2-4). The exudative AMD subtype corresponds 10 to 15% of AMD cases. It has been reported as the major cause of vision loss and blindness (5,6). In AMD, CNV is responsible for 80% of the cases presenting vision loss (7). The development of CNV has been shown to be associated with the involvement of the vascular endothelial growth factor (VEGF) (8). However, the implication of cellular signaling in exudative AMD have not yet been fully elucidated. However, the aging mechanism is considered one of the major exudative AMD risk markers. This mechanism can dysregulate cellular signaling, which controls homeostatic processes (9).

The use of curcumin has been revealed to possibly have major therapeutic benefits for disease treatment in clinical practice, including cancer and cardiovascular diseases (10-12). However, the number of available published studies concerning the possible therapeutic effects of curcumin in ophthalmological disorders, and particularly in exudative AMD, remains limited. Since combating avoidable visual impairment and blindness is of utmost importance for public health, the application of curcumin for the treatment of ophthalmological disorders (age-related cataracts, glaucoma, AMD, diabetic retinopathy) may bear promising results (13). The present review article focuses on the presentation of the possible effects of curcumin on exudative AMD by targeting oxidative stress, inflammation and angiogenesis through its mediation of Wingless/Int (Wnt)/β-catenin signaling.

2. Exudative AMD

Exudative AMD has been shown to be associated with choriocapillaris changes, whereas the RPE monolayer remains intact (14), ultimately leading to hypoxia stimulation in the overlying of RPE cells (15). The loss of choriocapillaris may result in the initiation of CNV. The mechanism of CNV enhances immature new blood vessels, which may invade Bruch's membrane from the choriocapillaris to extend in the subretinal or sub-RPE space (16).

Inflammatory mechanisms implicate macrophages (17) and microglia (18) in exudative AMD, along with cytokine release, as for example tumor necrosis factor-α (TNF-α) (19). In parallel with inflammation, several signaling pathways have been found to be associated with exudative AMD, including Wnt/β-catenin (20,21), transforming growth factor-β (TGF-β) (22,23) and PI3K/Akt/mTOR (24). Exudative AMD progresses through an inflammatory-induced angiogenesis process (25), with the implication of VEGF and platelet-derived growth factor (PDGF) (26,27). VEGF, generated by RPE cells, plays a major role in CNV (28) and the enhancement of VEGF may function favorably against CNV (29,30). Additionally, VEGF is a Wnt target (31,32). Inflammatory markers, including TNF-α and NF-κB, have been reported to activate the β-catenin signaling pathway, inducing its translocation into the nucleus and the subsequent transcription of the *VEGF* gene (33,34). An association between inflammation and the Wnt/β-catenin signaling pathway for the stimulation of VEGF in RPE cells has been previously reported (35).

3. Wnt/β-catenin signaling pathway

The Wnt signaling pathway receptor proteins (Fig. 1) are a family of secreted lipid-modified glycoproteins (36). Numerous pathological mechanisms can be regulated by this signaling, including the fibrotic process and angiogenic mechanism (37-39).

During ocular development, Wnt/β-catenin is mainly activated. Wnt/β-catenin signaling dysregulation enhances numerous ocular dysregulations, due to defects in cell fate differentiation (40). During lens development, Wnt/β-catenin signaling is activated in the periocular surface ectoderm and lens epithelium (41,42). For the development of the retinal epithelium, Wnt/β-catenin signaling is activated in the dorsal optic vesicle, and is also involved in the stimulation of the RPE at the optic vesicle stage. At this stage, Wnt/β-catenin signaling is localized in the peripheral RPE (43). The retinal vascular development is controlled by the regulation of the Wnt/β-catenin signaling (40). In the retinal vascular process, Wnt/β-catenin signaling is modulated by the erythroblast transformation-specific transcription factor, Erg, which plays a key role in the angiogenic process (44). Erg regulates the activation of the Wnt/β-catenin signaling pathway through the concurrent enhancement of β-catenin and Frizzled 4 (FZD4) transcription ((44). The formation of the low-density lipoprotein receptor-related protein 5 (LRP5)/LRP6 complex is required for the activation of FZD4/β-catenin signaling (45). LRP5 has been reported to play a crucial role through the formation of a complex with LRP6; however, it has a minimal effect on retinal vascularization (46,47). Disheveled forms a complex with AXIN1, in order to prevent β-catenin phosphorylation by glycogen synthase kinase-3β (GSK-3β). β-catenin accumulates into the cytoplasm, subsequently translocating to the nucleus and binding to the T-cell factor/lymphoid enhancer factor (TCF/LEF) co-transcription factors. The nuclear link enhances the activation of Wnt-response genes, including cyclin D1, c-Myc, pyruvate dehydrogenase kinase (PDK)1 and monocarboxylate transporter 1 (MCT-1) (48-52).

Following the inactivation of Wnt ligands, GSK-3β is activated and then phosphorylates cytoplasmic β-catenin. The destruction complex is formed by the tumor suppressor adenomatous polyposis coli (APC), AXIN, GSK-3β and ultimately, β-catenin. The disintegration of phosphorylated β-catenin is performed in the proteasome (53). Wnt inhibitors, including Dickkopf (DKK) family proteins and secreted Frizzled-related proteins (SFRPs), modulate the Wnt/β-catenin signaling through the prevention of its ligand-receptor actions (54) (Fig. 1).

GSK-3β, an intracellular serin-threonine kinase, is an important regulator of the Wnt/β-catenin signaling pathway (55), and controls various cell signaling routes, including cell membrane, neuronal polarity and inflammatory processes (56-58). GSK-3β concurrently decreases β-catenin cytoplasmic expression and β-catenin nuclear translocation (56). β-catenin, mTOR signaling, hypoxia-inducible factor 1-α (HIF-1α) and VEGF are downregulated, due to the increased activity of GSK-3β (59).

4. Wnt/β-catenin signaling pathway in exudative AMD

Various animal models (models of oxygen-induced retinopathy, streptozotocin rat model, rat model of CNV, rat, mouse, pig, primate, rabbit) have been utilized for the investigation of AMD (60), and previous studies have revealed that aberrantly activated Wnt/β-catenin signaling may be a pathogenic marker for AMD (33,61). Stimulated Wnt/β-catenin signaling has been observed in both human AMD macular tissues (21), and in murine laser-induced CNV models (20), which are mainly utilized to investigate the angiogenic form of AMD. The phosphorylation of LRP6 and the stimulation of β-catenin have been observed in a laser-induced CNV animal model (20) and in very-low-density lipoprotein (VLDL) receptor gene knockout ($VLDLR^{-/-}$) mice with abnormal intraretinal vessels (62,63). The downregulation

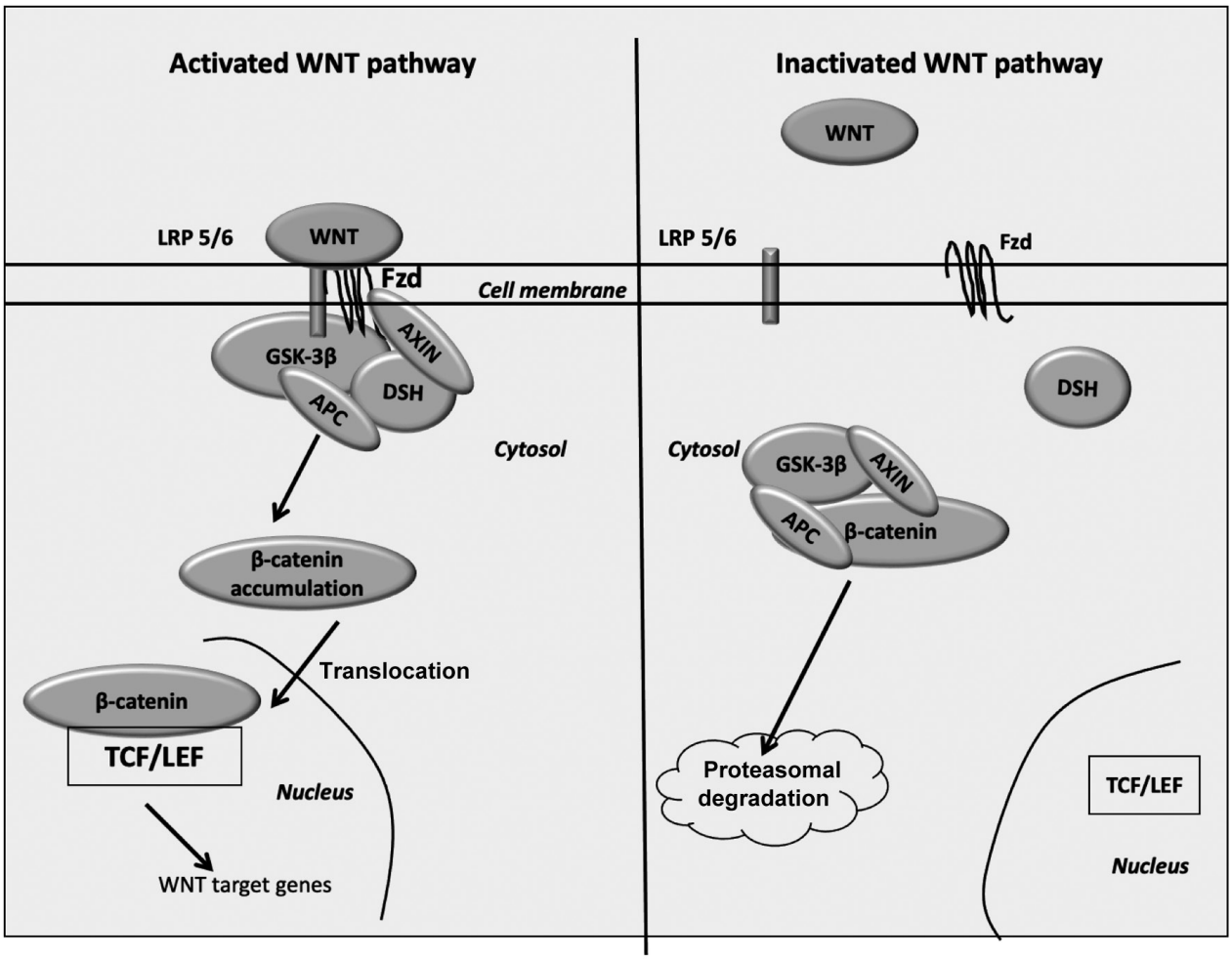

Figure 1. Activation and inactivation of Wnt/β-catenin signaling. During the activation of Wnt ligands, the stimulation of FZD4/β-catenin signaling requires the formation of the LRP5 /LRP6 complex. LRP5 plays a crucial role in the vascularization of the retina, whereas LRP6 has a less integral role in this. Dsh forms a complex with AXIN, to prevent the β-catenin phosphorylation by GSK-3β. β-catenin accumulates in the cytoplasm, to translocate to the nucleus and bind to the TCF/LEF co-transcription factors. The nuclear link enhances the activation of Wnt-response genes, including cyclin D1, c-Myc, PDK1 and MCT-1. During the inactivation of Wnt ligands, GSK-3β phosphorylates cytoplasmic β-catenin. The destruction complex is formed by APC, AXIN, GSK-3β and finally, β-catenin. In the proteasome, the destruction of phosphorylated β-catenin operates. Wnt inhibitors, including DKKs and SFRPs, modulate the Wnt/β-catenin signaling through the prevention of its ligand-receptor actions. Dsh, Disheveled; FZD, frizzled; LRP, low-density lipoprotein receptor-related protein; GSK-3β, glycogen synthase kinase-3β; TCF/LEF, T-cell factor/lymphoid enhancer factor; APC, tumor suppressor adenomatous polyposis coli; PDK1, pyruvate dehydrogenase kinase 1; MCT-1, monocarboxylate transporter 1; DKK, dickkopf; SFRPs, secreted Frizzled-related proteins.

of Wnt/β-catenin signaling with the use of an anti-LRP6 antibody or a DKK-1 agonist have been reported to impede the formation of neovascular lesions in murine CNV and VLDLR$^{-/-}$ models (20). The decrease in Wnt gene expression in mouse choroidal explants is associated with the limitation of laser-induced CNV severity (64).

The stimulation of the Wnt/β-catenin signaling has been shown to be associated with the degeneration of the focal retina and the subsequent formation of exudative lesions (21). Kallistatin, an endogenous inhibitor of the Wnt/β-catenin signaling pathway and a member of the serine proteinase inhibitor (SERPIN) family, has been reported to be decreased in patients with AMD (21). Kallistatin exerts anti-angiogenic and anti-inflammatory actions (33,65-69). Kallistatin forms a complex with LRP6, decreasing Wnt/β-catenin signaling activation (68,69). In murine models with focal retinal AMD-like lesions, the use of anti-LRP6 antibody has been found to decrease the Wnt/β-catenin signaling and arrest the initiation of lesions of the retina (21) (Table I).

Wnt/β-catenin signaling and angiogenesis in exudative AMD. Tissue factor (TF), a transmembrane cell-surface receptor for plasma coagulation factor VII, is one of the main regulators of the extrinsic coagulation signaling pathway (70). TF exerts angiogenic effects during the different stages of CNV development (71-73). The stimulation of TF has been found to be associated with exudative AMD retina (72), with its increase leading to the development of exudative AMD due to the inflammatory (72,74-76) and angiogenetic processes (76,77). TF stimulates VEGF activity and leads to the formation of vascular vessels, through the stimulation of the Wnt/β-catenin signaling (78). Mab2F1, a monoclonal antibody specific for LRP6, has been reported to directly inactivate Wnt/β-catenin signaling, in exudative AMD. In particular, the inhibition of the Wnt/β-catenin signaling in CNV by Mab2F1 leads to the reduction of the retinal vascular leakage (20,63). Moreover, the decrease in DKK-1 circulating levels has been shown to be associated with the initiation of exudative AMD (79).

Table I. The different pathways involved in the stimulation of Wnt/β-catenin signaling in exudative AMD and the possible actions of curcumin.

	Model	Target	Action	(Refs.)
Wnt/β-catenin signaling	ARPE-19 cells	Stimulation of Wnt/β-catenin signaling	Activation of VEGF, NF-κB and TNF-α	(33)
	Adult rats and laser-induced CNV mouse models	Wnt/β-catenin signaling	Mab2F1 inhibited the hypoxia-induced activation of Wnt signaling in cultured RPE cells	(20)
	Murine models of CNV and VLDLR$^{-/-}$ mice	Activation of DKK-1 expression	Diminution of Wnt signaling	(20,203)
	AMD patients	Kallistatin	Decrease Serpin expression and Wnt signaling	(21)
	Mouse model	Kallistatin	Blockage of LRP6 (compound of the β-catenin complex); decrease in inflammatory cytokines, including tumor necrosis factor α, interleukin 1β and interleukin 6	(68)
	KS-TG mice	Kallistatin	Wnt/β-catenin signaling is suppressed	(6)
	Murine ccl2/cx3cr1 deficiency	TF activation	CNV development	(71)
	Ccl2/Cx3cr1-deficient mice	TF activation	AMD retina development	(72)
	ARPE-19 cells	TF activation	Stimulation of the Wnt signaling subsequently stimulating VEGF	(78)
	ARPE-19 cells	Activation of Mab2F1	Decreased Wnt signaling and retinal vascular leakage	(63)
	AMD patients	Decreased DKK-1 expression	Increased Wnt signaling, development and severity of exudative AMD	(79)
	AMD patients	Increased TNF-α	Higher risk of choroidal neovascularization	(111,112)
	AMD patients	Inflammatory process	Stimulation of the Wnt signaling which stimulates VEGF	(25,115, 116)
	AMD patients	Stimulation of TNF-α	Stimulation of VEGF	(113-116)
	AMD patients	Stimulation of Wnt/β-catenin pathway	Stimulation of VEGF	(31,117)
	Choroid and retinal endothelial cells	Activation of HIF-1α	Stimulation of the Wnt signaling which stimulates VEGF	(118-120)
Curcumin	Human ARPE-19 cells	Modulation of p44/42 (ERK) Bax and Bcl-2	Decreased oxidative stress	(150)
	In vivo models	Diminution of IL-1, IL-6 and TNF-α, COX-2, NF-kB	Decrease inflammation	(178)
	U937 and Raji cells	Decreased VEGF	Decreased angiogenesis	(179)
	Hepatocellular carcinoma cell-implanted nude mice	Decreased VEGF and COX-2 expression	Decreased angiogenesis	(180)
	In vivo models	Decreased bFGF expression	Decreased corneal neovascularization	(182)
	Ehrlich ascites tumor (EAT) cells	Decreased bFGF expression	Decreased neovascularization	(183)

CNV, choroidal neovascularization; VLDLR, very-low-density lipoprotein receptor; AMD, age-related macular degeneration; LRP, low-density lipoprotein receptor-related protein; KS-TG, kallistatin-transgenic; TF, tissue factor; CCL2, chemokine (C-C motif) ligand 2; Cx3cr1, CX3C chemokine receptor 1; VEGF, vascular endothelial growth factor; Mab, monoclonal antibody; DKK-1, dickkopf-related protein 1; TNF-α, tumor necrosis factor-α; COX-2, cyclooxygenase 2; HIF-1α, hypoxia-inducible factor 1-α; NF-κB, nuclear factor-κB; IL, interleukin; bFGF, basic fibroblast growth factor.

Wnt/β-catenin signaling and oxidative stress in exudative AMD. The downregulation in the levels of DKK-1 has been found to be associated with the severity of exudative AMD and CNV development (79). Nevertheless, the cause for the decrease in the DKK-1 expression level remains unclear; however, previous research has revealed that circulating DKK-1 expression is produced from platelets (80). Wnt/β-catenin signaling stimulates the process of aerobic glycolysis (also known as the Warburg effect), by the simultaneous stimulation of PI3K/Akt signaling and HIF-1α, two crucial regulators of the Warburg effect (81-83).

The activation of PI3K/Akt signaling leads to the stimulation of glucose metabolism and the prevention of reactive oxygen species (ROS) production through the activation of HIF-1α, which diverts the glucose from the tricarboxylic acid cycle and the production of lactate (84).

ROS, a production of normal cell metabolism, can act either favorably or negatively for cells, depending mainly on the concentration. The principal source of ROS production is oxidative mechanisms in the mitochondria and several enzymatic interactions catalyzed by the oxidoreductase enzymes (85). Decreased concentrations of ROS interact as cell proliferation enhancers and subsequently pro-apoptotic enhancers. ROS stimulate a number of transcription factors, including NF-κB and activator protein 1 (AP-1) (86). ROS have also been reported to enhance angiogenic process and inflammation (87,88). However, increased ROS concentrations may be toxic and mutagenic, damaging lipids, proteins, DNA and ultimately enhancing apoptosis. The endogenous antioxidant defense mechanism is composed of antioxidant enzymes, including superoxide dismutase (SOD), catalase, glutathione peroxidase, heme oxygenase (HO-1) and non-enzymatic antioxidants, including decreased molecular weight scavengers [glutathione (GSH), uric acid, lipoic acid, ascorbic acid, tocopherol. Exogenous antioxidant defense system consists of antioxidants grouped into natural products and identical to natural ones but synthesized by the industry, including vitamins (89). The imbalance between ROS production and antioxidant processes defines oxidative stress (OS). OS plays a major role in disease initiation, including AMD, as well as in physiological processes, including aging (90-92).

HIF-1α is transcriptionally involved through PI3K/Akt signaling by eukaryotic translation initiation factor 4E-binding protein 1 and STAT3 (93-98). c-Myc has been reported to activate HIF-1α (99). HIF-1α stimulates the activity of numerous glycolytic enzymes, including PDK, responsible for the phosphorylation of pyruvate dehydrogenase (PDH). This results in PDH inactivation and leads to cytoplasmic pyruvate being converted into lactate by the activation of lactate dehydrogenase A (LDH-A) (100). HIF-1α and c-Myc are the main controlling factors of LDH-A (101-104). This process is characterized by increased levels of cytoplasmic lactate production (105), and has also been observed in exudative AMD (59,106). In exudative AMD, the overstimulation of the Wnt/β-catenin signaling pathway results in the activation of the Warburg effect and the subsequent enhancement of photoreceptor protection in retina cells, against OS damage (107,108).

Wnt/β-catenin signaling and inflammation in exudative AMD. Previous studies have revealed an association between Wnt/β-catenin signaling and inflammation, due to their effects on TNF-α and NF-κB signaling targets (37,109,110). TNF-α has been reported to be stimulated in AMD (111,112), while intercellular adhesion molecule (ICAM)-1 is produced in the RPE and exerts a marked effect on leukocyte adherence (113,114). Inflammation plays a crucial role in exudative AMD through the activation of the Wnt/β-catenin signaling pathway, ultimately resulting in the activation of VEGF (25,33,115,116). Thus, Wnt/β-catenin signaling activation has been considered to play an integral role in the development of AMD. Wnt/β-catenin signaling stimulation is associated with the degeneration of the focal retina and exudative lesions (21). The stimulation of Wnt/β-catenin signaling has been shown to be associated with the initiation of exudative lesions by its associations with pro-inflammatory markers (33).

5. Cellular signaling for CNV formation in exudative AMD

The mechanism of inflammation plays a crucial role in the development of CNV by the stimulation of VEGF (25,33,115,116). The stimulation of NF-κB signaling, a main inflammatory factor, has been found to be associated with the activation of Wnt/β-catenin signaling in AMD (35). The stimulation of Wnt/β-catenin signaling induces the upregulation of various factors, including VEGF, TNF-α and ICAM-1 (31,33,117). Subsequently, the stimulation of VEGF by TNF-α plays a role in CNV (118-121).

The downregulation of Wnt inhibitors, including DKK-1, has been shown to be associated with exudative lesions and the severity of CNV (79). In exudative AMD, VEGF overexpression may be enhanced by the stimulation of the Wnt/β-catenin signaling (31,33,117) and this occurs by a direct targeting link (20,122).

The activation of HIF-1α, enhanced by Wnt/β-catenin signaling, may result in the stimulation of VEGF activity, ultimately damaging choroid and retinal endothelial cell functions, subsequently stimulating angiogenesis (123-125).

LDH-A activation directly stimulates the expression of VEGF (106,126-128). Moreover, cytoplasmic lactate accumulation has been reported to lead to the upregulation of VEGF (129-131), and particularly in exudative AMD, the formation of CNV is enhanced by the stimulation of VEGF (118-121).

6. Curcumin

Curcumin, classified as bis-α, β-unsaturated β-diketone, is a natural well-known compound. Curcumin is the active component of *Curcuma longa L.,* which has been reported to exert a wide range of beneficial effects, including anticancer properties (132,133). Additionally, curcumin has been revealed to possess a number of therapeutic properties, including anti-inflammatory and anti-aging properties (134). In 1815, curcumin was initially investigated by Vogel and Pelletier from the rhizomes of *Curcuma longa* (135). Subsequently, in 1842, Vogel Jr purified curcumin. In 1910, another study revealed the chemical structure of curcumin, as diferuloylmethane, or 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E) (135). In 1913, for the first time, a method was developed for curcumin synthesis (136).

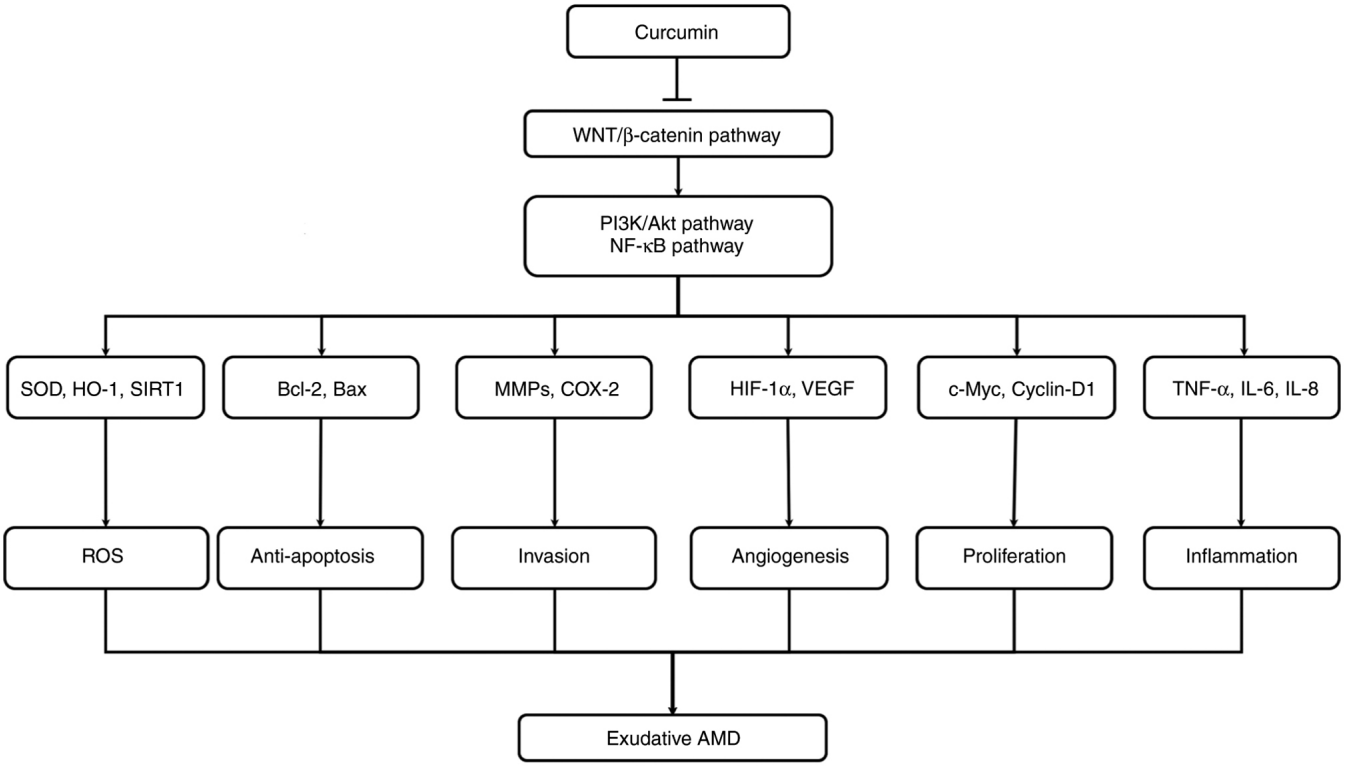

Figure 2. Potential actions of curcumin by inactivating the Wnt/β-catenin signaling for protective effects on exudative AMD. As regards oxidative stress, curcumin may enhance SIRT1 and modulate SOD and HO-1 to control ROS production. Curcumin may regulate apoptotic function through Bcl-2 and Bax, and also invasion by modulating MMPs and COX-2. Via the interaction between Wnt/β-catenin signaling (c-Myc and cyclin D1) and HIF-1α and subsequently VEGF expression, curcumin can reduce angiogenesis and cell proliferation. Moreover, by controlling the expression of inflammatory markers (TNF-α, IL-1 and IL-6) activated by Wnt/β-catenin signaling, curcumin can exert an anti-inflammatory effect. AMD, age-related macular degeneration; SOD, superoxide dismutase; HO-1, heme oxygenase 1; ROS, reactive oxygen species; MMPs, matrix metalloproteinases; COX-2, cyclooxygenase 2; HIF-1α, hypoxia-inducible factor 1-alpha; VEGF, vascular endothelial growth factor; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor-κB; IL, interleukin; SIRT1, sirtuin-1.

The predicted benefits of curcumin are restricted due to its reduced oral bioavailability, which can be attributed to its poor absorption, a high rate of metabolism and a rapid systemic increase in curcumin levels.

Previous studies have observed that curcumin pharmacokinetics include a reduced bioavailability (137), and increased pharmacological and clinical applications (138). However, several potential processes to overcome this poor bioavailability could be counteracted through alternative approaches. Various strategies can improve its bioavailability, including phospholipid complexes, liposomes and nanoparticles. A number of polymers h utilized to synthesize nano-formulations for curcumin use to enhance its biological metabolism (139). Biocompatible and biodegradable polymers have been utilized in the administration of therapeutics, due to their low toxicity risk (140). Previous findings of liposome formulations have resulted in the improvement of treatments for drug-resistant cancers and in the reduction of toxicity (141). Furthermore, other curcumin delivery processes have been applied, including nanogels (142), peptide and protein formulations (143) and cyclodextrin complexes (144).

Curcumin in exudative AMD. As regards AMD, curcumin has been reported to possibly counteract cell death through the effects on several cellular signaling pathways (i.e. VEGF, PI3K/Akt, TGF, FGF, COX-2, I-CAM-1, V-CAM-1) (145). These processes include the decrease in apoptotic rates of RPE cells and the diminution of inflammatory mechanisms (146). Curcumin may also reduce free radical concentrations and oxidative biomarker expression levels, including superoxide dismutase. Curcumin inhibits apoptosis to increase the viability of cells (147). It has been previously reported that, specific microRNAs controlling the antioxidant process, may be modulated by the administration of curcumin (148). Apart from this, the expression of HO-1, an enzyme serving cellular defense processes in AMD, is augmented by the effects of curcumin. Curcumin simultaneously decreases NF-κB activity and inflammatory gene expression (TNF, IL-1) (149).

Another protective effect of curcumin has been observed by counteracting OS induced in ARPE-19 cells (150). In ARPE-19 cells, curcumin can decrease p44/42 (ERK) apoptotic signaling, with a consecutive decrease in Bax and Bcl2 levels (Fig. 2). Furthermore, curcumin exerts a protective effect against OS, which may be a possible therapeutic approach for AMD (Table I).

Curcumin inhibits Wnt/β-catenin signaling. The use of curcumin has been reported to lead to cell cycle arrest in the G2/M stage of tumor cells, due to the decrease in Wnt/β-catenin signaling (151). Curcumin activates GSK-3β to decrease nuclear β-catenin translocation and subsequently, to inhibit the action of cyclin D1. In cancer cells, curcumin analogs dysregulate the translocation of β-catenin into

the nucleus (152). In xenograft mouse models, curcumin decreases 12-0-tetradecanoylphorbol-13-acetate-induced Wnt signaling (153). Additionally, curcumin and its analog, CHC007, may decrease complex β-catenin/TCF/LEF levels in various tumor cells (154). Furthermore, curcumin increased the GSK-3β mRNA level in DAOY medulloblastoma cells to decrease Wnt/β-catenin signaling (155). By the decrease in Wnt/β-catenin signaling, curcumin diminishes cyclin D1 and is responsible for the diminution of brain tumor growth (155) (Fig. 2).

Antioxidant properties of curcumin in exudative AMD. Curcumin belongs to natural antioxidants. The effects of curcumin on OS involve numerous processes. Curcumin may scavenge different forms of OS, including the production of ROS and reactive nitrogen species (156). It can directly regulate GSH activity (157). Moreover, curcumin may decrease ROS-generating enzymes, including cyclooxygenase 2 (COX-2) (158).

In vitro biochemical have studies revealed that the COX-2 pathway catalyzes the oxidation of the 5-lipoxygenase (5-LOX) product 5S-HETE to form a di-endoperoxide (158) and 5-OH-PGH_2, equivalent to the prostaglandin endoperoxide PGH_2 of the COX-2 pathway (159). A previous study has suggested that the stimulation of 12/15-lipoxygenase may lead to the dysregulation of the retinal endothelial cell barrier, demonstrated as increased vascular permeability through the involvement of NADPH oxidases and the subsequent activation of VEGF (160). An inhibitor of 5-LOX, pigment epithelium-derived factor receptor, obstructed RPE cell death signaling which is involved by oxidative stress (161). Lipid peroxidation stimulates redox-sensitive inflammatory factors, including the NF-κB pathway, resulting in inflammation during the progression of AMD (162,163). Curcumin may exert beneficial anti-inflammatory effects via the modulation of the 5-LOX pathway (159,164). Curcumin inhibits 5-LOX activity in polymorphonuclear leukocytes and reduces leukotriene C_4 biosynthesis in limb edema and in anaphylaxis animal models (165,166).

Moreover, curcumin is a chain-breaking antioxidant and a lipophilic component; this renders it an efficient scavenger of peroxyl radicals (136,167). Curcumin can enhance the levels of GSH (168), but can decrease the activity of nitric oxide synthase in murine macrophages and can enhance the HO expression in several cell subtypes (169). A decrease in sirtuin-1 (SIRT1) levels has been shown to be associated with a reduction in SOD levels. SIRT1 deacetylates SOD (170). SIRT1 is an NAD-dependent enzyme deacetylating several substrates and regulating metabolism, including aging. The main role of SIRT1 is the alleviation of inflammatory process by the decrease in NF-κB signaling and by the reduction of OS. Previous findings have observed that the inhibition of SIRT1 is associated AMD (171). SIRT1 has also been reported to decrease OS by possessing neuroprotective action in mice with optic nerve crush injury (172). Moreover, a recent study observed that curcumin activated SIRT1 to decrease OS (173) (Fig. 2).

Anti-inflammatory properties of curcumin in exudative AMD. Curcumin has been proven to inhibit NF-κB signaling (174,175). Recent research has demonstrated that curcumin may counteract inflammation by acting as a peroxisome proliferator-activated receptor agonist (176). Moreover, curcumin may decrease TNF-α expression and downregulate the production of cytokines, including interleukin (IL)-1, IL-6 and IL-8, and chemokines. Curcumin may also reduce proinflammatory enzyme expression, including COX-2 (157,177). In parallel, curcumin can exert anti-inflammatory effects by decreasing IL-1, IL-6 and TNF-α levels (178) (Fig. 2).

Anti-angiogenic properties of curcumin in exudative AMD. Curcumin has been shown to inhibit angiogenesis through the suppression of VEGF production in U937 and Raji cells (179). Moreover, COX-2 and VEGF have been found to be directly suppressed by curcumin in HepG2 hepatoma cells (180).

Curcumin (3,000 mg/kg body weight) administration has been also associated with a decrease in tumor angiogenesis, through the inhibition of VEGF and COX-2 expression (180). These effects have been also reported to be exerted through the liposomal availability of curcumin and by attenuating the NF-κB signaling pathway (181). Moreover, curcumin may decrease angiogenesis in basic fibroblast growth factor (bFGF)-induced corneal neovascularization (182). Furthermore, curcumin may decrease the activity of FGF-induced neovascularization (183). Previous studies have revealed the angiogenic synergy between bFGF and VEGF pathway (184-186). bFGF may also increase the expression of pro-angiogenic factors, including VEGF, to regulate the angiogenic processes (187,188). As a result, curcumin may decrease the expression of VEGF through the inhibition of bFGF expression.

Curcumin may inhibit the activity of the urokinase plasminogen activator system (uPA; (189). uPA complexes with a specific receptor (uPAR), through the EGF-like domain in the urokinase amino-terminal fragment (ATF). This effect has been reported to result in a decrease in endothelial cell migration and a decrease in bFGF, TGF, TNF-α, hepatocyte growth factor and VEGF release (190). Additionally, curcumin may inhibit MMP-2 expression by interacting via FGF-2 angiogenic signaling (191) (Fig. 2).

Limitations of curcumin use and new particles. Different properties of curcumin confer anti-inflammatory and antioxidant activities. Curcumin has been investigated in congenital and degenerative eye disorders of both the anterior and posterior segments, and has been previously utilized as a possible therapeutic (192-194). However, the major issue concerning the oral use of curcumin remains the reduced curcumin bioavailability, due to a low gastrointestinal absorption with a rapid hepatic and intestinal metabolism. Therefore, to counteract these limitations, numerous methods are investigated, including curcumin analogues, enhancers and delivery systems. Promising substances are the pro-drug diphosphorylated curcumin, marked by a high molecular stability in the aqueous media (195) and the curcumin pro-drug curcumin diethyl disuccinate (196). Bioavailability enhancers have been considered, with the use of piperine being highly promising,

having the ability to diminish curcumin hepatic and intestinal glucuronidation (197), leading to increase curcumin bioavailability (198). Nanoparticles and liposomes present high interest to also enhance curcumin bioavailability (199). Nevertheless, to the best of our knowledge, the aforementioned strategies have not yet been investigated for ocular disorder treatment, with the sole exception of the use of a biodegradable curcumin-loaded scleral plug for therapy of posterior ocular diseases in rabbit ocular model (200). Furthermore, a curcumin-phospholipid lecithin formulation, known as Meriva®, has been reported to enhance visual acuity and can diminish macular edema among diabetic retinopathy patients (201). Nevertheless, in the therapy of chronic anterior uveitis with complications, curcumin has demonstrated promising results (202).

7. Conclusion and future perspectives

Curcumin presents a wide range of pharmacological actions, including antioxidant, anti-inflammatory and anti-angiogenic activities in exudative AMD. The role of curcumin in OS, angiogenesis and inflammatory mechanisms, through its action of de-activating the Wnt/β-catenin signaling pathway, may indicate that it can decrease these pathological conditions and may prove to be an interesting pharmacological agent in exudative AMD. However, future clinical and pre-clinical studies are warranted to investigate the role of curcumin as a therapeutic agent in AMD.

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Competing interests

The author declares that he has no competing interests.

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