

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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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).

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Abbreviations: COX-2, cyclooxygenase 2; TNF- α , tumor necrosis factor- α ; ROS, reactive oxygen species; NF- κ B, nuclear factor- κ B; 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

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- κ B, 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-3 β (GSK-3 β). 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-3 β is activated and then phosphorylates cytoplasmic β -catenin. The destruction complex is formed by the tumor suppressor adenomatous polyposis coli (APC), AXIN, GSK-3 β 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-3 β , 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-3 β concurrently decreases β -catenin cytoplasmic expression and β -catenin nuclear translocation (56). β -catenin, mTOR signaling, hypoxia-inducible factor 1- α (HIF-1 α) and VEGF are downregulated, due to the increased activity of GSK-3 β (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

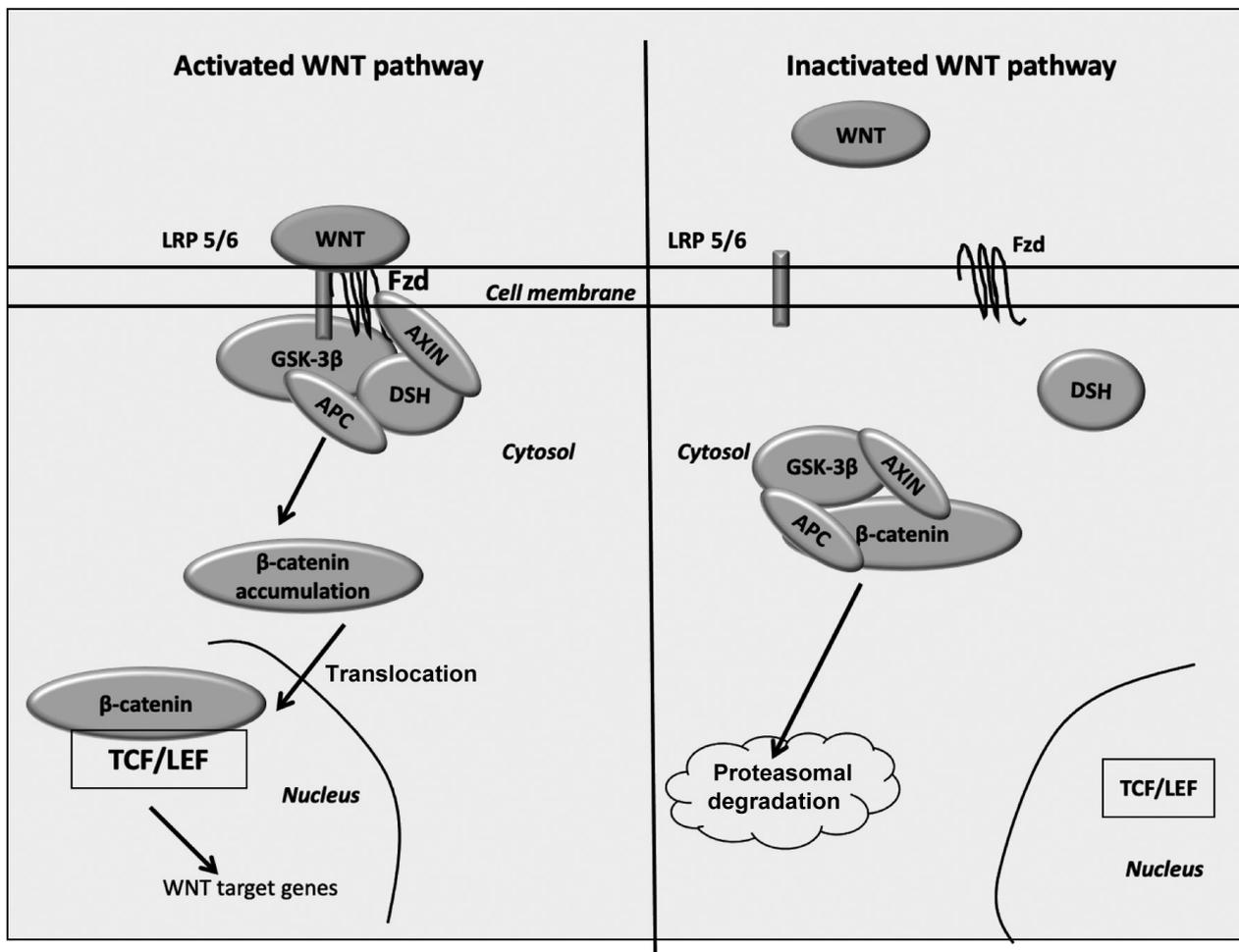


Figure 1. Activation and inactivation of Wnt/ β -catenin signaling. During the activation of Wnt ligands, the stimulation of FZD4/ β -catenin signaling requires the formation of the LRP5/LRP6 complex. LRP5 plays a crucial role in the vascularization of the retina, whereas LRP6 has a less integral role in this. Dsh forms a complex with AXIN, to prevent the β -catenin phosphorylation by GSK-3 β . 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-3 β phosphorylates cytoplasmic β -catenin. The destruction complex is formed by APC, AXIN, GSK-3 β 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-3 β , glycogen synthase kinase-3 β ; 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 angiogenic 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- κ B 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 1 β 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-1 α	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)
	<i>In vivo</i> models	Diminution of IL-1, IL-6 and TNF- α , COX-2, NF- κ B	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)
	<i>In vivo</i> 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-1 α , hypoxia-inducible factor 1- α ; NF- κ B, nuclear factor- κ B; 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).

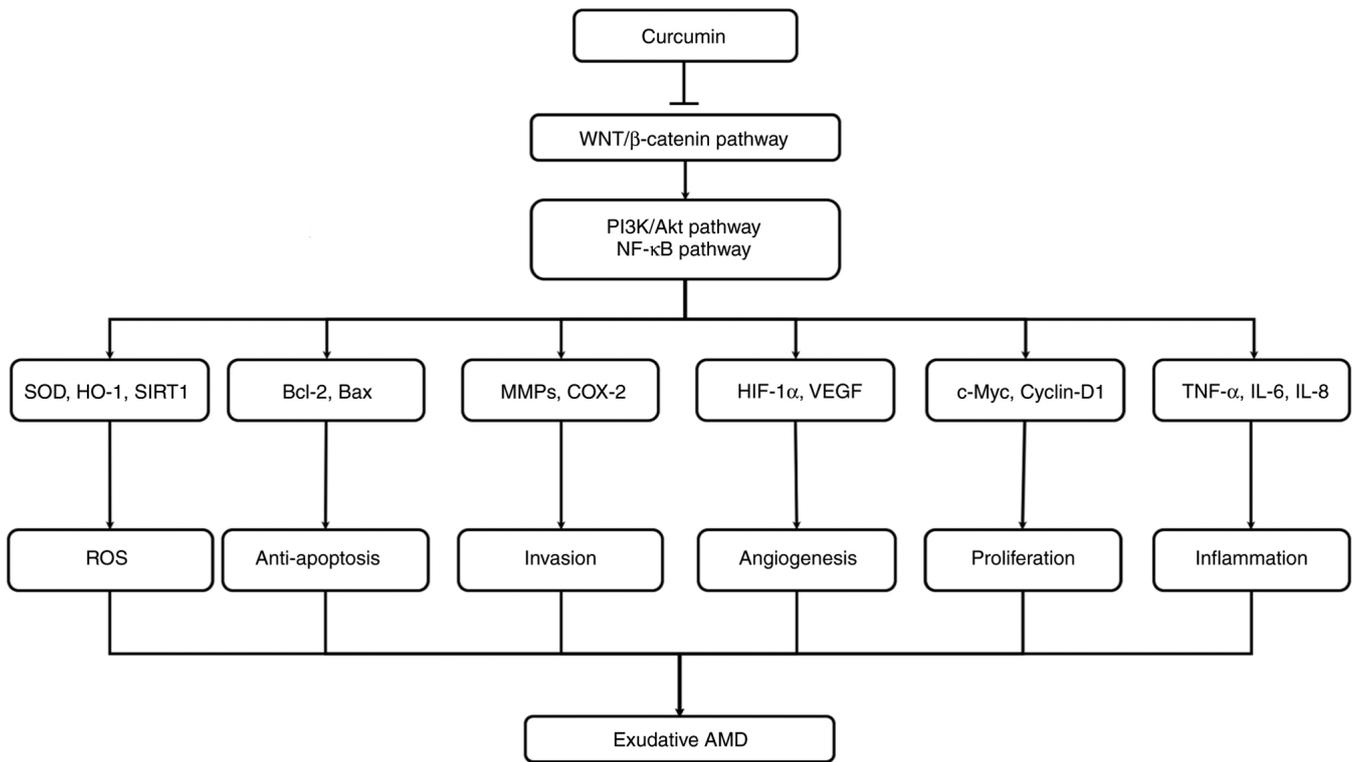


Figure 2. Potential actions of curcumin by inactivating the Wnt/ β -catenin signaling for protective effects on exudative AMD. As regards oxidative stress, curcumin may enhance SIRT1 and modulate SOD and HO-1 to control ROS production. Curcumin may regulate apoptotic function through Bcl-2 and Bax, and also invasion by modulating MMPs and COX-2. Via the interaction between Wnt/ β -catenin signaling (c-Myc and cyclin D1) and HIF-1 α 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-1 α , hypoxia-inducible factor 1-alpha; VEGF, vascular endothelial growth factor; TNF- α , tumor necrosis factor- α ; NF- κ B, nuclear factor- κ B; 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- κ B 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-3 β 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-3 β 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 studies have 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-PGH₂, equivalent to the prostaglandin endoperoxide PGH₂ 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- κ B 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 C₄ 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 peroxy 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- κ B 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- κ B

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- κ B 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.

References

- Bird AC: Therapeutic targets in age-related macular disease. *J Clin Invest* 120: 3033-3041, 2010.
- Radomska-Leśniewska DM, Skopiński P, Bałan BJ, Białoszewska A, Józwiak J, Rokicki D, Skopińska-Różewska E, Borecka A and Hevelke A: Angiomodulatory properties of *Rhodiola* spp. and other natural antioxidants. *Cent Eur J Immunol* 40: 249-262, 2015.
- Radomska-Leśniewska DM, Bałan BJ and Skopiński P: Angiogenesis modulation by exogenous antioxidants. *Cent Eur J Immunol* 42: 370-376, 2017.
- Vallée A, Lecarpentier Y, Guillevin R and Vallée JN: PPAR γ agonists: Potential treatments for exudative age-related macular degeneration. *Life Sci* 188: 123-130, 2017.
- Coffe V, Carbajal RC and Salceda R: Glucose metabolism in rat retinal pigment epithelium. *Neurochem Res* 31: 103-108, 2006.
- Kaur C, Foulds WS and Ling EA: Hypoxia-ischemia and retinal ganglion cell damage. *Clin Ophthalmol* 2: 879-889, 2008.
- Ferris FL, Fine SL and Hyman L: Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 102: 1640-1642, 1984.
- Barchitta M and Maugeri A: Association between vascular endothelial growth factor polymorphisms and age-related macular degeneration: An updated meta-analysis. *Dis Markers* 2016: 8486406, 2016.
- Yin F, Boveris A and Cadenas E: Mitochondrial energy metabolism and redox signaling in brain aging and neurodegeneration. *Antioxid Redox Signal* 20: 353-371, 2014.
- Vallée A, Lecarpentier Y, Guillevin R and Vallée JN: opposite interplay between the canonical WNT/ β -catenin pathway and PPAR Gamma: A potential therapeutic target in gliomas. *Neurosci Bull* 34: 573-588, 2018.
- Vallée A, Lecarpentier Y and Vallée JN: Curcumin: A therapeutic strategy in cancers by inhibiting the canonical WNT/ β -catenin pathway. *J Exp Clin Cancer Res* 38: 323, 2019.
- Yeung AWK, Horbańczuk M, Tzvetkov NT, Mocan A, Carradori S, Maggi F, Marchewka J, Sut S, Dall'Acqua S, Gan RY, *et al*: Curcumin: Total-scale analysis of the scientific literature. *Molecules* 24: 1393, 2019.
- Kao YW, Hsu SK, Chen JY, Lin IL, Chen KJ, Lee PY, Ng HS, Chiu CC and Cheng KC: Curcumin metabolite tetrahydrocurcumin in the treatment of eye diseases. *Int J Mol Sci* 22: 212, 2020.
- Bhutto I and Lutty G: Understanding age-related macular degeneration (AMD): Relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. *Mol Aspects Med* 33: 295-317, 2012.
- McLeod DS, Grebe R, Bhutto I, Merges C, Baba T and Lutty GA: Relationship between RPE and choriocapillaris in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 50: 4982-4991, 2009.
- Takata S, Masuda T, Nakamura S, Kuchimaru T, Tsuruma K, Shimazawa M, Nagasawa H, Kizaka-Kondoh S and Hara H: The effect of triamcinolone acetonide on laser-induced choroidal neovascularization in mice using a hypoxia visualization bio-imaging probe. *Sci Rep* 5: 9898, 2015.
- Sakurai E, Anand A, Ambati BK, van Rooijen N and Ambati J: Macrophage depletion inhibits experimental choroidal neovascularization. *Invest Ophthalmol Vis Sci* 44: 3578-3585, 2003.
- Indaram M, Ma W, Zhao L, Fariss RN, Rodriguez IR and Wong WT: 7-Ketocholesterol increases retinal microglial migration, activation, and angiogenicity: A potential pathogenic mechanism underlying age-related macular degeneration. *Sci Rep* 5: 9144, 2015.
- Terasaki H, Kase S, Shirasawa M, Otsuka H, Hisatomi T, Sonoda S, Ishida S, Ishibashi T and Sakamoto T: TNF- α decreases VEGF secretion in highly polarized RPE cells but increases it in non-polarized RPE cells related to crosstalk between JNK and NF- κ B pathways. *PLoS One* 8: e69994, 2013.
- Hu Y, Chen Y, Lin M, Lee K, Mott RA and Ma J: Pathogenic role of the Wnt signaling pathway activation in laser-induced choroidal neovascularization. *Invest Ophthalmol Vis Sci* 54: 141-154, 2013.
- Tuo J, Wang Y, Cheng R, Li Y, Chen M, Qiu F, Qian H, Shen D, Penalva R, Xu H, *et al*: Wnt signaling in age-related macular degeneration: Human macular tissue and mouse model. *J Transl Med* 13: 330, 2015.
- Nussenblatt RB and Ferris F: Age-related macular degeneration and the immune response: Implications for therapy. *Am J Ophthalmol* 144: 618-626, 2007.

23. Radeke MJ, Radeke CM, Shih YH, Hu J, Bok D, Johnson LV and Coffey PJ: Restoration of mesenchymal retinal pigmented epithelial cells by TGF β pathway inhibitors: Implications for age-related macular degeneration. *Genome Med* 7: 58, 2015.
24. Lin CH, Li CH, Liao PL, Tse LS, Huang WK, Cheng HW and Cheng YW: Silibinin inhibits VEGF secretion and age-related macular degeneration in a hypoxia-dependent manner through the PI-3 kinase/Akt/mTOR pathway. *Br J Pharmacol* 168: 920-931, 2013.
25. Ambati J: Age-related macular degeneration and the other double helix. The Cogan lecture. *Invest Ophthalmol Vis Sci* 52: 2165-2169, 2011.
26. Blasiak J, Petrovski G, Veréb Z, Facskó A and Kaarniranta K: Oxidative stress, hypoxia, and autophagy in the neovascular processes of age-related macular degeneration. *Biomed Res Int* 2014: 768026, 2014.
27. Jaffe GJ, Elliott D, Wells JA, Prenner JL, Papp A and Patel S: A Phase I study of Intravitreal E10030 in combination with ranibizumab in neovascular age-related macular degeneration. *Ophthalmology* 123: 78-85, 2016.
28. Kwak N, Okamoto N, Wood JM and Campochiaro PA: VEGF is major stimulator in model of choroidal neovascularization. *Invest Ophthalmol Vis Sci* 41: 3158-3164, 2000.
29. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP and Schneider S; ANCHOR Study Group: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 355: 1432-1444, 2006.
30. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY and Kim RY; MARINA Study Group: Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 355: 1419-1431, 2006.
31. Zhang X, Gaspard JP and Chung DC: Regulation of vascular endothelial growth factor by the Wnt and K-ras pathways in colonic neoplasia. *Cancer Res* 61: 6050-6054, 2001.
32. Katoh Y and Katoh M: Comparative integromics on VEGF family members. *Int J Oncol* 28: 1585-1589, 2006.
33. Zhou T, Hu Y, Chen Y, Zhou KK, Zhang B, Gao G and Ma J: The pathogenic role of the canonical Wnt pathway in age-related macular degeneration. *Invest Ophthalmol Vis Sci* 51: 4371-4379, 2010.
34. Ma B and Hottiger MO: Crosstalk between Wnt/ β -catenin and NF- κ B signaling pathway during inflammation. *Front Immunol* 7: 378, 2016.
35. Wang H and Hartnett ME: Regulation of signaling events involved in the pathophysiology of neovascular AMD. *Mol Vis* 22: 189-202, 2016.
36. Al-Harathi L: Wnt/ β -catenin and its diverse physiological cell signaling pathways in neurodegenerative and neuropsychiatric disorders. *J Neuroimmune Pharmacol* 7: 725-730, 2012.
37. Logan CY and Nusse R: The Wnt signaling pathway in development and disease. *Annu Rev Cell Dev Biol* 20: 781-810, 2004.
38. Klaus A and Birchmeier W: Wnt signalling and its impact on development and cancer. *Nat Rev Cancer* 8: 387-398, 2008.
39. Fuhrmann S: Wnt signaling in eye organogenesis. *Organogenesis* 4: 60-67, 2008.
40. Fujimura N: WNT/ β -catenin signaling in vertebrate eye development. *Front Cell Dev Biol* 4: 138, 2016.
41. Machon O, Kreslova J, Ruzickova J, Vacik T, Klimova L, Fujimura N, Lachova J and Kozmik Z: Lens morphogenesis is dependent on Pax6-mediated inhibition of the canonical Wnt/beta-catenin signaling in the lens surface ectoderm. *Genesis* 48: 86-95, 2010.
42. Carpenter AC, Smith AN, Wagner H, Cohen-Tayar Y, Rao S, Wallace V, Ashery-Padan R and Lang RA: Wnt ligands from the embryonic surface ectoderm regulate 'bimetallic strip' optic cup morphogenesis in mouse. *Development* 142: 972-982, 2015.
43. Hägglund AC, Berghard A and Carlsson L: Canonical Wnt/ β -catenin signalling is essential for optic cup formation. *PLoS One* 8: e81158, 2013.
44. Birdsey GM, Shah AV, Dufton N, Reynolds LE, Osuna Almagro L, Yang Y, Aspalter IM, Khan ST, Mason JC, Dejana E, *et al*: The endothelial transcription factor ERG promotes vascular stability and growth through Wnt/ β -catenin signaling. *Dev Cell* 32: 82-96, 2015.
45. Ye X, Wang Y, Cahill H, Yu M, Badea TC, Smallwood PM, Peachey NS and Nathans J: Norrin, frizzled-4, and Lrp5 signaling in endothelial cells controls a genetic program for retinal vascularization. *Cell* 139: 285-298, 2009.
46. Zhou Y, Wang Y, Tischfield M, Williams J, Smallwood PM, Rattner A, Taketo MM and Nathans J: Canonical WNT signaling components in vascular development and barrier formation. *J Clin Invest* 124: 3825-3846, 2014.
47. Huang W, Li Q, Amiry-Moghaddam M, Hokama M, Sardi SH, Nagao M, Warman ML and Olsen BR: Critical endothelial regulation by LRP5 during retinal vascular development. *PLoS One* 11: e0152833, 2016.
48. Shtutman M, Zhurinsky J, Simcha I, Albanese C, D'Amico M, Pestell R and Ben-Ze'ev A: The cyclin D1 gene is a target of the beta-catenin/LEF-1 pathway. *Proc Natl Acad Sci USA* 96: 5522-5527, 1999.
49. Nusse R: Wnt signaling. *Cold Spring Harb Perspect Biol* 4: a011163, 2012.
50. Clevers H and Nusse R: Wnt/ β -catenin signaling and disease. *Cell* 149: 1192-1205, 2012.
51. Sprowl-Tanio S, Habowski AN, Pate KT, McQuade MM, Wang K, Edwards RA, Grun F, Lyou Y and Waterman ML: Lactate/pyruvate transporter MCT-1 is a direct Wnt target that confers sensitivity to 3-bromopyruvate in colon cancer. *Cancer Metab* 4: 20, 2016.
52. Pate KT, Stringari C, Sprowl-Tanio S, Wang K, TeSlaa T, Hoverter NP, McQuade MM, Garner C, Digman MA, Teitell MA, *et al*: Wnt signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer. *EMBO J* 33: 1454-1473, 2014.
53. Gao C, Xiao G and Hu J: Regulation of Wnt/ β -catenin signaling by posttranslational modifications. *Cell Biosci* 4: 13, 2014.
54. Cruciat CM and Niehrs C: Secreted and transmembrane Wnt inhibitors and activators. *Cold Spring Harb Perspect Biol* 5: a015081, 2013.
55. Aberle H, Bauer A, Stappert J, Kispert A and Kemler R: Beta-catenin is a target for the ubiquitin-proteasome pathway. *EMBO J* 16: 3797-3804, 1997.
56. Wu D and Pan W: GSK3: A multifaceted kinase in Wnt signaling. *Trends Biochem Sci* 35: 161-168, 2010.
57. Hur EM and Zhou FQ: GSK3 signalling in neural development. *Nat Rev Neurosci* 11: 539-551, 2010.
58. Ambacher KK, Pitzul KB, Karajgikar M, Hamilton A, Ferguson SS and Cregan SP: The JNK- and AKT/GSK3 β -signaling pathways converge to regulate puma induction and neuronal apoptosis induced by trophic factor deprivation. *PLoS One* 7: e46885, 2012.
59. Yokosako K, Mimura T, Funatsu H, Noma H, Goto M, Kamei Y, Kondo A and Matsubara M: Glycolysis in patients with age-related macular degeneration. *Open Ophthalmol J* 8: 39-47, 2014.
60. Grossniklaus HE, Kang SJ and Berglin L: Animal models of choroidal and retinal neovascularization. *Prog Retin Eye Res* 29: 500-519, 2010.
61. Wang Z, Liu CH, Huang S and Chen J: Wnt Signaling in vascular eye diseases. *Prog Retin Eye Res* 70: 110-133, 2019.
62. Wang Z, Cheng R, Lee K, Tyagi P, Ding L, Kompella UB, Chen J, Xu X and Ma JX: Nanoparticle-mediated expression of a wnt pathway inhibitor ameliorates ocular neovascularization. *Arterioscler Thromb Vasc Biol* 35: 855-864, 2015.
63. Chen Y, Hu Y, Lu K, Flannery JG and Ma JX: Very low density lipoprotein receptor, a negative regulator of the wnt signaling pathway and choroidal neovascularization. *J Biol Chem* 282: 34420-34428, 2007.
64. Lin JB, Sene A, Wiley LA, Santeford A, Nudleman E, Nakamura R, Lin JB, Moolani HV and Apte RS: WNT7A/B promote choroidal neovascularization. *Exp Eye Res* 174: 107-112, 2018.
65. Park K, Lee K, Zhang B, Zhou T, He X, Gao G, Murray AR and Ma JX: Identification of a novel inhibitor of the canonical Wnt pathway. *Mol Cell Biol* 31: 3038-3051, 2011.
66. Dai Z, Lu L, Yang Z, Mao Y, Lu J, Li C, Qi W, Chen Y, Yao Y, Li L, *et al*: Kallikrein-binding protein inhibits LPS-induced TNF- α by upregulating SOCS3 expression. *J Cell Biochem* 114: 1020-1028, 2013.
67. Zhang J, Yang Z, Li P, Bledsoe G, Chao L and Chao J: Kallistatin antagonizes Wnt/ β -catenin signaling and cancer cell motility via binding to low-density lipoprotein receptor-related protein 6. *Mol Cell Biochem* 379: 295-301, 2013.
68. Lu SL, Tsai CY, Luo YH, Kuo CF, Lin WC, Chang YT, Wu JJ, Chuang WJ, Liu CC, Chao L, *et al*: Kallistatin modulates immune cells and confers anti-inflammatory response to protect mice from Group A streptococcal infection. *Antimicrob Agents Chemother* 57: 5366-5372, 2013.
69. McBride JD, Jenkins AJ, Liu X, Zhang B, Lee K, Berry WL, Janknecht R, Griffin CT, Aston CE, Lyons TJ, *et al*: Elevated circulation levels of an antiangiogenic SERPIN in patients with diabetic microvascular complications impair wound healing through suppression of Wnt signaling. *J Invest Dermatol* 134: 1725-1734, 2014.

70. Bach RR: Initiation of coagulation by tissue factor. *CRC Crit Rev Biochem* 23: 339-368, 1988.
71. Tuo J, Bojanowski CM, Zhou M, Shen D, Ross RJ, Rosenberg KI, Cameron DJ, Yin C, Kowalak JA, Zhuang Z, *et al*: Murine *ccl2/cx3cr1* deficiency results in retinal lesions mimicking human age-related macular degeneration. *Invest Ophthalmol Vis Sci* 48: 3827-3836, 2007.
72. Chan CC, Ross RJ, Shen D, Ding X, Majumdar Z, Bojanowski CM, Zhou M, Salem N Jr, Bonner R and Tuo J: *Ccl2/Cx3cr1*-deficient mice: An animal model for age-related macular degeneration. *Ophthalmic Res* 40: 124-128, 2008.
73. Chu XK, Wang Y, Ardeljan D, Tuo J and Chan CC: Controversial view of a genetically altered mouse model of focal retinal degeneration. *Bioengineered* 4: 130-135, 2013.
74. Tuo J, Ross RJ, Herzlich AA, Shen D, Ding X, Zhou M, Coon SL, Hussein N, Salem N Jr and Chan CC: A high omega-3 fatty acid diet reduces retinal lesions in a murine model of macular degeneration. *Am J Pathol* 175: 799-807, 2009.
75. Tuo J, Pang JJ, Cao X, Shen D, Zhang J, Scaria A, Wadsworth SC, Pechan P, Boye SL, Hauswirth WW and Chan CC: AAV5-mediated sFLT01 gene therapy arrests retinal lesions in *Ccl2(-)/Cx3cr1(-)* mice. *Neurobiol Aging* 33: 433.e1-e10, 2012.
76. Zhang J, Tuo J, Cao X, Shen D, Li W and Chan CC: Early degeneration of photoreceptor synapse in *Ccl2/Cx3cr1*-deficient mice on *Crb1(rd8)* background. *Synapse* 67: 515-531, 2013.
77. Clemons TE, Milton RC, Klein R, Seddon JM and Ferris FL III; Age-Related Eye Disease Study Research Group: Risk factors for the incidence of advanced age-related macular degeneration in the age-related eye disease study (AREDS) AREDS report no. 19. *Ophthalmology* 112: 533-539, 2005.
78. Wang Y, Sang A, Zhu M, Zhang G, Guan H, Ji M and Chen H: Tissue factor induces VEGF expression via activation of the Wnt/ β -catenin signaling pathway in ARPE-19 cells. *Mol Vis* 22: 886-897, 2016.
79. Qiu F, Liu Z, Zhou Y, He J, Gong S, Bai X, Zeng Y, Liu Z and Ma JX: Decreased circulating levels of dickkopf-1 in patients with exudative age-related macular degeneration. *Sci Rep* 7: 1263, 2017.
80. Voorzanger-Rousselot N, Goehrig D, Facon T, Clézardin P and Garnero P: Platelet is a major contributor to circulating levels of Dickkopf-1: Clinical implications in patients with multiple myeloma. *Br J Haematol* 145: 264-266, 2009.
81. Esen E, Chen J, Karner CM, Okunade AL, Patterson BW and Long F: WNT-LRP5 signaling induces Warburg effect through mTORC2 activation during osteoblast differentiation. *Cell Metab* 17: 745-755, 2013.
82. Pate KT, Stringari C, Sprowl-Tanio S, Wang K, TeSlaa T, Hoverter NP, McQuade MM, Garner C, Digman MA, Teitell MA, *et al*: Wnt signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer. *EMBO J* 33: 1454-1473, 2014.
83. Thompson CB: Wnt meets Warburg: Another piece in the puzzle? *EMBO J* 33: 1420-1422, 2014.
84. Lum JJ, Bui T, Gruber M, Gordan JD, DeBerardinis RJ, Covello KL, Simon MC and Thompson CB: The transcription factor HIF-1 α plays a critical role in the growth factor-dependent regulation of both aerobic and anaerobic glycolysis. *Genes Dev* 21: 1037-1049, 2007.
85. Manea A: NADPH oxidase-derived reactive oxygen species: Involvement in vascular physiology and pathology. *Cell Tissue Res* 342: 325-339, 2010.
86. Radoska-Leśniewska DM, Hevelke A, Skopiński P, Bałan B, Józwiak J, Rokicki D, Skopińska-Różewska E and Białoszewska A: Reactive oxygen species and synthetic antioxidants as angiogenesis modulators: Clinical implications. *Pharmacol Rep* 68: 462-471, 2016.
87. Mittal M, Siddiqui MR, Tran K, Reddy SP and Malik AB: Reactive oxygen species in inflammation and tissue injury. *Antioxid Redox Signal* 20: 1126-1167, 2014.
88. Kim YW, West XZ and Byzova TV: Inflammation and oxidative stress in angiogenesis and vascular disease. *J Mol Med (Berl)* 91: 323-328, 2013.
89. Brambilla D, Mancuso C, Scuderi MR, Bosco P, Cantarella G, Lempereur L, Di Benedetto G, Pezzino S and Bernardini R: The role of antioxidant supplement in immune system, neoplastic, and neurodegenerative disorders: A point of view for an assessment of the risk/benefit profile. *Nutr J* 7: 29, 2008.
90. Carmeliet P and Jain RK: Molecular mechanisms and clinical applications of angiogenesis. *Nature* 473: 298-307, 2011.
91. Kim YW and Byzova TV: Oxidative stress in angiogenesis and vascular disease. *Blood* 123: 625-631, 2014.
92. Vallée A, Lecarpentier Y, Vallée R, Guillevin R and Vallée JN: Circadian rhythms in exudative age-related macular degeneration: The key role of the canonical WNT/ β -catenin pathway. *Int J Mol Sci* 21: 820, 2020.
93. Brugarolas JB, Vazquez F, Reddy A, Sellers WR and Kaelin WG: TSC2 regulates VEGF through mTOR-dependent and -independent pathways. *Cancer Cell* 4: 147-158, 2003.
94. Düvel K, Yecies JL, Menon S, Raman P, Lipovsky AI, Souza AL, Triantafellow E, Ma Q, Gorski R, Cleaver S, *et al*: Activation of a metabolic gene regulatory network downstream of mTOR complex 1. *Mol Cell* 39: 171-183, 2010.
95. Jung JE, Lee HG, Cho IH, Chung DH, Yoon SH, Yang YM, Lee JW, Choi S, Park JW, Ye SK and Chung MH: STAT3 is a potential modulator of HIF-1-mediated VEGF expression in human renal carcinoma cells. *FASEB J* 19: 1296-1298, 2005.
96. Land SC and Tee AR: Hypoxia-inducible factor 1 α is regulated by the mammalian target of rapamycin (mTOR) via an mTOR signaling motif. *J Biol Chem* 282: 20534-20543, 2007.
97. Toschi A, Lee E, Gadir N, Ohh M and Foster DA: Differential dependence of hypoxia-inducible factors 1 α and 2 α on mTORC1 and mTORC2. *J Biol Chem* 283: 34495-34499, 2008.
98. Xu Q, Briggs J, Park S, Niu G, Kortylewski M, Zhang S, Gritsko T, Turkson J, Kay H, Semenza GL, *et al*: Targeting Stat3 blocks both HIF-1 and VEGF expression induced by multiple oncogenic growth signaling pathways. *Oncogene* 24: 5552-5560, 2005.
99. Kim J, Gao P, Liu YC, Semenza GL and Dang CV: Hypoxia-inducible factor 1 and dysregulated c-Myc cooperatively induce vascular endothelial growth factor and metabolic switches hexokinase 2 and pyruvate dehydrogenase kinase 1. *Mol Cell Biol* 27: 7381-7393, 2007.
100. Suda T, Takubo K and Semenza GL: Metabolic regulation of hematopoietic stem cells in the hypoxic niche. *Cell Stem Cell* 9: 298-310, 2011.
101. Firth JD, Ebert BL and Ratcliffe PJ: Hypoxic regulation of lactate dehydrogenase A. Interaction between hypoxia-inducible factor 1 and cAMP response elements. *J Biol Chem* 270: 21021-21027, 1995.
102. Lewis BC, Shim H, Li Q, Wu CS, Lee LA, Maity A and Dang CV: Identification of putative c-Myc-responsive genes: Characterization of rcl, a novel growth-related gene. *Mol Cell Biol* 17: 4967-4978, 1997.
103. Semenza GL, Jiang BH, Leung SW, Passantino R, Concordet JP, Maire P and Giallongo A: Hypoxia response elements in the Aldolase A, Enolase 1, and lactate dehydrogenase A gene promoters contain essential binding sites for hypoxia-inducible factor 1. *J Biol Chem* 271: 32529-32537, 1996.
104. Shim H, Dolde C, Lewis BC, Wu CS, Dang G, Jungmann RA, Dalla-Favera R and Dang CV: c-Myc transactivation of LDH-A: implications for tumor metabolism and growth. *Proc Natl Acad Sci USA* 94: 6658-6663, 1997.
105. Warburg O: On the origin of cancer cells. *Science* 123: 309-314, 1956.
106. Koukourakis MI, Giatromanolaki A, Sivridis E, Bougioukas G, Didilis V, Gatter KC and Harris AL; Tumour and Angiogenesis Research Group: Lactate dehydrogenase-5 (LDH-5) overexpression in non-small-cell lung cancer tissues is linked to tumour hypoxia, angiogenic factor production and poor prognosis. *Br J Cancer* 89: 877-885, 2003.
107. Vallée A, Lecarpentier Y, Guillevin R and Vallée JN: Aerobic glycolysis hypothesis through WNT/ β -catenin pathway in exudative age-related macular degeneration. *J Mol Neurosci* 62: 368-379, 2017.
108. Lévillard T and Sahel JA: Metabolic and redox signaling in the retina. *Cell Mol Life Sci* 74: 3649-3665, 2017.
109. Oguma K, Oshima H and Oshima M: Inflammation, tumor necrosis factor and Wnt promotion in gastric cancer development. *Future Oncol* 6: 515-526, 2010.
110. Schön S, Flierman I, Ofner A, Stahringer A, Holdt LM, Kolligs FT and Herbst A: β -catenin regulates NF- κ B activity via TNFRSF19 in colorectal cancer cells. *Int J Cancer* 135: 1800-1811, 2014.
111. Oh H, Takagi H, Takagi C, Suzuma K, Otani A, Ishida K, Matsumura M, Ogura Y and Honda Y: The potential angiogenic role of macrophages in the formation of choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 40: 1891-1898, 1999.
112. Cousins SW, Espinosa-Heidmann DG and Csaky KG: Monocyte activation in patients with age-related macular degeneration: A biomarker of risk for choroidal neovascularization? *Arch Ophthalmol* 122: 1013-1018, 2004.

113. Duguid IG, Boyd AW and Mandel TE: Adhesion molecules are expressed in the human retina and choroid. *Curr Eye Res* 11 (Suppl): S153-S159, 1992.
114. Elnér SG, Elnér VM, Pavilack MA, Todd RF III, Mayo-Bond L, Franklin WA, Strieter RM, Kunkel SL and Huber AR: Modulation and function of intercellular adhesion molecule-1 (CD54) on human retinal pigment epithelial cells. *Lab Invest* 66: 200-211, 1992.
115. Anderson DH, Mullins RF, Hageman GS and Johnson LV: A role for local inflammation in the formation of drusen in the aging eye. *Am J Ophthalmol* 134: 411-431, 2002.
116. Donoso LA, Kim D, Frost A, Callahan A and Hageman G: The role of inflammation in the pathogenesis of age-related macular degeneration. *Surv Ophthalmol* 51: 137-152, 2006.
117. Easwaran V, Lee SH, Inge L, Guo L, Goldbeck C, Garrett E, Wiesmann M, Garcia PD, Fuller JH, Chan V, *et al*: Beta-Catenin regulates vascular endothelial growth factor expression in colon cancer. *Cancer Res* 63: 3145-3153, 2003.
118. Ip MS, Scott IU, Brown GC, Brown MM, Ho AC, Huang SS and Recchia FM; American Academy of Ophthalmology: Anti-vascular endothelial growth factor pharmacotherapy for age-related macular degeneration: A report by the American Academy of Ophthalmology. *Ophthalmology* 115: 1837-1846, 2008.
119. Wolf S: Current status of anti-vascular endothelial growth factor therapy in Europe. *Jpn J Ophthalmol* 52: 433-439, 2008.
120. Menon G and Walters G: New paradigms in the treatment of wet AMD: The impact of anti-VEGF therapy. *Eye (Lond)* 23 (Suppl 1): S1-S7, 2009.
121. Grisanti S, Zhu Q, Tatar O, Lueke J, Lueke M, Tura A and Grisanti S: Differential expression of vascular endothelial growth factor- α isoforms in neovascular age-related macular degeneration. *Retina* 35: 764-772, 2015.
122. Liu X: Overstimulation can create health problems due to increases in PI3K/Akt/GSK3 insensitivity and GSK3 activity. *Springerplus* 3: 356, 2014.
123. Zhang P, Wang Y, Hui Y, Hu D, Wang H, Zhou J and Du H: Inhibition of VEGF expression by targeting HIF-1 α with small interference RNA in human RPE cells. *Ophthalmologica* 221: 411-417, 2007.
124. Zhang P, Zhang X, Hao X, Wang Y, Hui Y, Wang H, Hu D and Zhou J: Rac1 activates HIF-1 in retinal pigment epithelium cells under hypoxia. *Graefes Arch Clin Exp Ophthalmol* 247: 633-639, 2009.
125. Arjamaa O, Nikinmaa M, Salminen A and Kaarniranta K: Regulatory role of HIF-1 α in the pathogenesis of age-related macular degeneration (AMD). *Ageing Res Rev* 8: 349-358, 2009.
126. Koukourakis MI, Giatromanolaki A, Sivridis E, Gatter KC, Trarbach T, Folprecht G, Shi MM, Lebowitz D, Jalava T, Laurent D, *et al*: Prognostic and predictive role of lactate dehydrogenase 5 expression in colorectal cancer patients treated with PTK787/ZK 222584 (vatalanib) antiangiogenic therapy. *Clin Cancer Res* 17: 4892-4900, 2011.
127. Giatromanolaki A, Sivridis E, Gatter KC, Turley H, Harris AL and Koukourakis MI; Tumour and Angiogenesis Research Group: Lactate dehydrogenase 5 (LDH-5) expression in endometrial cancer relates to the activated VEGF/VEGFR2(KDR) pathway and prognosis. *Gynecol Oncol* 103: 912-918, 2006.
128. Kolev Y, Uetake H, Takagi Y and Sugihara K: Lactate dehydrogenase-5 (LDH-5) expression in human gastric cancer: Association with hypoxia-inducible factor (HIF-1 α) pathway, angiogenic factors production and poor prognosis. *Ann Surg Oncol* 15: 2336-2344, 2008.
129. Dhup S, Dadhich RK, Porporato PE and Sonveaux P: Multiple biological activities of lactic acid in cancer: Influences on tumor growth, angiogenesis and metastasis. *Curr Pharm Des* 18: 1319-1330, 2012.
130. Polet F and Feron O: Endothelial cell metabolism and tumour angiogenesis: Glucose and glutamine as essential fuels and lactate as the driving force. *J Intern Med* 273: 156-165, 2013.
131. San-Millán I and Brooks GA: Reexamining cancer metabolism: Lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. *Carcinogenesis* 38: 119-133, 2017.
132. Liu W, Zhai Y, Heng X, Che FY, Chen W, Sun D and Zhai G: Oral bioavailability of curcumin: problems and advancements. *J Drug Target* 24: 694-702, 2016.
133. Vallée A and Lecarpentier Y: Curcumin and endometriosis. *Int J Mol Sci* 21: 2440, 2020.
134. Kotha RR and Luthria DL: Curcumin: Biological, Pharmaceutical, Nutraceutical, and Analytical Aspects. *Molecules* 24: 2930, 2019.
135. Prasad S, Gupta SC, Tyagi AK and Aggarwal BB: Curcumin, a component of golden spice: From bedside to bench and back. *Biotechnol Adv* 32: 1053-1064, 2014.
136. Priyadarsini KI: The chemistry of curcumin: From extraction to therapeutic agent. *Molecules* 19: 20091-20112, 2014.
137. Zhang L, Zhu W, Yang C, Guo H, Yu A, Ji J, Gao Y, Sun M and Zhai G: A novel folate-modified self-microemulsifying drug delivery system of curcumin for colon targeting. *Int J Nanomedicine* 7: 151-162, 2012.
138. Shen L, Liu CC, An CY and Ji HF: How does curcumin work with poor bioavailability? Clues from experimental and theoretical studies. *Sci Rep* 6: 20872, 2016.
139. Sun M, Su X, Ding B, He X, Liu X, Yu A, Lou H and Zhai G: Advances in nanotechnology-based delivery systems for curcumin. *Nanomedicine (Lond)* 7: 1085-1100, 2012.
140. Naksuriya O, Okonogi S, Schiffelers RM and Hennink WE: Curcumin nanoformulations: A review of pharmaceutical properties and preclinical studies and clinical data related to cancer treatment. *Biomaterials* 35: 3365-3383, 2014.
141. Malam Y, Loizidou M and Seifalian AM: Liposomes and nanoparticles: Nanosized vehicles for drug delivery in cancer. *Trends Pharmacol Sci* 30: 592-599, 2009.
142. Lee WH, Loo CY, Young PM, Traini D, Mason RS and Rohanzadeh R: Recent advances in curcumin nanoformulation for cancer therapy. *Expert Opin Drug Deliv* 11: 1183-1201, 2014.
143. Hatefi A and Amsden B: Biodegradable injectable in situ forming drug delivery systems. *J Control Release* 80: 9-28, 2002.
144. Yallapu MM, Jaggi M and Chauhan SC: Beta-Cyclodextrin-curcumin self-assembly enhances curcumin delivery in prostate cancer cells. *Colloids Surf B Biointerfaces* 79: 113-125, 2010.
145. Radoska-Leśniewska DM, Osiecka-Iwan A, Hyc A, Gózdź A, Dąbrowska AM and Skopiński P: Therapeutic potential of curcumin in eye diseases. *Cent Eur J Immunol* 44: 181-189, 2019.
146. Zhu W, Wu Y, Meng YF, Wang JY, Xu M, Tao JJ and Lu J: Effect of curcumin on aging retinal pigment epithelial cells. *Drug Des Devel Ther* 9: 5337-5344, 2015.
147. Jiang X, Li S, Qiu X, Cong J, Zhou J and Miu W: Curcumin inhibits cell viability and increases apoptosis of SW620 human colon adenocarcinoma cells via the caudal type homeobox-2 (CDX2)/Wnt/ β -catenin pathway. *Med Sci Monit* 25: 7451-7458, 2019.
148. Howell JC, Chun E, Farrell AN, Hur EY, Caroti CM, Iuvone PM and Haque R: Global microRNA expression profiling: Curcumin (diferuloylmethane) alters oxidative stress-responsive microRNAs in human ARPE-19 cells. *Mol Vis* 19: 544-560, 2013.
149. Mandal MNA, Patlolla JMR, Zheng L, Agbaga MP, Tran JT, Wicker L, Kasus-Jacobi A, Elliott MH, Rao CV and Anderson RE: Curcumin protects retinal cells from light- and oxidant stress-induced cell death. *Free Radic Biol Med* 46: 672-679, 2009.
150. Muangnoi C, Sharif U, Ratnatilaka Na Bhuket P, Rojsitthisak P and Paraoan L: Protective effects of curcumin ester prodrug, curcumin diethyl disuccinate against H₂O₂-Induced oxidative stress in human retinal pigment epithelial cells: Potential therapeutic avenues for age-related macular degeneration. *Int J Mol Sci* 20: 3367, 2019.
151. Kim HJ, Park SY, Park OJ and Kim YM: Curcumin suppresses migration and proliferation of Hep3B hepatocarcinoma cells through inhibition of the Wnt signaling pathway. *Mol Med Rep* 8: 282-286, 2013.
152. Leow PC, Bahety P, Boon CP, Lee CY, Tan KL, Yang T and Ee PL: Functionalized curcumin analogs as potent modulators of the Wnt/ β -catenin signaling pathway. *Eur J Med Chem* 71: 67-80, 2014.
153. Kolb TM and Davis MA: The tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA) provokes a prolonged morphologic response and ERK activation in Tsc2-null renal tumor cells. *Toxicol Sci* 81: 233-242, 2004.
154. Balasubramanyam K, Varier RA, Altaf M, Swaminathan V, Siddappa NB, Ranga U and Kundu TK: Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. *J Biol Chem* 279: 51163-51171, 2004.

155. He M, Li Y, Zhang L, Li L, Shen Y, Lin L, Zheng W, Chen L, Bian X, Ng HK and Tang L: Curcumin suppresses cell proliferation through inhibition of the Wnt/ β -catenin signaling pathway in medulloblastoma. *Oncol Rep* 32: 173-180, 2014.
156. Menon VP and Sudheer AR: Antioxidant and anti-inflammatory properties of curcumin. *Adv Exp Med Biol* 595: 105-125, 2007.
157. Marchiani A, Rozzo C, Fadda A, Delogu G and Ruzza P: Curcumin and curcumin-like molecules: From spice to drugs. *Curr Med Chem* 21: 204-222, 2014.
158. Schneider C, Boeglin WE, Yin H, Stec DF and Voehler M: Convergent oxygenation of arachidonic acid by 5-lipoxygenase and cyclooxygenase-2. *J Am Chem Soc* 128: 720-721, 2006.
159. Giménez-Bastida JA, González-Sarriás A, Laparra-Llopis JM, Schneider C and Espín JC: Targeting mammalian 5-lipoxygenase by dietary phenolics as an anti-inflammatory mechanism: A systematic review. *Int J Mol Sci* 22: 7937, 2021.
160. Othman A, Ahmad S, Megyerdi S, Mussell R, Choksi K, Maddipati KR, Elmarakby A, Rizk N and Al-Shabraway M: 12/15-Lipoxygenase-derived lipid metabolites induce retinal endothelial cell barrier dysfunction: Contribution of NADPH oxidase. *PLoS One* 8: e57254, 2013.
161. Subramanian P, Mendez EF and Becerra SP: A novel inhibitor of 5-Lipoxygenase (5-LOX) prevents oxidative stress-induced cell death of retinal pigment epithelium (RPE) cells. *Invest Ophthalmol Vis Sci* 57: 4581-4588, 2016.
162. Yadav UCS and Ramana KV: Regulation of NF- κ B-induced inflammatory signaling by lipid peroxidation-derived aldehydes. *Oxid Med Cell Longev* 2013: 690545, 2013.
163. Ruan Y, Jiang S and Gericke A: Age-related macular degeneration: Role of oxidative stress and blood vessels. *Int J Mol Sci* 22: 1296, 2021.
164. Yabas M, Orhan C, Er B, Tuzcu M, Durmus AS, Ozercan IH, Sahin N, Bhanuse P, Morde AA, Padigaru M and Sahin K: A next generation formulation of curcumin ameliorates experimentally induced osteoarthritis in rats via regulation of inflammatory mediators. *Front Immunol* 12: 609629, 2021.
165. Li X, Lu Y, Jin Y, Son JK, Lee SH and Chang HW: Curcumin inhibits the activation of immunoglobulin e-mediated mast cells and passive systemic anaphylaxis in mice by reducing serum eicosanoid and histamine levels. *Biomol Ther (Seoul)* 22: 27-34, 2014.
166. Manjunatha H and Srinivasan K: Protective effect of dietary curcumin and capsaicin on induced oxidation of low-density lipoprotein, iron-induced hepatotoxicity and carrageenan-induced inflammation in experimental rats. *FEBS J* 273: 4528-4537, 2006.
167. Priyadarsini KI, Maity DK, Naik GH, Kumar MS, Unnikrishnan MK, Satav JG and Mohan H: Role of phenolic O-H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. *Free Radic Biol Med* 35: 475-484, 2003.
168. Piwocka K, Jaruga E, Skierski J, Gradzka I and Sikora E: Effect of glutathione depletion on caspase-3 independent apoptosis pathway induced by curcumin in Jurkat cells. *Free Radic Biol Med* 31: 670-678, 2001.
169. Motterlini R, Foresti R, Bassi R and Green CJ: Curcumin, an antioxidant and anti-inflammatory agent, induces heme oxygenase-1 and protects endothelial cells against oxidative stress. *Free Radic Biol Med* 28: 1303-1312, 2000.
170. Cao K, Dong YT, Xiang J, Xu Y, Hong W, Song H and Guan ZZ: Reduced expression of SIRT1 and SOD-1 and the correlation between these levels in various regions of the brains of patients with Alzheimer's disease. *J Clin Pathol* 71: 1090-1099, 2018.
171. Golestaneh N, Chu Y, Cheng SK, Cao H, Poliakov E and Berinstein DM: Repressed SIRT1/PGC-1 α pathway and mitochondrial disintegration in iPSC-derived RPE disease model of age-related macular degeneration. *J Transl Med* 14: 344, 2016.
172. Zuo L, Khan RS, Lee V, Dine K, Wu W and Shindler KS: SIRT1 promotes RGC survival and delays loss of function following optic nerve crush. *Invest Ophthalmol Vis Sci* 54: 5097-5102, 2013.
173. Li K, Zhai M, Jiang L, Song F, Zhang B, Li J, Li H, Li B, Xia L, Xu L, *et al*: Tetrahydrocurcumin ameliorates diabetic cardiomyopathy by attenuating high glucose-induced oxidative stress and fibrosis via activating the SIRT1 Pathway. *Oxid Med Cell Longev* 2019: 6746907, 2019.
174. Ghasemi F, Shafiee M, Banikazemi Z, Pourhanifeh MH, Khanbabaee H, Shamshirian A, Amiri Moghadam S, ArefNezhad R, Sahebkar A, Avan A and Mirzaei H: Curcumin inhibits NF- κ B and Wnt/ β -catenin pathways in cervical cancer cells. *Pathol Res Pract* 215: 152556, 2019.
175. Olivera A, Moore TW, Hu F, Brown AP, Sun A, Liotta DC, Snyder JP, Yoon Y, Shim H, Marcus AI, *et al*: Inhibition of the NF- κ B signaling pathway by the curcumin analog, 3,5-Bis(2-pyridinylmethylidene)-4-piperidone (EF31): Anti-inflammatory and anti-cancer properties. *Int Immunopharmacol* 12: 368-377, 2012.
176. da Cruz BO, Cardozo LFM de F, Magliano DC and Stockler-Pinto MB: Nutritional strategies to modulate inflammation pathways via regulation of peroxisome proliferator-activated receptor β / δ . *Nutr Rev* 78: 207-214, 2020.
177. Lin YG, Kunnumakkara AB, Nair A, Merritt WM, Han LY, Armaiz-Pena GN, Kamat AA, Spannuth WA, Gershenson DM, Lutgendorf SK, *et al*: Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor-kappaB pathway. *Clin Cancer Res* 13: 3423-3430, 2007.
178. Zhang ZB, Luo DD, Xie JH, Xian YF, Lai ZQ, Liu YH, Liu WH, Chen JN, Lai XP, Lin ZX and Su ZR: Curcumin's metabolites, tetrahydrocurcumin and octahydrocurcumin, possess superior anti-inflammatory effects in vivo through suppression of TAK1-NF- κ B pathway. *Front Pharmacol* 9: 1181, 2018.
179. Chen W, Chen Y and Cui G: Effects of TNF-alpha and curcumin on the expression of VEGF in Raji and U937 cells and on angiogenesis in ECV304 cells. *Chin Med J (Engl)* 118: 2052-2057, 2005.
180. Yoysungnoen P, Wirachwong P, Bhattarakosol P, Niimi H and Padumraj S: Effects of curcumin on tumor angiogenesis and biomarkers, COX-2 and VEGF, in hepatocellular carcinoma cell-implanted nude mice. *Clin Hemorheol Microcirc* 34: 109-115, 2006.
181. Li L, Braiteh FS and Kurzrock R: Liposome-encapsulated curcumin: In vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis. *Cancer* 104: 1322-1331, 2005.
182. Arbisser JL, Klauber N, Rohan R, van Leeuwen R, Huang MT, Fisher C, Flynn E and Byers HR: Curcumin is an in vivo inhibitor of angiogenesis. *Mol Med* 4: 376-383, 1998.
183. Gururaj AE, Belakavadi M, Venkatesh DA, Marmé D and Salimath BP: Molecular mechanisms of anti-angiogenic effect of curcumin. *Biochem Biophys Res Commun* 297: 934-942, 2002.
184. Zahra FT, Sajib MS and Mikelis CM: Role of bFGF in acquired resistance upon Anti-VEGF therapy in cancer. *Cancers (Basel)* 13: 1422, 2021.
185. Compagni A, Wilgenbus P, Impagnatiello MA, Cotten M and Christofori G: Fibroblast growth factors are required for efficient tumor angiogenesis. *Cancer Res* 60: 7163-7169, 2000.
186. Nissen LJ, Cao R, Hedlund EM, Wang Z, Zhao X, Wetterskog D, Funari K, Bråkenhielm E and Cao Y: Angiogenic factors FGF2 and PDGF-BB synergistically promote murine tumor neovascularization and metastasis. *J Clin Invest* 117: 2766-2777, 2007.
187. Casanovas O, Hicklin DJ, Bergers G and Hanahan D: Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell* 8: 299-309, 2005.
188. Choi HJ, Armaiz-Pena GN, Pradeep S, Cho MS, Coleman RL and Sood AK: Anti-vascular therapies in ovarian cancer: Moving beyond anti-VEGF approaches. *Cancer Metastasis Rev* 34: 19-40, 2015.
189. Aggarwal BB and Natarajan K: Tumor necrosis factors: Developments during the last decade. *Eur Cytokine Netw* 7: 93-124, 1996.
190. Li H, Soria C, Griscelli F, Opolon P, Soria J, Yeh P, Legrand C, Vannier JP, Belin D, Perricaudet M and Lu H: Amino-terminal fragment of urokinase inhibits tumor cell invasion in vitro and in vivo: Respective contribution of the urokinase plasminogen activator receptor-dependent or -independent pathway. *Hum Gene Ther* 16: 1157-1167, 2005.
191. Aggarwal BB, Kumar A and Bharti AC: Anticancer potential of curcumin: Preclinical and clinical studies. *Anticancer Res* 23: 363-398, 2003.
192. Wang LL, Sun Y, Huang K and Zheng L: Curcumin, a potential therapeutic candidate for retinal diseases. *Mol Nutr Food Res* 57: 1557-1568, 2013.
193. Pittalà V, Fidilio A, Lazzara F, Platania CBM, Salerno L, Foresti R, Drago F and Bucolo C: Effects of novel nitric oxide-releasing molecules against oxidative stress on retinal pigmented epithelial cells. *Oxid Med Cell Longev* 2017: 1420892, 2017.
194. Bucolo C, Drago F, Maisto R, Romano GL, D'Agata V, Maugeri G and Giunta S: Curcumin prevents high glucose damage in retinal pigment epithelial cells through ERK1/2-mediated activation of the Nrf2/HO-1 pathway. *J Cell Physiol* 234: 17295-17304, 2019.

195. Vyas A, Dandawate P, Padhye S, Ahmad A and Sarkar F: Perspectives on New Synthetic curcumin analogs and their potential anticancer properties. *Curr Pharm Des* 19: 2047-2069, 2013.
196. Muangnoi C, Ratnatilaka Na Bhuket P, Jithavech P, Supasena W, Paraoan L, Patumraj S and Rojsitthisak P: Curcumin diethyl disuccinate, a prodrug of curcumin, enhances anti-proliferative effect of curcumin against HepG2 cells via apoptosis induction. *Sci Rep* 9: 11718, 2019.
197. Otori H, Yamakoshi H, Tomizawa M, Shibuya M, Kakudo Y, Takahashi A, Takahashi S, Kato S, Suzuki T, Ishioka C, *et al*: Synthesis and biological analysis of new curcumin analogues bearing an enhanced potential for the medicinal treatment of cancer. *Mol Cancer Ther* 5: 2563-2571, 2006.
198. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R and Srinivas PS: Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med* 64: 353-356, 1998.
199. Sai N, Dong X, Huang P, You L, Yang C, Liu Y, Wang W, Wu H, Yu Y, Du Y, *et al*: A novel gel-forming solution based on PEG-DSPE/Solutol HS 15 Mixed Micelles and Gellan Gum for ophthalmic delivery of curcumin. *Molecules* 25: 81, 2019.
200. Zhang J, Sun H, Zhou N, Zhang B and Ma J: Preparation and evaluation of biodegradable scleral plug containing curcumin in rabbit eye. *Curr Eye Res* 42: 1597-1603, 2017.
201. Mazzolani F, Togni S, Giacomelli L, Eggenhoffner R and Franceschi F: Oral administration of a curcumin-phospholipid formulation (Meriva®) for treatment of chronic diabetic macular edema: A pilot study. *Eur Rev Med Pharmacol Sci* 22: 3617-3625, 2018.
202. Allegri P, Mastromarino A and Neri P: Management of chronic anterior uveitis relapses: Efficacy of oral phospholipidic curcumin treatment. Long-term follow-up. *Clin Ophthalmol* 4: 1201-1206, 2010.
203. Chen J and Smith LEH: Retinopathy of prematurity. *Angiogenesis* 10: 133-140, 2007.



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