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## Review Article

## Overview: Versatility of curcumin in management of diabetic retinopathy

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## ABSTRACT

**Introduction:** On a worldwide scale, the diabetic retinopathy (DR) is listing the primary causes of the loss of sight in the individuals. The main reason behind the occurrence of DR is diabetes mellitus (DM) and diabetic macular edema (DME). Diabetic retinopathy have some types of it i.e Non- proliferative diabetic retinopathy (NPDR) and Proliferative diabetic retinopathy (PDR). Where NPDR is an initial stage and PDR is the severe stage where the person loss the eye sight due to various factors which causes changes in the retinal micro vascularisation.

**Materials and Methods:** Use of Curcumin in Diabetic Retinopathy may help as a treatment and preventive action for all the stages of DR with its active constituent in various ways. We are focusing on some highlights of curcumin as an active drug to prevent and management of the DR.

**Results and Conclusions:** As the given review presenting the versatility of natural source of medicine like a curcumin can be the best choice of drug for diabetic retinopathy due to its various effects like protect the loss of retinal ganglionic cells, neuroprotective effect by inhibiting oxidative damage to microglia, also act as anti- inflammatory agent, anti VEGF agent, a recognized PPAR-gamma agonist. Hence, In future Curcumin can be preferably useful for management of all the stages involved in Diabetic Retinopathy.

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## 1. Introduction

Diabetic Retinopathy is currently the most popular microvascular consequence of diabetes, and it is still one of the leading causes of blindness in adults aged 20 to 74 worldwide. The two most prevalent visual outcomes of DR are proliferative DR (PDR) and diabetic macular edema (DME). Almost all individuals with Type 1 diabetes and more than 60–70 percent of those with Type 2 diabetes have some kind of retinopathy after 20 years.<sup>1</sup> It's been classified as a microvascular illness of the retina, and it's characterised by aberrant retinal vessel development that leads to

haemorrhages and tractional retinal detachment, resulting in visual loss.<sup>2,3</sup> Diabetic complications, in an additional factor to the core illness, are predicted to have far-reaching consequences for patient care in the future. Diabetes is a hyperglycemic condition, and DR is the outcome of the retina's microvascular deterioration over time. The WHO estimates that DR accounts for around 5% of all blindness worldwide. Aside from the fact that laser photocoagulation treatment has long been the standard of care, the use of intravitreal VEGF medicines and steroids has revolutionised diabetic macular oedema treatment in recent years.<sup>4,5</sup> Diabetic retinopathy (DR) is a metabolic disorder and a long-term inflammatory disease in which the retina's blood vessels and photoreceptors are destroyed. The vasculature

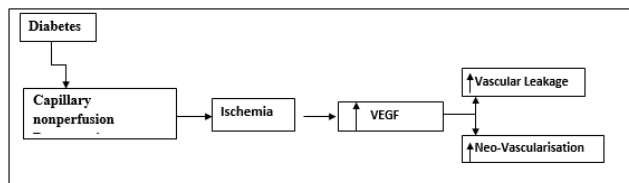
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displays indications of local hypertension in diabetes mellitus, including basement membrane thickening. This causes the pericytes' tight connections to be disrupted. It induces pericyte apoptosis and angiogenesis-promoting cellular mediators to be released.<sup>6</sup> Hyperglycemia also boosts free radicals and causes oxidative stress pathways, all of which contribute to the pathophysiology of DR.<sup>7</sup>

Proliferative DR (PDR) and Non-proliferative DR (NPDR) are the two levels of DR. Intra-retinal microvasculature abnormalities define NPDR, which can be further split to mild, moderate, and severe phases that correspond to long-term diabetic macular edema (DME). DME is caused by permeability and protein/fluid production in two disc thickness of the macular area, and it is one of the center reason of full vision emperiment in people with chronic hyperglycemia.<sup>8</sup> The most common symptoms of DR are ischemia, microaneurysms, haemorrhages, retinal edoema, neuronal degeneration, and neovascularization. Two separate DR phases can be identified based on neovascularisation. Figure 1.

NPDR is defined by blood flow changes, pericyte loss, and basement membrane thickening, whereas PDR is defined by sight-threatening neovascularization.<sup>9</sup>



**Fig. 1:** Stages in occurrence of diabetic retinopathy

### 1.1. Pathophysiology

The retina is made up of many cells, and good vision is dependent on healthy cell-to-cell connection. Diabetes affects almost all of the retina's main cells, as well as neurons (bipolar, photoreceptors, amacrine, horizontal and ganglions) and vascular cells (endothelial cells and pericytes).<sup>10</sup>

These cells are get in an action before they are damaged, which alters the production pattern of a variety of mediators such as vasoactive agents, adhesion molecules growth factors, coagulation factors and resulting in increased blood flow, induced capillary permeability, extracellular matrix proliferation, abnormal cell turnover (apoptosis, proliferation), and swelling of procoagulant basal membranes and proaggregant patterns, and at the end angiogenesis.<sup>11,12</sup>

Hyperglycemia leads to microvascular alterations that lead to retinopathy. The process causing retinopathy has been linked to at least four different metabolic pathways Examples include increased protein kinase C (PKC) isoform

activation, polyol pathway flux, glycation product (AGE) synthesis, and elevation of hexosamine pathway flux. When these processes interact, they induce oxidative stress and inflammation, compromising vascular wall integrity and leading to increased vascular permeability, obstruction, and ischemia.<sup>3</sup>

The change in the BRB is a characteristic of diabetic retinopathy aetiology. At the retinal capillary level, the BRB is made up of endothelial cell–cell contacts, the pericytes, and basal membrane that cover the capillaries on the exterior. In diabetes, the BRB experiences three changes: I, endothelial cell–cell connections are broken, II. the basement membrane thickens, and III. pericytes are selectively lost. When the BRB breaks, it causes hard exudates, intra retinal haemorrhages, and macular oedema.<sup>4</sup>

One of the first histopathological abnormalities found in diabetic retinopathy is selective pericyte loss. Pericyte loss causes localised capillary wall weakening also unrestrained focal endothelial cell growth, which leads to microaneurysm development.<sup>1</sup> Endothelial cells die later, resulting in acellular capillaries and retinal non-perfusion. Both of these cell types die as a result of apoptotic, or programmed cell death, in diabetes. Apoptosis-induced neuronal death may happen in the ganglia cells layer before vascular damage.<sup>4</sup>

## 2. Vegf in Diabetic Retinopathy

VEGF is one of six known members of the angiogenic growth factor family, which includes VEGF-A (often known as just VEGF), foetal growth factor, VEGFB, and others.<sup>11</sup> VEGF-C, VEGF-D, and VEGF-E are three types of VEGF. The first and most important is VEGF-A. Angiogenesis is a prominent kind of type. It raises the rate of growth. Endothelial cells go through mitosis and migrate, and they are engaged in regulation of integrin v3 as well as blood vessel formation. Fenestrations and lumen Furthermore, it is chemotactic for NO, which is produced by macrophages and granulocytes and leads to the formation of macrophages and granulocytes.<sup>13</sup> Vasodilation occurs as a result of the release. VEGF-B has a role in embryonic development. Angiogenesis is a process that occurs in myocardial tissue. VEGF-C is a kind of growth factor. VEGF-D, a key prolymphangiogenesis factor, is required. for bronchiolar lymphatic vasculature development. Viruses include VEGF-E. PlGF has a role in vasculogenesis.<sup>3</sup>

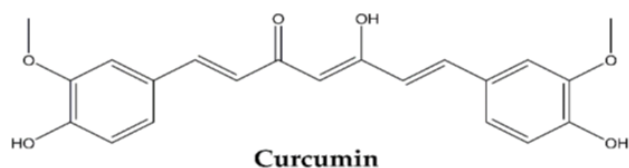
VEGF comes in a variety of forms, some of which are more harmful than others. In the clear and a vascular adult mouse cornea, two main VEGF isoform splicing variants, VEGF120 (121) and VEGF164 (165), were studied. In comparison to VEGF120, VEGF164 (165) was shown to be so effective in increasing ICAM-1 activation on endothelial cells, increasing corneal inflammation, and inducing monocytic chemotaxis. VEGF164 (165) was found to be more successful in generating corneal inflammation, neovascularization, and angiogenesis than the other two

main VEGF isoforms.<sup>14</sup> Aiello and Cavallerano performed a study in 1994 that people with PDR had a high stage of vitreal VEGF and that laser photocoagulation treatment lowers these levels dramatically.<sup>3</sup> Robinson et al. Published a paper shortly after that demonstrated that inhibiting VEGF prevented the proliferative retinopathy development in mice.<sup>15</sup> Furthermore, Tolentino et al. Delivered injections of intravitreal VEGF and showed the potential to produce iris vascularization and retinopathy in non-human primates, exhibiting the opposite effect.<sup>3</sup>

These positive lab results inspired efforts to develop a VEGF-targeted medicinal approach for the therapy of PDR. VEGF promotes retinal blood vessels production of ICAM-1 in vivo, according to Lu et al., and later investigations have shown that VEGF is critical for monocyte chemotaxis.<sup>16</sup> recognising that the biology of DR may be interpreted in terms of a leukocytic influx and an inflammatory condition. Inhibiting VEGF downregulates counts of retinal leukocyte in experimental diabetes and enhances ICAM-1 expression and diabetic retinal leukocyte stickiness in vivo, according to jousen et al.<sup>17</sup>

### 3. Introduction to Curcumin

Curcumin is a polyphenolic chemical found in the *Curcuma longa* L. plant. It's a part of the Zingiberaceae family.<sup>18</sup> For millennia, a type of curcumin-based items (such as capsules, energy drinks, pills, cosmetics, ointments, and soaps) have been used as medications or spices in China, the United States, India, and South Africa.<sup>6</sup> The rhizomes of *Curcuma longa* are the most valuable portion of the plant. In fact, after boiling and drying under the sunrays, the rhizomes are crushed to form a yellow-orange powder with curcumin as its biological active component.<sup>19</sup> Curcuminoids such as curcumin, monodemethoxycurcumin, and bis-demethoxycurcumin, as well as sesquiterpenoids such as curcumenes and turmerones, are found in it.<sup>20</sup>



Curcumin, also known as diferuloylmethane, is a bis-unsaturated-diketone with the chemical formula 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione.<sup>18</sup>

Curcumin may be found in two different tautomeric forms: keto-enol and di-keto. If there is curcumin in polar organic solvents, the keto-enol tautomer is the most common. It has the chemical formula C<sub>21</sub>H<sub>20</sub>O<sub>6</sub> (MW

of 368.38 gram per mol) and a melting point of 183 °C. It appears solid at room temperature.<sup>19</sup> Curcumin, in addition to being well-known as a spice, has a number of medicinal properties. It can, for example, prevent ovarian, prostate, breast, and stomach cancers as an anticancer agent. Curcumin also has anti-inflammatory properties and can be utilised to treat COPD, hepatic inflammation, and even acute vascular inflammation. Curcumin has been reported to have renoprotective properties as a natural antioxidant.<sup>21</sup> Curcumin's pharmacological actions are related to the fact that it targets several pathways, intracellular components, and important enzymes.<sup>22</sup>

Transcription factors (e.g., nuclear factor [NF]-κB, activator protein [AP]-1, the earliest developmental response gene [Egr]-1, NF-E2-related factor [Nrf2] and -catenin), vascular epithelial growth factor (e.g. phosphorylase kinase [PhK], PKC and protamine kinase), growth regulators and their integrins (e.g., transforming growth factor [TGF]-, transcription factors coactivators (e.g., p300), connective tissue growth factor [CTGF]).<sup>23–25</sup>

Curcumin was poorly soluble in water and decomposed into many compounds under physiological circumstances, raising issues regarding the bioactive form responsible for its activities. Turmeric extract, turmeric, curcumin-rich *curcuma longa* extract, curcumin-enriched materials, and curcumin were all beneficial.<sup>20</sup> A curcuminoid-enriched turmeric extract contained purcuminoids (purified demethoxycurcumin, bisdemethoxycurcumin), purcumin (purified curcumin), hydrophilic metabolites. and lipophilic metabolites.<sup>19</sup> Concerns was raised about the purity of the chemical utilised in clinical studies. Another problem was the necessity of high doses of this chemical (> 3.6 gm per day in people) to produce therapeutical results.<sup>26</sup>

#### 3.1. Curcumin in DR

Inflammation, oxidative stress-mediated response, and angiogenesis have all been linked to pathologic pathways implicated in retinal disorders. Curcumin in the diet and curcumin-based medications have been shown to have therapeutic promise in the prevention of vision-threatening retinal disorders.<sup>23</sup> Curcumin may not only lower oxidative stress, but it may also block the buildup of nitrotyrosine in the retina, effectively minimising retinal damage caused by nitrotyrosine accumulation.<sup>21</sup>

Curcumin inhibited the degradation of cellular organelles and enhanced the thickening of the retina's capillary basement membrane. Curcumin works by downregulating the pro-angiogenic vascular endothelial growth factor (VEGF), downregulating TNF-, and upregulate the antioxidant enzymes SOD and catalase. During the course of DR, extracellular matrix synthesis diminishes as cells get damaged by retinopathy.<sup>6</sup> In one experiment, they noticed a decrease in oxidative stress and curcumin's capacity to preserve the secretary function of alpha-

crystallin in streptozotocin-induced diabetic rats. Under hyperglycemic circumstances, curcumin can also suppress VEGF expression in the retina.<sup>19</sup> Figure 2

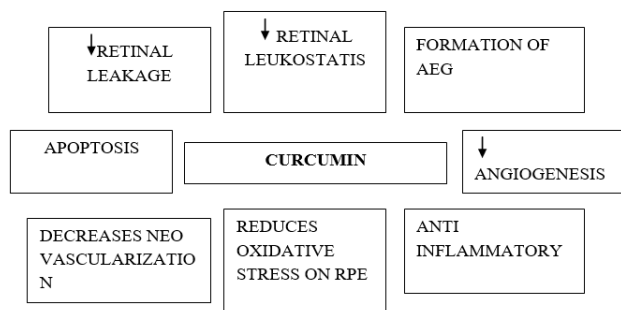


Fig. 2: Effects of curcumin

#### 4. Protective Effects of Curcumin in DR

##### 4.1. Anti-inflammatory

Inflammation performs a lead reason in the onset and progression of DR. Some studies have found that the occurrence of DR is similar to chronic inflammation, and that the amount of proinflammatory cytokines increases in diabetic humans and animals' retinas and vitreous.<sup>8</sup> Leukostasis is a prominent factor in inflammatory processes that has been recorded to be greatly elevated in diabetic animals' retinas, suggesting that it may contribute to capillary non-perfusion in DR.<sup>1</sup> Curcumin inhibits PGE2 synthase 1 as well as cyclooxygenase-2 (COX-2) which produces 5-lipoxygenase and prostaglandin E2 (PGE2), which is stimulated by inflammation (5-LOX).<sup>19</sup> Curcumin inhibits both pro-inflammatory cytokines and oxidative stress, which may help to prevent diabetic retinopathy.<sup>26</sup>

Curcumin also reduces IB gene expression and modifies the expression like nuclear factor-B (NF-B) and Activator protein-1 (AP-1). The last two genes are transcriptional factors. That regulate a variety of biological functions AP-1 promotes cell proliferation whereas NF-B promotes inflammation, immunological activity, and cell proliferation. The activation of lipoxygenase (5-LOX), cyclooxygenase-2 (COX-2) and xanthine oxidase by NF-B promotes inflammation.<sup>19</sup> The decreased expression of NF-B, another significant feature of curcumin that contributes to its anti-inflammatory actions, is expected to suppress COX-2.<sup>26</sup>

##### 4.2. Anti-angiogenic

Angiogenesis can be increased by pro-inflammatory substances stimulating the VEGF signalling pathway among inflammatory cells and VE cells in a dose dependent form. Curcumin not only suppresses aberrant angiogenesis directly,<sup>21</sup> it also inhibits it indirectly. Curcumin stops

the angiogenesis in the choroidal vasculature of the rat retina, according to a research. Curcumin improves the tortuosity, shrinkage, narrowing, and micro-aneurysms of diabetic microvasculature. Curcumin therapy causes regeneration and repair mechanisms in the choroidal microvasculature.<sup>6</sup> Curcumin also inhibits angiogenesis indirectly by modulating cell adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), leukocyte stucked molecule-1 (LAM-1) (ELAM-1) and endothelial vascular cell adhesion molecule-1 (VCAM-1).<sup>19</sup>

Curcumin can also inhibit metalloproteinases (MMPs), the plasminogen activator system urokinase (uPA) and the serine protease family. Curcumin inhibits endothelial cell migration as well as the synthesis of tgf (TGF), TNF, VEGF, and hepatocyte inducer factor (HGF) due to its unique property. Finally, many of the characteristics highlighted here indicate that curcumin possibly advantageous in a range of angiogenesis-related disorders, such as eye diseases.<sup>19</sup>

#### 5. Anti-Hyperglycemic and Anti-Hyperlipidemic

Hyperglycemia has unavoidably been identified as the primary aetiology of DR. Oxidative stress is linked to hyperglycemia-induced metabolic pathways in DR.<sup>21</sup> Hyperglycemia stimulates endothelial proliferation, neovascularization and apoptosis by regulating the activity of vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1) and transforming growth factor (TGF-1). Also ROS stimulates the hexosamine pathway by inhibiting glyceraldehyde-3-phosphate dehydrogenase (GAPDH), resulting in the stimulation of the AGE pathway and subsequent damage. ROS initiates mitochondrial malfunction, results in superoxide generation and free radical damage, as well as mutations in mitochondrial DNA, which results in mitochondrial DNA damage in diabetic retinal part.<sup>18</sup>

Under hyperglycemic circumstances, curcumin can also suppress expression levels in the retina. After curcumin therapy, Khimmaktong et al. Studied stages of retinal regeneration. And documented a normalisation of diabetic microvasculature, with narrowing, and micro-aneurysms, reduced tortuosity. Curcumin may modulate the PI3K/ROS/mTOR/AKT signalling pathway to reduce high glucose-induced inflammatory damage in RPEC.<sup>19</sup> Triglyceride levels are linked to the occurrence and severe condition of DR, and long-term cholesterol reduction medication can help people with DR glucose levels avoid laser therapy. De Melo et al. performed a double-blind, randomised, placebo-controlled, study to see if those over the age of 18 should take curcumin or a placebo. They discovered that, when compared to the placebo, during a four-week follow-up, curcumin supplementation lowered fasting blood glucose concentrations in those with a particular level of blood glucose abnormalities but not in people who were

not diabetic. Curcumin and its substituted derivatives have been reported to considerably lower blood glucose and glycosylated haemoglobin levels, increase cell function, prevent cell lysis, reduce insulin resistance, and postpone the onset and development of diabetes in mice and rats.<sup>21</sup>

## 6. Conclusion

Regardless of the fact that the prevalence of DR continues to rise, new therapy options, particularly VEGF-targeting medicines, have considerably improved management of DME and PDR outcomes in the last decade. Nonetheless, there is a compelling need for effective novel and non-invasive therapies for all stages of DR, which drives ongoing research into the various ways in which diabetes affects the retina. As the Curcumin plays an important part in the various ways by being a traditional medicine from ancient times, it can be useful to prevent and treat all the stages of DR as it offers neuroprotective effect by inhibiting oxidative damage to microglia, protect the loss of retinal ganglionic cells, also act as anti-inflammatory agent, anti VEGF agent, a recognized PPAR-gamma agonist. The curcumin can be the first choice to treat DR and other eye diseases for many other reasons as well, like its harmless nature, low cost, and effectiveness for the protection and treatment of a variety of eye problems, such as glaucoma, dry eye, and conjunctivitis, etc.

## 7. Source of Funding

None.

## 8. Conflict of Interest

None.

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