

Review Article

Therapeutic implications of curcumin in the prevention of diabetic retinopathy via modulation of anti-oxidant activity and genetic pathways

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Abstract: Diabetic Retinopathy (DR) is one of the most common complications of diabetes mellitus that affects the blood vessels of the retina, leading to blindness. The current approach of treatment based on anti-inflammatory, anti-angiogenesis drugs and laser photocoagulation are effective but also shows adverse affect in retinal tissues and that can even worsen the visual abilities. Thus, a safe and effective mode of treatment is needed to control or delaying the DR. Based on the earlier evidence of the potentiality of natural products as anti-oxidants, anti-diabetic and antitumor, medicinal plants may constitute a good therapeutic approach in the prevention of DR. Curcumin, constituents of dietary spice turmeric, has been observed to have therapeutic potential in the inhibition or slow down progression of DR. In this review, we summarize the therapeutic potentiality of curcumin in the delaying the DR through antioxidant, anti-inflammatory, inhibition of Vascular Endothelial Growth and nuclear transcription factors. The strength of involvement of curcumin in the modulation of genes action creates a strong optimism towards novel therapeutic strategy of diabetic retinopathy and important mainstay in the management of diabetes and its complications DR.

Keywords: Medicinal plants, curcumin, VEGF and diabetic retinopathy

Introduction

Diabetes mellitus is a major public health concern worldwide, where treatment would cost around 34 billion Dollars per year [1-3]. The exact mechanism of the development and progression of Diabetes and consequently DR is not well known. But it is thought that genetic and metabolic alterations play a significant role in the development and progression of diabetes and its complications. Diabetic Retinopathy (DR) is a complication of diabetes mellitus that affects the blood vessels of the retina, leading to blindness [4, 5]. The current mode of treatment of DR is based on the control of oxidative stress; neural and vascular risk factors and laser photocoagulation [6, 7] are effective but also exhibits adverse side effects. Therefore, safe and sound mode of management is needed to control the development and progression

of DR. Based on the evidence during last two decades of medicinal plants in various diseases, naturally occurring antioxidants, anti-tumour, anti-diabetic activities in medicinal plants may constitute a good therapeutic approach in the prevention of various diseases [8-10]. The use of medicinal plants and its products has been discussed in modern scientific literatures, Ayurveda, Unani medicine as well as in religious books.

The Holy Prophet Mohammed (Peace Be Upon Him) used various plants and recommended various medicinal plants for cure of numerous diseases [11, 12]. The constituent of turmeric, Curcumin is derived from the rhizome of the Indian plant *Curcuma longa* and shows a vital role in disease control. Earlier studies reported that curcumin as anti-protozoal, anti-bacterial, anti-oxidant, anti-tumour and anti-diabetic [13-

Curcumin in the prevention of diabetic retinopathy



Figure 1. Turmeric plant.

17] and play a significant role in the delaying or inhibition of various diseases. Turmeric and its constituents are good substitute in the prevention or slow down the development of diabetes and Diabetic Retinopathy and also they are inexpensive, safe and easy to access. In this review, we sum up the understanding of effect of curcumin in the prevention or slow down the Diabetic Retinopathy through the regulation of gene action and other factors.

Botanical information of turmeric plant

Family: Zingiberaceae; Genus: *Curcuma*; Most common species: *Curcuma longa*; Number of *Curcuma* Species: more than sixty; Part used: Rhizome (Root); Origin: South Asia; mainly China and India.

Composition, structure and function of turmeric and their constituents

Turmeric is a spice that is often used as food flavoring in Asian dishes (**Figure 1**). It belongs to the ginger family. Earlier investigators have shown that turmeric and their constituents play a vital role in the prevention of various types of diseases. Turmeric contains curcuminoids, which includes curcumin (**Figure 2**), demethoxycurcumin and bisdemethoxycurcumin. Curcumin play a vital effect in prevention of diseases and has been proved as anti-oxidant [18, 19].

All constituents of turmeric including curcumin play an important effect in the prevention of

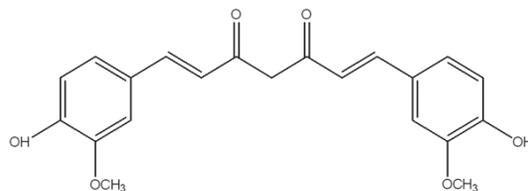


Figure 2. Chemical structure of curcumin.

various types of diseases including Diabetic Retinopathy [20-25]. Mainly two types of compound have been identified in turmeric as phenolic compounds and terpenoids. Terpenoids, a subclass of the prenyllipids synthesized by plants such as turmeric and are the most used group of natural products. The terpenoids, is component found in turmeric and has shown anti-bacterial role in earlier study [26].

The exact mechanism of action of terpenoids in the regulation of DR is not completely known but it might be has significant role in activation and inhibition of gene action. An experimental study in animal model showed that constituents of turmeric such as curcuminoids and sesquiterpenoids acts as hypoglycemic through the activation of peroxisome proliferators-activated receptor- γ (PPAR- γ) and also suppression of high blood glucose levels [27, 28]. Curcumin is a phenolic compound of turmeric that plays a vital role in regulation of oxidative stress and gene action [29-32]. The constituents of turmeric play vital role in the prevention of DR through activation and inactivation of genetic pathways (**Figure 3**).

Effect of curcumin in the prevention or slow-down of diabetic retinopathy

Diabetic Retinopathy (DR) is a complication of diabetes mellitus that affects the blood vessels of the retina [4, 5]. The exact causes of the development and progression of DR is not fully known. But it is thought that various factor such as oxidative stress, genetic and metabolic alterations involve in the development and progression of diabetes and its complication DR. The current approach based on allopath treatment as anti-inflammatory and anti-angiogenesis drugs are expensive and also show an adverse side effect in the retinal tissues. Natural products in the form of turmeric and its constituents curcumin play an important role in the prevention of DR.

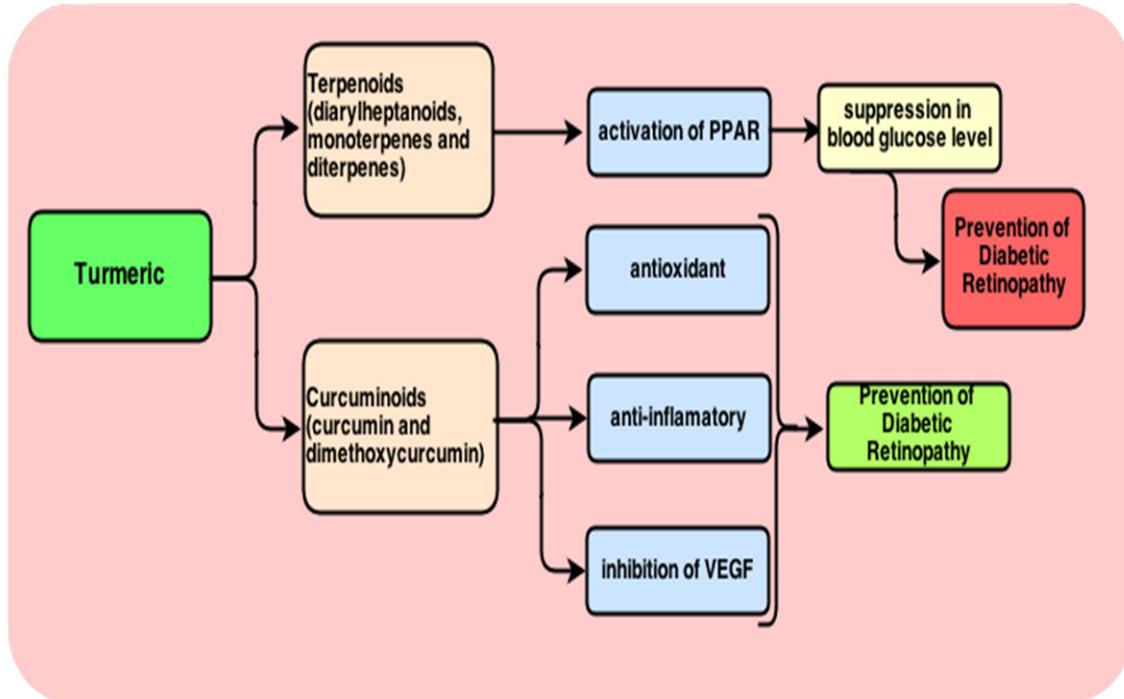


Figure 3. Turmeric and their constituents play a vital role in the management of Diabetic Retinopathy.

Antioxidant activity of curcumin

Antioxidants are also known as free radical scavengers. In our body free radical production is balanced by the antioxidative defence system [33] and imbalance between reactive oxygen species (ROS) generation and its neutralization by antioxidant defences [34, 35] creates oxidative stress.

The high oxidative stress [36-39] and reactive oxygen species (ROS) shows an important link between high glucose and the metabolic abnormalities and finally involve in the development of diabetic complications [40]. High glucose concentrations play an important effect in free-radical production via advanced glycation end products (AGEs) [41], protein kinase C activation [42], and aldose reductase pathway [43].

The prevention of activities of free radical is important step in the management of disease. Medicinal plants and their constituents play a vital and significant action in neutralize or inhibit the free radical through antioxidant activity. The phytochemicals shows effect as antioxidants by scavenging free radicals, and many have therapeutic potential for free radical asso-

ciated disorders [44, 45]. Curcumin, chief constituents of turmeric play significant role in diseases prevention through the antioxidant activities. An experiment based on diabetes induced animal model showed that curcumin plays a significant effect to rescue the retinal glutathione levels, important determinant of redox signaling [46].

Earlier reports have also shown that Diabetic-induced oxidative stress shows a role in the activation of transcription factor, NF- κ B in the retina [47-49]. Also turmeric and its constituents curcumin play a vital role in the prevention of diabetes-induced decrease in the total antioxidant capacity of the retina [50, 51]. Moreover, curcumin inhibits the activation of NF- κ B, accumulation of 8-OHdG and nitrotyrosine in the retina in diabetes [52]. A recent experimental study has shown that retinal glutathione levels and antioxidant enzymes such as superoxide dismutase and catalase were significantly decrease in the diabetic group; on the other hand, curcumin positively modulated the antioxidant system [52]. The curcumin with dose (1 g/kg body weight) significantly increases the endogenous glutathione levels and the activities of superoxide dismutase and catalase [52].

Anti-inflammatory effect of curcumin

Inflammation is one of the important physiologic defence mechanisms against various factors such as infection, burn, toxic chemicals, allergens and other stimuli [53]. The uncontrolled inflammation plays an important role in various types of chronic illnesses [54].

The current treatment based on anti-inflammatory drugs are effective and give immediate response but these drugs have adverse side effect. However, safe and effective natural product is needed to control the inflammatory activity.

Earlier studies have shown that turmeric and their constituents play a significant effect in the control of various diseases via anti-inflammatory action. An important findings regarding turmeric effect have shown that inflammatory biomarkers such as 5-hydroxy-eicosatetraenoic acid (5-HETE), cyclooxygenase (COX), and lipoxygenase (LOX) are targeted by curcumin and curcumin's anti-inflammatory activities also showed the inhibition of arachidonic acid metabolism [55, 56].

Transcription factors nuclear factor- κ B (NF- κ B) shows a vital role in regulation of expression of genes [57, 58]. Suppression of NF- κ B activation shows a role in the down-regulation of COX-2 and iNOS expression, inhibiting the inflammatory process and tumorigenesis [59, 60]. Curcumin have potential benefits in inhibiting the development of Diabetic Retinopathy [51]. Furthermore, curcumin also showed vital effect in both oxidative changes as well as tumor necrosis factor (TNF)- α inhibition in the retina of hyperglycemic rats [51, 52]. Another study in the support of curcumin effect have shown that dietary supplementation of curcumin significantly inhibits cytokines, such as interleukin 1beta, tumor necrosis factor alpha, VEGF and the diabetes-induced activation of NF- κ B in the retinas of STZ-induced diabetic rats [51, 52].

Effect of curcumin on angiogenesis

Angiogenesis process is highly regulated process; angiogenic factors such as vascular endothelial growth factor (VEGF) which act as stimulators, angiostatin and pigment epithelium-derived factor (PEDF) which act as angiogenic inhibitors [61-64]. VEGF is important

angiogenic factor in the development and progression of various types of diseases and play a vital role in the development of Diabetic Retinopathy (**Figure 4**). The present treatment based on anti-angiogenic factor is effective but also shows side effect. Therefore, a safe and effective drug is required to control the DR. Curcumin, is a safe and inexpensive substitute in the management of Diabetic Retinopathy via anti-angiogenic effect. A study reported that curcumin inhibits the increased VEGF levels in the retina and abolish IL-18 induced increase in VEGF production [51]. Another study in animal model showed that VEGF expression was high in diabetic retina when compared to control retina at both transcript and protein level whereas curcumin treated group showed a significant inhibition of the expression of VEGF in diabetic retina [65].

Earlier report in vitro showed that curcumin shows a vital effect in the induction of apoptosis in human retinal endothelial cells and decrease VEGF release [51]. Curcumin has shown effect in the inhibition of PKC β II translocation induced by VEGF in HRECs and PKC activation also up regulate VEGF expression [66].

Important recent study based on clinical trial has shown that anti-VEGF agents are efficient in the treatment of DR [67, 68].

Stromal cell-derived factor 1 (SDF-1) is an important factor in angiogenesis and high level of SDF-1 has been noticed in diabetic subjects with proliferative Diabetic Retinopathy (PDR) [69, 70]. Curcumin showed a significant effect in decrease the stromal cell-derived factor-1 induced migration of human retinal endothelial cells (HRECs) [71].

Effect of curcumin on the transcription factor EGR-1

EGR-1 is transcription factor and encodes a nuclear phosphoprotein involved in the various processes in response to signals [72-75]. EGR-1 role has been observed in tumour, diabetes and other disease. The regulation or suppression of EGR1 is critical step in the control of diseases. An important study showed that curcumin inhibit the EGR1 and EGR1 mediated gene expression in endothelial cells and fibroblast cells [76]. Another finding in support of curcumin effect has shown that Curcumin

Curcumin in the prevention of diabetic retinopathy

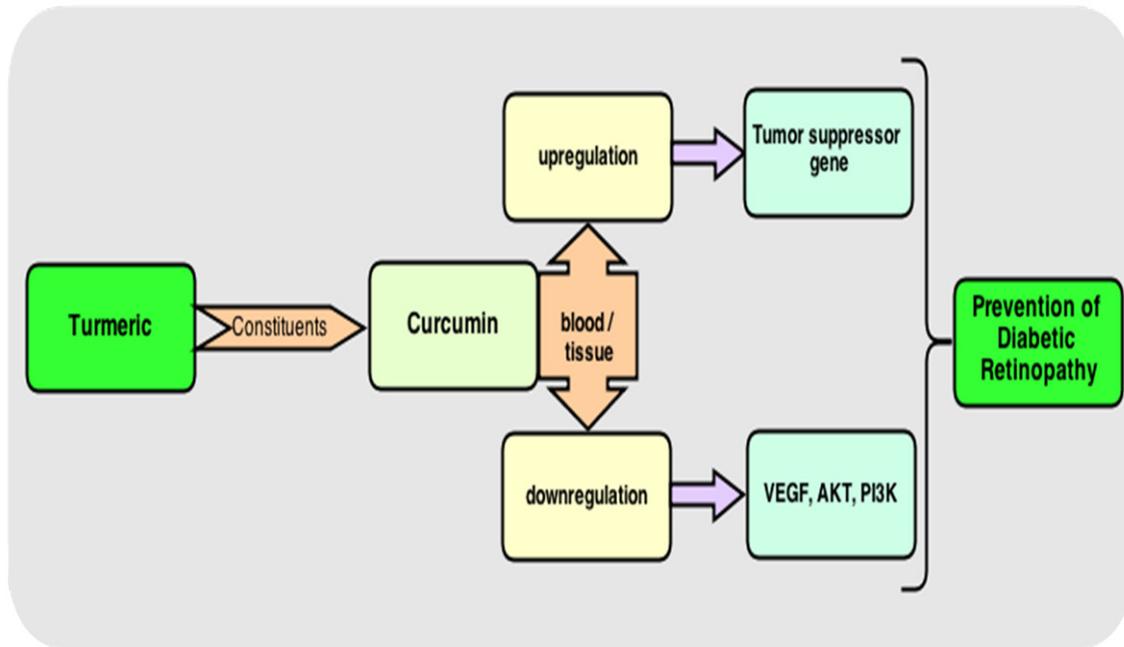


Figure 4. Turmeric and its constituents shows a significant effect in the control of Diabetic Retinopathy via inhibition of VEGF action.

down-regulated the expression EGR1 and Icam1 in 661W cells and EGR1 in rat retina with light-damage [77].

Some other genes alteration such as PPAR- γ and histone acetylation has been noticed in the development of diabetes and DR.

A report in the support of curcumin effect has shown that oral administration of curcumin with dose 0.05% w/w in diets for 9 weeks inhibited the diabetes-induced increase in acetylated histones in the retinas [78]. Curcumin suppress blood glucose levels, increase the antioxidant status of pancreatic β -cells, and enhance the activation of PPAR- γ [27].

The study based on clinical trials showed that the effect of curcumin in the control of various types of diseases including DR [79-83]. Numerous clinical trial based study has been completed and several study are in the process to evaluate the effect of curcumin in the management of cancer, diabetes and other diseases. A study based on curcumin has shown Curcumin showed a vital role in the general health improvement of colorectal cancer via the mechanism of increased p53 expression in tumor cells [79].

Several reports has shown the effect of curcumin in treatment of eye related diseases or evaluated the efficacy of curcumin in treatment of eye diseases [84-86]. Based on clinical trial study on the effectiveness of curcumin, curcumin is safe remedy in the treatment of eye related diseases.

Conclusions

Safe, effective and inexpensive treatment is needed to control development and progression of DR. The genetic alterations are a major culprit in the development of diabetes and its complication DR. The turmeric and its constituents act as molecular targets and it has proved therapeutic potential in DR prevention. The strength of involvement of curcumin in the control of genes action creates a strong optimism towards the novel therapeutic strategy of diabetic retinopathy. The features of being no side effect, affordable and easy to access, turmeric and its constituents curcumin, is the mainstay in the control of Diabetic Retinopathy.

Disclosure of conflict of interest

The authors have no conflict of interests to disclose.

Curcumin in the prevention of diabetic retinopathy

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Curcumin in the prevention of diabetic retinopathy

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Curcumin in the prevention of diabetic retinopathy

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