# Effect of Curcumin on VEGF Expression and Cell Migration in Human Pterygium Fibroblast

**Dinda Zhafira[1,2], Yulia Primitasari[1,2], Delfitri Lutfi[1,2], Evelyn Komaratih[1,2], Luki Indriaswati[1,2], Chrismawan Ardianto[3]**

[1]Department of Ophthalmology, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia
[2]Department of Ophthalmology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[3]Faculty of Pharmacy Universitas Airlangga, Surabaya, Indonesia
Email: yulia-p@fk.unair.ac.id

**KEYWORDS**
*Curcumin, VEGF, Cell Migration, Pterygium, Non-Communicable Disease.*

**ABSTRACT**
This review investigates the effects of curcumin, a polyphenol derived from turmeric, on vascular endothelial growth factor (VEGF) expression and cell migration in human pterygium fibroblasts (HPFs). Pterygium, a degenerative and inflammatory condition of the ocular surface, is characterized by excessive fibrovascular growth often linked to UV radiation exposure. The study highlights curcumin's anti-inflammatory, anti-angiogenic, and antioxidant properties, demonstrating its ability to significantly reduce VEGF expression and inhibit cell migration in HPFs. The findings suggest that curcumin may serve as a novel adjuvant therapy to decrease pterygium recurrence by targeting key pathways involved in its pathogenesis, thus offering a promising alternative to traditional surgical interventions.

## INTRODUCTION

Pterygium is a degenerative and inflammatory condition of the ocular surface characterized by the growth of triangular-shaped fibrous tissue from the conjunctiva onto the cornea. While it occurs worldwide, it is usually found in warm and dry climates. Its prevalence can reach up to 22% in equatorial regions and less than 2% in areas above 40 degrees latitude [1, 2]. The condition is believed to result from microtrauma to the cornea and conjunctiva caused by exposure to sunlight and dust. Studies in Nigeria, South India, and Southwest China indicate that outdoor workers are more frequently affected than those who work indoors [3, 4]. Although its exact cause remains unclear, research shows that pterygium consists of proliferation from fibrovascular tissue and is highly associated with ultraviolet (UV) radiation exposure [5, 6, 7]. Other contributing factors may include inflammation, fibrovascular growth, and genetic predisposition. DNA damage has also been implicated in its development, as UV radiation is known to activate growth factors, inflammatory cells, and pro-inflammatory cytokines, potentially causing DNA damage in susceptible individuals. Despite this, there is no comprehensive understanding of the interplay between these factors in pterygium formation [8] [9, 10].

Additionally, there is evidence that pterygium has elevated expression of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) [11]. As a result, these growth factors might either directly or indirectly contribute to pterygium pathogenesis. Compared to normal fibroblasts, pterygium fibroblasts are tumor-like altered cells that grow faster in medium with low serum concentrations [12]. The first-choice therapy for pterygium is surgical excision; nevertheless, patients are burdened by the high recurrence rate [13, 14]. As a result, pterygium therapy is still highly debatable. There is an urgent need to find effective medications to treat pterygium.

The main curcuminoid in the well-known spice turmeric is curcumin, a yellow-colored polyphenol that is extracted from the plant Curcuma longa [15]. The, anti-angiogenic, anti-inflammatory, wound-healing, and antioxidant properties of curcumin have been extensively researched [16, 17]. Curcumin, both in vitro and in vivo has shown antitumor effects that are mediated by a diverse range of pathways. Numerous cancer cell types are inhibited in their ability to proliferate and undergo apoptosis in vitro by curcumin [18]. Curcumin was shown in prior research to strongly reduce HPF proliferation, leading to

HPF arrest in the G0/G1 phase [19]. This review is sought to discuss regarding the effect of of curcumin on VEGF expression and cell migration in Human Pterygium Fibroblast.

**Pathogenesis of pterygium**

Pterygium is a limbus-derived fibrovascular development and epithelial hyperplasia. Through a dynamic process that includes inflammation, angiogenesis, tissue turnover, and cell proliferation, these altered limbal cells move in the direction of the cornea. The first trigger is thought to be UV radiation, which stimulates epithelial cells close to the limbus to release growth factors and cytokines that lead to tissue turnover, inflammation, fibrovascular proliferation, angiogenesis, and anti-apoptosis. Damage to Bowman's membrane, a sign of pterygium invasion, is one example of this [20].

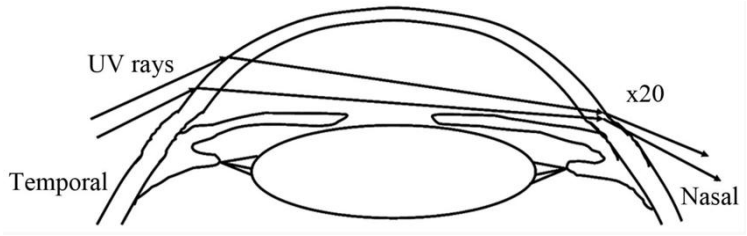


**Figure 1. Estimated UV Light Travel Path in the Anterior Segment [21]**

The main cause of pterygium development is generally acknowledged to be prolonged ultraviolet (UV) exposure. Numerous epidemiological research suggests a connection between UV exposure and pterygium development. The region between 30° north and south of the equator has been referred to as the "pterygium zone," where the population is impacted by greater levels of UV radiation. Furthermore, a more than 20-fold increase in radiation has been linked to nasal pterygium susceptibility, increasing the region's vulnerability to UV-induced damage and pterygium formation. UV light that strikes from the lateral of the eye goes into the anterior chamber and concentrate at the medial of corneal limbus, where they produce a peak light intensity that is 20 times higher than the light's original intensity at the eye [21].

The three types of UV radiation that come from sun exposure are UVA (wavelength 320–400 nm), which is a major pigmentation inducer and causes premature skin ageing, immunosuppression, and carcinogenesis; UVB (wavelength 280–320 nm), which causes sunburn, immunosuppression, and carcinogenesis, among other biological events. Of the three UV photons, UVC (wavelength 200–280 nm) contains the most energy and is highly mutagenic [22, 23].

Reactive oxygen species (ROS) are increased in pterygium as a result of UV-B exposure and can contribute to DNA damage. Reactive oxygen species (ROS) are a natural byproduct of cell metabolism that, depending on their quantity, may be advantageous or detrimental to cells and the body. ROS function as transductors and inducers of transcription, death, and cell growth at low doses. ROS are cytotoxic, cause inflammation, mutagenic to proteins, lipids, and DNA, and induce cell death when present in high amounts [18].

Pterygium formation is multifactorial and involves complex processes such as pro-inflammatory activity, ECM modification, cell proliferation and survival, or proangiogenic. This is in addition to UVB exposure, which plays a significant role in the process of pterygium development. Pro-inflammatory cytokines are necessary for the direct or indirect contribution of each component that initiates the creation and development of pterygium [24].

**Angiogenesis in Pterygium Formation**

The process of creating new blood vessels from pre-existing ones is known as angiogenesis. Numerous physiological functions, including development and differentiation, ovulation, wound healing, and pathological states, are based on it. Cell-derived angiogenetic factors are activated during the vascularization process. Numerous molecules, including VEGF-VEGFRs, ephrin-Eph receptors, angiopoietin-Tie, and the Delta-Notch system, have been shown to be crucial to the angiogenesis process in recent decades. Vascular Endothelial Growth Factor (VEGF) and its receptor (VEGFR) are two of these chemicals that control angiogenesis, which is the creation of new blood vessels from pre-existing ones, and vasculogenesis, which is the growth of blood vessels from precursor cells during early embryogenesis [25].

In pterygium tissue, there is a high expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). It is also claimed that these growth factors cause fibroblast and vascular endothelial cells in pterygium to migrate, proliferate, and differentiate [26]. In eye disorders, VEGF is crucial in initiating angiogenesis and raising vascular permeability. Because of the inflammatory response to several stimuli, such as UV exposure, corneal fibroblasts can create VEGF. VEGF levels were shown to be greater in pterygium tissue than in normal conjunctiva in in vitro research [27, 28]. In vitro research on human pterygium fibroblast cells also revealed that supernatant cultures of these cells had noticeably greater levels of VEGF mRNA expression than cultures treated with curcumin [29] [18].

According to research that has already been done, angiogenesis and lymphangiogenesis are related following corneal and/or conjunctival inflammation. Research indicates that angiogenesis and lymphangiogenesis both play a part in corneal immunity. It is also suggested that immunological processes may play a role in the development of pterygium. But according to research that demonstrated a larger ratio of blood vessels to lymphatic vessels in pterygium tissue, the most important element in pterygium is still the development of new blood vessels [30].

Inflammatory mediators are thought to be present in considerable quantities and are important in the development of pterygium, according to the pathophysiology of the condition. Following UV-B irradiation, pterygium has been shown to have elevated levels of interleukin 1 (IL-1), 6 (IL-6), and 8 (IL-8), as well as Tumour Necrosis Factor-α (TNF-α). Higher amounts of NF-kB and p50 proteins were discovered in pterygium in a different investigation using nuclear extracts from the tissue and healthy conjunctiva. This study also discovered that pterygium has active NF-kB pathways, both direct and indirect, which are linked to acute and delayed inflammatory processes. These processes contribute to the pathogenesis of pterygium by influencing the expression of pro-apoptotic and anti-apoptotic genes and cell cycle proteins, increasing cell motility and invasiveness, and attracting inflammatory cells to pterygium tissue, among other biological effects [31].

Growth factors have the ability to accelerate cell division, initiate mitosis, and cause cell cycle proliferation. Growth factors and their receptors have been identified in pterygium, where they cause fibroblasts, vascular cells, or epithelial cells to proliferate and/or migrate. These activities lead to pterygium's hyperplasia, fibrosis, and angiogenesis. Cell proliferation is a feature of pterygium pathogenesis, and it is intimately linked to growth factors including transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) [31].

**Current therapy for alleviating the risk of pterygium recurrencies**

To lessen the recurrence of pterygium, a number of agents can be employed. These substances can be applied before, during, or after surgery. Subconjunctival injections are used

preoperatively prior to surgery. Intraoperative application of the agents to the exposed sclera followed by rinsing is the most popular technique of usage. Topical use by the patient in the form of specially prepared drops or subconjunctival injection are examples of postoperative usage. The most often used medications are bevacizumab, 5-fluorouracil (5-FU), and mitomycin C (MMC) [32].

MMC is an alkylating substance that prevents the creation of deoxyribonucleic acid (DNA). Cell death results from the inability to repair the genotoxic damage induced by alkylation, which is generated by blocking DNA synthesis. Regardless of the cell cycle, MMC affects all cells, including those that are not now synthesising DNA. When MMC comes into contact with cells that are in the late G1 phase and early S phase of the cell cycle, it inhibits DNA synthesis, which results in fewer mitoses [32].

After pterygium surgery, MMC can be used topically or as eye drops before, during, or after the procedure. MMC is typically administered intraoperatively for three to five minutes and comes in doses ranging from 0.02 to 0.04%. When compared to bare sclera excision, nearly all of the trials that have been done to assess the use of MMC have demonstrated a statistically significant decrease in pterygium recurrence [32].

**Curcumin as a Novel Adjuvant Therapy for Decreasing VEGF Expression and Cell Migration in Human Pterygium Fibroblast**

Asthma, anorexia, coughing, liver illness, diabetes, heart disease, wound healing, and Alzheimer's disease are just a few of the ailments that have long been treated with curcumin, a product of curcuma longa, a polyphenol. Numerous investigations have demonstrated the anti-inflammatory, anti-infective, antioxidant, hepatoprotective, cardioprotective, thrombosuppressive, anti-arthritic, chemopreventive, and anticarcinogenic properties of curcumin. [18, 33]

Reactive nitrogen species (RNS) and ROS are two types of free radicals that curcumin, a naturally occurring antioxidant, can withstand. Enzymes that produce ROS, including xanthine hydrogenase/oxidase and lipoxygenase/cyclooxygenase, can have their activity modulated by curcumin. Figure 2 explains how curcumin has antioxidant effects by raising the expression of SOD (superoxide dismutase) and catalase, as well as H0-1 [33].

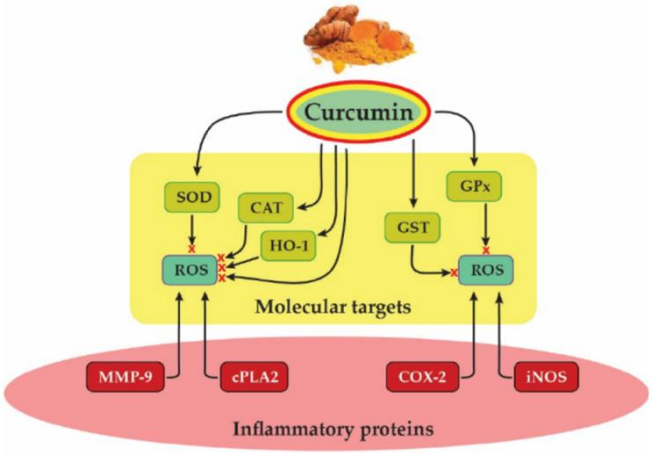


**Figure 2. Antioxidant and Anti-inflammatory effect of Curcumin [34]**

By causing pterygium fibroblast cells to undergo apoptosis and preventing VEGF production, curcumin can decrease pterygium growth in addition to its antioxidant benefits. Although fibroblasts in pterygium can express a lot of VEGFS, curcumin treatment can cause a considerable drop in VEGF concentrations. Curcumin contains antioxidant and anti-angiogenic properties, and it may be used as a treatment for conditions with significant angiogenesis activity [18].

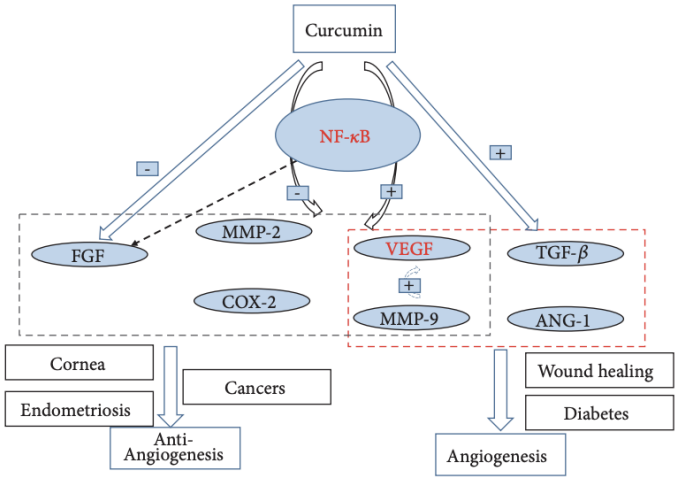


**Figure 3. Mechanism of curcumin's effect on angiogenesis [35]**

It is claimed that curcumin exhibits antiangiogenic properties in both in vitro and in vivo settings. Curcumin can reduce angiogenesis brought on by hypoxia and decreased VEGF expression, as well as suppress VEGF expression in an in vitro endometriosis model. By lowering VEGF expression in breast tumour xenograft models, curcumin can also prevent the angiogenesis process in tumours in vivo. Curcumin has been shown to suppress angiogenesis by lowering VEGF expression in diabetic retinopathy, diabetic nephropathy, and corneal disease in addition to carcinogenic instances.

Many different kinds of cancer cells release VEGF, a well-known hormone that promotes angiogenesis and tumour development. Since VEGF expression is frequently required for tumour angiogenesis, efforts to limit VEGF expression have been studied to be developed as a cancer therapy [36]. One of the key elements influencing the growth, invasion, and metastasis of a tumour during its development is said to be VEGF [37]. Compared to conjunctival fibroblasts, HPFs release more VEGF. There have been ongoing debates about the use of bevacizumab as an adjuvant treatment for pterygium since the initial theory regarding the possible advantages of anti-VEGF therapy in this condition was put up [38]. According to study, curcumin-treated groups' mRNA expression of VEGF can drop to 0.8–0.42-fold. Even though HPFs may release a lot of VEGFS, after receiving curcumin therapy, the concentration of VEGF dramatically dropped. The most powerful inhibitory impact was produced by a curcumin concentration of 80 µmol/l, and the effects were dose-dependent. Another in vitro study also show that Curcumin successfully decreases VEGF expression with dose of 200 µmol/L in Human Pterygium Fibroblast culture cell [29].

Zhang et al.'s 2014 study looked at how curcumin affected the hepatic stellate cells in liver fibrosis. According to the study, curcumin reduces the expression of angiogenesis markers in liver fibrosis, hence inhibiting hepatic vascularization. Curcumin inhibits the ERK and PI3K/AKT/mTOR pathways via activating peroxisome proliferator-activated receptor-γ (PPAR-γ), which results in PDGF-βR transrepression. Cells' production of VEGF mRNA is inhibited when this route is blocked. Cell motility is impacted by the FAK/RhoA cascade, which is likewise inhibited by PDGF-bR [39].

In laryngeal squamous cell carcinomas, curcumin inhibits the JAK2/STAT3 pathway, which in turn modifies the production of VEGF [40]. Curcumin primarily targets the PI3K/Akt/IKK signalling axis, which in turn causes the downregulation of VEGF, the simultaneous activation of caspases, and the simultaneous but separate repression of the mTOR and NF-κB pathways. Apoptosis is induced, angiogenesis is inhibited, and eventually the advancement of adenoid cystic carcinoma is inhibited as a result of these processes [41]. These processes might be new therapeutic targets. Thus, our results imply that curcumin inhibits VEGF production and induces HPF cell migration to limit pterygium growth.

## CONCLUSION

In conclusion, curcumin, a polyphenol derived from turmeric, exhibits significant potential as a therapeutic agent in the management of pterygium by effectively reducing VEGF expression and inhibiting cell migration in human pterygium fibroblasts. The anti-inflammatory, anti-angiogenic, and antioxidant properties of curcumin contribute to its ability to modulate key pathways involved in pterygium pathogenesis, particularly in response to UV-induced damage. Given the high recurrence rates associated with traditional surgical interventions, the incorporation of curcumin as an adjuvant therapy may offer a promising strategy to enhance treatment outcomes and mitigate the risk of pterygium recurrence. Further research is warranted to explore the full therapeutic potential of curcumin in clinical settings, as well as its mechanisms of action in the context of pterygium and other related ocular conditions.

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