Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 22s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Epigallocatechin-3-Gallate As A Potential Modulator of Tgf- B And Tnf- A Expression In Human Pterygium Fibroblasts: A Literature Review

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Cite this paper as: Maharani Kartika Anggraeni,Evelyn Komaratih,Muhammad Firmansjah,Wimbo Sasono,Luki Indriaswati,Ratna Parma Jaya, Djoko Agus Purwanto, (2025). Epigallocatechin-3-Gallate As A Potential Modulator of Tgf-B And Tnf- A Expression In Human Pterygium Fibroblasts: A Literature Review. *Journal of Neonatal Surgery*, 14 (22s), 489-494

ABSTRACT

Pterygium is a chronic ocular surface disorder characterized by fibrovascular proliferation, often resulting in visual impairment and high recurrence rates after treatment. Fibrosis and inflammation are key pathological processes, with Transforming Growth Factor Beta (TGF-β) and Tumor Necrosis Factor Alpha (TNF-α) playing central roles. This literature review aims to explore the potential of Epigallocatechin-3-gallate (EGCG) in modulating the expression of TGF-β and TNF-α in human pterygium fibroblasts, and to evaluate its efficacy as an anti-inflammatory and antifibrotic agent in pterygium management. A comprehensive review of relevant in vitro and experimental studies was conducted, focusing on the biological effects of EGCG on pterygium fibroblast behavior, including proliferation, migration, cytokine expression, and apoptosis, particularly through TGF-β and TNF-α signaling pathways. EGCG has been shown to significantly reduce the expression of TGF-β and TNF-α, inhibit fibroblast proliferation and migration, and promote apoptosis in pterygium fibroblasts. Its mechanisms involve modulation of fibrotic and inflammatory signaling pathways. EGCG demonstrates promising therapeutic potential as an adjuvant agent in the treatment of pterygium. Its ability to target both inflammation and fibrosis suggests a role in reducing recurrence rates and improving treatment outcomes. Further studies are needed to support its clinical application.

Keyword: *EGCG, TGF- β, TNF- α, pterygium, antifibrotic, anti-inflammatory, antiangiogenic..*

1. BACKGROUND

Pterygium is a common pathological condition characterized by the growth of fibrovascular tissue and the formation of a wing-shaped conjunctival extension over the corneal surface. The global recurrence rate of pterygium is high, ranging from 10% to 80%, while in Indonesia, it is estimated to range between 24% and 89%. The persistent recurrence and progression of pterygium present a chronic clinical challenge for ophthalmologists in Indonesia that remains inadequately addressed. Pterygium may lead to cosmetic concerns and, in advanced stages, a reduction in visual acuity. This visual impairment may result from chronic inflammation, irregular astigmatism, optical axis occlusion, and restricted ocular motility. Consequently, individuals with pterygium may require multiple surgical interventions.1–3

Basic Fibroblast Growth Factor (bFGF) is a growth factor that emerges following prolonged inflammation and DNA damage. It plays a pivotal role in several biological processes, including cell migration, differentiation, proliferation, apoptosis, and angiogenesis. These mechanisms collectively facilitate the invasive behavior of pterygium cells. The induction of bFGF has been observed in response to various stimuli, including ultraviolet (UV) radiation exposure. Apoptosis, a biological process defined as programmed cell death, has been closely associated with the pathogenesis of pterygium. Fibrosis is also strongly linked to the onset of pterygium, as elevated levels of fibrotic activity are directly correlated with a higher risk of recurrence.4

Reducing fibrosis may help limit the progression of pterygium. This process is associated with apoptosis-related proteins, particularly survivin, Bcl-2, Bax, and Bcl-w, which are involved in the regulation of cell death. Studies examining the expression and apoptosis of Basic Fibroblast Growth Factor (bFGF) in Human Pterygium Fibroblasts (HPF) remain limited

in scope. The primary therapeutic modalities currently employed in contemporary surgical techniques include conjunctival flaps, conjunctival autografts, bare sclera excision, and the application of amniotic membrane.4

The effectiveness of these various approaches in addressing the issue—particularly in preventing recurrence—remains inadequately resolved. The use of primary treatment in combination with adjuvant therapies, such as epigallocatechin-3-gallate (EGCG), a compound found in green tea extract, has shown significant promise for therapeutic application. Green tea, formally known as *Camellia sinensis*, is recognized for its high catechin content. These compounds have demonstrated beneficial effects in ocular treatments, particularly as antifibrotic, anti-inflammatory, and antioxidant agents. Epigallocatechin-3-gallate (EGCG) has shown potential for use in several formulations, including ocular solutions.[5,6]

Several studies have demonstrated that administration of EGCG at a concentration of 25 µM significantly reduced pterygium cell proliferation by 16.78% ($p<0.001$) and 24.09% ($p<0.001$), along with a marked inhibition of cell migration by 35.22% ($p<0.001$) and 25.20% ($p=0.019$), respectively. Treatment with epigallocatechin-3-gallate (EGCG) has shown efficacy in reducing recurrence rates and fibroblast migration in pterygium in vitro, without adverse effects on conjunctival cells. The use of EGCG as an adjuvant therapy in the management of primary pterygium is therefore recommended.[7]

The presence of mycolic acid and mycophenolic acid in pterygium cases has been shown to reduce the production of basic fibroblast growth factor (bFGF) during the wound healing process. A decrease in bFGF expression significantly inhibits fibroblast cell proliferation. EGCG has been shown to influence the downregulation of bFGF expression and induce apoptosis in Human Pterygium Fibroblasts (HPF). Therefore, the inclusion of EGCG as a supplementary therapeutic agent—known for its minimal side effects—is expected to be an effective strategy in reducing the risk of pterygium recurrence in future cases.[8,9]

TGF-β in the Pathogenesis of Pterygium

Inflammatory mediators are abundantly present in pterygium, making them key contributors to its growth. Elevated concentrations of interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) have been observed in pterygium tissues, primarily as a result of ultraviolet (UV) radiation exposure. Cyclooxygenase-2 (COX-2) is also upregulated in pterygium and is believed to contribute to increased prostaglandin production and the activation of inflammatory cascades.[10]

Growth factors are small molecules capable of inducing cell growth, initiating mitosis, and promoting proliferation within the cell cycle. Several growth factors—including Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor-Beta (TGF-β), Basic Fibroblast Growth Factor (bFGF), Insulin-like Growth Factor (IGF), Nerve Growth Factor (NGF), and Connective Tissue Growth Factor (CTGF)—have been studied in relation to pterygium.[11]

TGF-β regulates tissue healing mechanisms, including fibroblast proliferation, angiogenesis, and the modulation of production and degradation of matrix proteins such as collagen and fibronectin. Previous studies have demonstrated that the concentration of FGF-2 is elevated in pterygium compared to normal tissue, with FGF-2 capable of inducing cyclooxygenase-2 (COX-2), a key enzyme involved in the inflammatory response.[10]

TGF-β1 is localized in the limbal stroma of the normal human cornea, TGF-β2 is distributed throughout all corneal layers, and TGF-β3 is found in both the central and peripheral corneal stroma. TGF-β receptors are present in every layer of the cornea. During corneal wound healing, the expression of TGF-β receptors—namely TGF-βRI and TGF-βRII—increases, with TGF-βRII being associated with epithelial cell motility and activated by EGF or TGF-β1. TGF-β1 promotes fibroblast

migration, proliferation, and differentiation, and can induce the angiogenic growth factor VEGF. Immunolabeling of TGF-β is weak in normal conjunctival fibroblasts. This contrasts with primary pterygium, where stromal cells exhibit high levels of angiogenic growth factors such as TGF-β. These findings suggest that such growth factors may interact directly in the etiology of pterygium. The presence of activated fibroblasts is a result of TGF-β overexpression. Consequently, our data suggest that TGF-β may serve as a potential therapeutic target in the treatment of pterygium.[12]

The phenotype, regulation, and function of fibroblasts are significantly influenced by TGF-β. Upon stimulation by TGF-β, fibroblasts become activated and undergo phenotypic transformation into myofibroblasts, which serve as the primary effector cells in the fibrotic process. The myofibroblast phenotype is characterized by the development of gap junctions and a contractile apparatus, which includes associated contractile proteins such as alpha-smooth muscle actin (α-SMA) and non-muscle myosin.[13]

The production of α-SMA induced by TGF-β requires the involvement of Smad3, as well as signaling pathways such as Focal Adhesion Kinase (FAK), c-Jun N-terminal kinase (JNK), transforming growth factor-beta-activated kinase (TAK), and PI3 kinase/Akt. Myofibroblasts play a critical role in tissue repair during wound healing. However, under pathological conditions, activated myofibroblasts can act as cellular effectors in the fibrotic process.[13]

In addition to facilitating myofibroblast transdifferentiation, TGF-β also promotes matrix deposition by enhancing matrix protein synthesis through altered signaling balance regulating matrix degradation. TGF-β can induce the transcription of type I collagen genes through a Smad3-dependent mechanism. Furthermore, TGF-β inhibits the activity of matrix metalloproteinases (MMPs) and promotes the production of protease inhibitors, including Plasminogen Activator Inhibitor-1 (PAI-1) and Tissue Inhibitor of Metalloproteinases (TIMP). Activation of the Smad3 signaling pathway is essential for TGF-β–induced extracellular matrix protein production and excessive TIMP expression.[13]

TNF-α in the Pathogenesis of Pterygium

The pathophysiology of pterygium remains poorly understood; however, epidemiological studies suggest that environmental stress may play a role.[8] Among the suspected agents, ultraviolet (UV) irradiation has received the most attention. UV radiation can induce the release of proinflammatory cytokines—including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-alpha (TNF-α)—from the corneal epithelium, conjunctiva, and pterygium tissues.[14–16] Specific proinflammatory cytokines, such as TNF-α and IL-1β, have been shown to induce proliferation of cultured Tenon's capsule fibroblasts and enhance the production of matrix metalloproteinases (MMPs) in cultured pterygium fibroblasts.[16,17] Consequently, Solomon et al. have proposed that TNF-α and IL-1β play critical roles in the pathogenesis of pterygium.

Solomon et al. proposed that specific environmental stressors associated with pterygium trigger the release of proinflammatory cytokines by the ocular surface epithelium, inflammatory cells in the tear film, or both. Among these cytokines, TNF-α and IL-1β stimulate pterygium body fibroblasts, leading to a phenotype that expresses various proteinases involved in extracellular matrix remodeling, angiogenesis, and fibroblast proliferation. These characteristics are considered critical for the development and recurrence of pterygium.[16]

MMP-1, MMP-2, MMP-3, TIMP-1, and TIMP-3 have been found at higher levels in pterygium tissue, as well as in cultured pterygium epithelial cells and fibroblasts, compared to the conjunctiva.[18,19] Siak et al. reported that TNF-α activates the nuclear factor-kappa B (NF-κB) pathway in pterygium fibroblasts, resulting in increased levels of MMP-1, MMP-2, and

MMP-3.[20] The intracellular extracellular signal-regulated mitogen-activated protein kinase 1/2 (ERK1/2 MAPK) pathway is also involved in UVB-induced MMP-1 production in pterygium.[18] Recent evidence indicates that bevacizumab reduces MMP-1 levels in human Tenon's fibroblasts derived from both primary and recurrent pterygium.[21] MMP-3 and secreted protein acidic and rich in cysteine (SPARC) have been shown to be upregulated and localized in the pterygium epithelium, suggesting their possible collaboration in accounting for the varied phenotypes of pterygium.[22] A recent study demonstrated that cyclosporine A reduces MMP-3 and MMP-13 production in cultured pterygium fibroblasts.[23] Both the precursor and active forms of MMP-7 are present in the epithelium and blood vessels of pterygium, but not in conjunctival vessels. TNF-α has also been shown to facilitate VEGF-C production.[24] Increased VEGF expression promotes angiogenesis and lymphangiogenesis, potentially altering the normal metabolism of conjunctival cells and contributing to their transformation into pterygium cells. 5-fluorouracil, a novel drug aimed at preventing pterygium recurrence, has recently been shown to have no effect on VEGF expression in pterygium tissue.[25]

The Effects of EGCG on TGF-β and TNF-α

Tea (*Camellia sinensis*), a member of the Theaceae family, is among the most widely consumed beverages globally. In Chinese culture, green tea has historically been regarded as possessing therapeutic properties for the prevention and treatment of various diseases. Contemporary scientific research has expanded our understanding of the biological and pharmacological properties of green tea, highlighting its antioxidant and anti-inflammatory activities.[26]

The biologically active components in tea are known as catechins, a type of polyphenol. Epigallocatechin-3-gallate (EGCG) is the primary catechin compound and the most biologically active form among all catechins, exhibiting notable benefits such as anticancer, antimicrobial, antioxidant, anti-inflammatory, and antifibrotic properties. Studies have shown that EGCG possesses anti-inflammatory, antioxidant, and antiangiogenic effects in various ocular disease models. Furthermore, EGCG has demonstrated the ability to induce apoptosis and suppress cell proliferation and metastasis in several types of cancer.[26]

EGCG can induce cell cycle arrest at the G2/M phase and increase the sub-G1 population. This mechanism involves the downregulation of cyclin D1 production and the upregulation of cyclin-dependent kinase (CDK) inhibitors, leading to CDK inactivation and ultimately resulting in cell death.[27]

EGCG is capable of suppressing the expression of anti-apoptotic proteins Bcl-2 and Bcl-XL, while simultaneously enhancing the expression of pro-apoptotic proteins Bax and Bak. These effects occur through three primary mechanisms: activation of caspase-3 and caspase-9, modulation of mitochondrial function, and cleavage of poly(ADP-ribose) polymerase (PARP) activity. EGCG also reduces the activation of extracellular signal-regulated kinases (ERK) and the transcription factors Fos and Jun. By upregulating pro-apoptotic Bax and downregulating anti-apoptotic Bcl-2, EGCG promotes apoptosis through multiple pathways.[27]

The inhibitory effect of EGCG on cell proliferation is associated with its ability to suppress the phosphorylation of nuclear factor-kappa B (NF-κB), a sequence-specific transcription factor responsive to oxidative stress. EGCG has been shown to significantly inhibit the phosphorylation of mitogen-activated protein kinases (MAPKs), including p38, JNK, and NF-κB, as well as activator protein-1 (AP-1), which is activated in response to various growth stimuli.[27]

Tissue fibrosis development in all organs is significantly regulated by TGF-β, whose activation promotes the differentiation of fibroblasts into myofibroblasts and the expression of α-smooth muscle actin (α-SMA). Identifying antifibrotic agents with

minimal side effects is essential, as mitomycin C (MMC)—despite its effectiveness in inhibiting fibroblast proliferation—has been associated with a range of serious adverse effects, including delayed wound healing, scleral thinning, and corneal complications. In this context, epigallocatechin-3-gallate (EGCG), a natural polyphenol found in green tea, has emerged as a promising therapeutic candidate due to its antifibrotic, anti-inflammatory, and antioxidant properties. EGCG has been shown to inhibit fibroblast proliferation, suppress α-SMA expression, and modulate TGF-β signaling, thereby offering a safer alternative to MMC in managing fibrotic conditions such as pterygium.[27]

Transforming Growth Factor-Beta (TGF-β) is the principal growth factor responsible for cell proliferation. During the proliferative phase of wound healing, TGF-β facilitates the conversion of fibroblasts into myofibroblasts, subsequently leading to fibrosis. Fibrosis, which is often indicative of pterygium recurrence, typically results from excessive wound healing following surgical excision of the pterygium. TGF-β induces fibrosis in pterygium by activating myofibroblasts and enhancing extracellular matrix synthesis. The early phase (1 hour) and subsequent phase (5 days) of wound healing mark the initiation of active TGF-β isoform ratios. TGF-β expression peaks on the second day after injury and rises again on the fifth day. Several studies have shown that fibrosis, which facilitates pterygium recurrence, may be suppressed by targeting TGF-β or its precursor myofibroblast populations.[28,29]

2. CONCLUSION

This literature review explores the involvement of Transforming Growth Factor Beta (TGF-β) and Tumor Necrosis Factor Alpha (TNF-α) in the development and recurrence of pterygium, a common ocular condition characterized by fibrovascular proliferation on the cornea. The review highlights the potential of Epigallocatechin-3-gallate (EGCG), a catechin found in green tea, as a promising adjuvant therapy due to its antifibrotic, anti-inflammatory, and antioxidant properties. EGCG has demonstrated the ability to reduce pterygium cell proliferation and migration, suppress fibrosis by modulating TGF-β and TNF-α signaling pathways, and induce apoptosis in pterygium fibroblasts. This manuscript proposes that inhibiting TGF-β and TNF-α through EGCG may significantly reduce pterygium recurrence and improve therapeutic outcomes, thereby presenting an innovative strategy to address this complex ocular disorder.

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