The Role of Epigallocatechin-3-gallate (EGCG) In Inhibiting MMP3 Expression and Human Pterygium Fibroblast Migration: A Review

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ABSTRACT
Background: Pterygium is characterized by the overgrowth of fibroblasts and the remodeling of the extracellular matrix (ECM), driven by MMPs. The review outlines the pathophysiology of pterygium, emphasizing the role of MMP-3 in cell motility, proteolysis, and angiogenesis. The recurrence rate of pterygium following surgical excision remains a significant challenge, with current adjuvant therapies like mitomycin-C presenting serious side effects. Methods: The review synthesizes findings from various studies on the effects of EGCG on MMP-3 expression and fibroblast migration. It discusses the mechanisms by which EGCG inhibits MMP-3 activity and its potential impact on pterygium progression. Findings: EGCG has been shown to inhibit MMP-3 expression and activity in several models, including mouse Lewis lung carcinoma-derived cells and photoaged hairless mouse models. It also suppresses the migration of human pterygium fibroblast cells, potentially preventing pterygium formation. EGCG's ability to reduce oxidative stress and modulate inflammatory pathways further supports its therapeutic potential. Conclusion: EGCG emerges as a promising agent for inhibiting MMP-3 expression and human pterygium fibroblast migration, offering a safer alternative to current adjuvant therapies. Its anti-inflammatory, antioxidant, and anti-angiogenic properties make it a potential therapeutic option for managing pterygium, warranting further clinical investigation.

1. Introduction

Pterygium is a wing-shaped growth of degenerative fibrovascular tissue that extends from the conjunctiva to involve the superficial cornea that occurs in the interpalpebral fissure [1, 2]. The degenerative and inflammatory condition known as pterygium develops on the surface of the eye where the corneal conjunctiva develops into a fibrous tissue that resembles a triangle. Pterygium often grows from the side of the nose, but can also grow temporally or in both directions, and can grow unilaterally or bilaterally. Multiple complex variables, such as DNA abnormalities related to angiogenesis, migration, proliferation, and repair, influence pterygium formation. Thus far, specialists have reached a consensus about the pathogenesis of pterygium, which include exposure to UV light, human papillomavirus (HPV) infection, inflammation, persistent irritation from dust, wind, or other external stimulants, angiogenesis, lymphangiogenesis, and genetic predisposition [3, 4, 5].

The prevalence of pterygium ranges from 0.7 to 31% worldwide, with the equatorial region having the highest proportion at 22%. The "pterygium belt" region, which includes various countries in Asia, is situated at the Equator's 30 degree north and 30-degree south latitudes. These areas have a higher prevalence of pterygium. In Indonesia, West Sumatra Province has the highest pterygium prevalence rate (9.3%), while DKI Jakarta Province has the lowest prevalence rate (0.4%) [3, 6, 7].

A wound after surgically excising pterygium may remain on the surface of the eyeball, causing HPF cell migration to attempt to heal the wound. The correct structure of multicellular organisms is built and maintained by the process of cell migration. Tissue homeostasis, wound healing, and a robust immune response are all facilitated by cell migration. Fibroblast cell migration may be seen in vitro because the cells allow the fibroblasts to release extracellular matrix (ECM) proteins and proliferate when they move to the wound site. After pterygium excision surgery, wound healing will also release an endopeptide enzyme called MMP-3, which has the potential to degrade all of the extracellular matrix (ECM) in connective tissue and cell surface molecules. MMPs may modify the extracellular matrix (ECM) during the initial stages of pterygium invasion. The pterygium apex's fibroblasts express MMP-3 at high quantities. MMP-3 has a significant role in cell motility, proteolysis, and angiogenesis because it activates pro-MMPs such MMP-1, MMP-9, and MMP-13 and stimulates angiostatin. Within 48 hours, MMP expression in HPF cells is visible [8, 9].

The recurrence rate of pterygium following excision has been the subject of numerous modified procedures studies during the past ten years. Adjuvant therapy, such as the use of the antimetabolite mitomycin-C (MMC), is one such strategy. Clinical practitioners frequently employ the antimetabolite mitomycin C, which has been shown to lower the recurrence rate of pterygium. However, a number of serious post-administration complications, including scleral calcification, corneal edoema, and corneal perforation, have created new difficulties in the management of pterygium. Owing to these issues, a number of scientists have started working on the development of an alternative adjuvant medication called epigallocathecin-3-gallate (EGCG), which has few side effects. EGCG is a naturally occurring component that may be grown anywhere in the globe, including Indonesia. It is derived from Camellia sinensis green tea extract. Due to its bioactivity, EGCG is given particular consideration in the creation of potentially useful medications that include antibacterial, anticancer, antioxidant, and antiallergic properties. It is commonly known that EGCG inhibits MMP-3 and fibroblast cell migration in human pterygium fibroblasts (HPF), which in turn inhibits angiogenesis and inflammation [10, 11, 12].

Therefore, this literature review is sought to comprehensively discuss regarding the role of EGCG in preventing the recurrence of pterygium especially through specific mechanism which is inhibiting the expression of MMP3 and HPF migration.

Patophysiology of pterygium

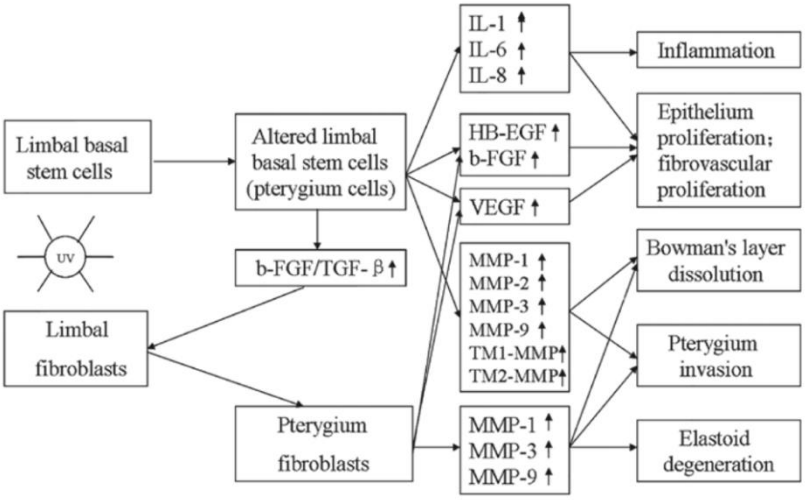

Figure 1. Possible contributions of UV light to the pterygium pathogenesis.

Pterygium is initiated by UV radiation-mediated modification of limbal stem cells. Increased expression of growth factors, MMPs, and a variety of inflammatory cytokines by pterygium cells leads to fibrogenesis, vascularization, and invasion of the pterygium. In a b FGF/TGF β dependent way, limbal fibroblasts triggered by UV light or pterygium cells release increased levels of MMPs and other growth factors. These mechanisms facilitate the extracellular matrix remodelling, Bowman's membrane disruption, and pterygium invasion. The terms ultraviolet, interleukin, heparin-binding epidermal growth factor, basic fibroblast growth factor, vascular endothelial cell growth factor, matrix metalloproteinase, and transforming growth factor-β are defined as follows: UV, b-FGF, VEGF, and TGF-β. [13]

The cornea's limbal stem cells become insufficient as a result of UV radiation. Tissue growth factors are activated as a result, and this promotes angiogenesis and cell division. UV rays promote conjunctivalization of the cornea, damaging the limbal stem cells, and aggressive fibroblasts penetrate the cornea. The aberrant pterygial epithelium may be the consequence of mutations in the p53 tumour suppressor gene brought on by UV exposure [14, 13].

Recent research has suggested that the pathophysiology of the pterygium may potentially include the human papillomavirus [15]. According to recent research, the human papillomavirus can contribute to the pathophysiology of pterygium. These results suggest that pterygium may originate from uncontrolled cell growth and is not only a degenerative condition. Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) may be responsible for tissue remodelling, inflammation, Bowman's layer disintegration, and corneal pterygium invasion near the advancing border of the pterygium [16]. Additionally, a conjunctive invasion of the surrounding cornea was proposed as a possible outcome of a localised limbal stem cell shortage in a pterygium.

Role of Matrix metalloproteinase (MMP) and migration of HPF fibroblast cells

Pterygium is a clinically apparent tissue resulting from an inflammatory process, immunoglobulin deposition, and plasma cell, T-lymphocyte, and mast cell infiltration. Pterygium's histological characteristics include inflammatory cell infiltration, migration, and proliferation along with extracellular matrix remodelling brought on by the activity of growth factors, MMPs, and pro-inflammatory cytokines. The cornea's wound healing cascade is intimately connected to these characteristics. Cumulative UV exposure activates pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8 in the pterygium, attracting inflammatory cells and causing a notable rise in mast cell counts in the stroma. Growth factors like TGF-β or pro-inflammatory cytokines can induce bFGF and VEGF expression in pterygium, which is followed by a reduction in anti-angiogenic molecules such Pigment Epithelium Derived Factor (PEDF) [9, 17, 18].

MMP is essential for the development of pterygiums because of the excessive proliferation and invasion of fibroblasts that harm the corneal stroma and basal lamina at the apex of the pterygium. MMP produced by pterygium cells dissolves the basal lamina and stimulates the proliferation of stromal fibroblasts. Abnormal ECM buildup and inflammatory cell infiltration coexist with stromal fibroblast and vascular overgrowth. One important pathomechanism in pterygium is ECM remodelling. Following Bowman's membrane injury, versican, collagen III, and fibronectin were among the ECM genes that were elevated in pterygium and elastosis tissue. A portion of these alterations are linked to the function of MMPs, which support pterygium's locally invasive characteristics [4, 9].

Pterygium progression is mostly caused by MMP overexpression in the limbus's basal epithelial cells. Numerous studies have demonstrated a close correlation between MMPs and tumour progression/invasion, suggesting that MMPs may modify the extracellular matrix (ECM) during the early stages of pterygium invasion. MMP activity is going to go up when pterygium lesions invade them. MMPs that were expressed in several tissues were divided into five groups according to their cellular localization and substrate specificity. Membrane type MMPs (MT-MMPs), gelatinase (MMP-3, MMP-9), collagenase (MMP-1, MMP-8, and MMP-13), stromelysin (MMP-3, MMP-10, MMP-31, and MMP-32) and additional enzymes are included in this category [8, 9, 17].

Pterygium tissue was observed to contain elevated levels of MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, and MMP-14. Pterygium will cause fibroblast tissue to become activated, particularly near the apex of the pterygium. This will induce fibrillar collagen to divide in the basal lamina, with MMP-1 and MMP-3 being the primary causes of this process. MMP-1 and MMP-3 are extensively expressed by fibroblasts in the apex of the pterygium, and both enzymes are quite active. Furthermore, MMP-2 and MMP-9 were found in the pterygium apex's basement membrane. Pterygium is a stem cell-derived disease characterised by premalignant lesions. The epithelial cells at the tip of the pterygium in Fuchs flecks have a tendency to become stem cells, which migrate to Bowman's layer and cause damage to it, as well as angiogenesis, matrix remodelling, and cell proliferation. This process may be closely linked to the overexpression of MMPs, which are distinct from cytokines and growth factors [4, 8, 9].

MMP-3 breaks down ECM, which aids in tumour infiltration. Growth factors that promote angiogenesis, including as VEGF and bFGF, are released as a result of ECM breakdown, and MMP-3 has a major impact on angiogenesis by generating angiostatin. MMP-3 is thought to be a broad inflammatory agent that may cause inflammation throughout the body. Moreover, MMP-3 may activate pro-MMPs including MMP-1, MMP-9, and MMP-13. This has a wide range of impacts, including angiogenesis, proteolysis, and cell migration [8, 9, 19].

Building and preserving a multicellular organism's appropriate structure depends heavily on cell migration. From the vast migration of epithelial sheets during gastrulation to the movement of individual cells during the creation of the nervous system, one may claim that cell motility plays a role in morphogenesis. Cell migration is necessary for healthy immune response, wound healing, and tissue homeostasis in adult organisms; aberrantly migrating cells are detected in a variety of clinical situations. As our knowledge of cell migration advances, some goals we may set for ourselves include reducing the spread of particularly harmful cancer cells, reducing the invasion of white blood cells during inflammatory processes, and improving wound healing. There are two primary components to cell migration. The first section focuses on the isolation and migration of single cells, such as fibroblasts pushing through connective tissue or leukocytes migrating as part of an immune response. The cells that migrate collectively as a part of multicellular sheets or groups are covered in the second section. This second kind of migration occurs frequently during development, healing of wounds, and spread of some cancers [20].

Fibroblasts are crucial for the healing of wounds. Both in vivo and in vitro, fibroblasts move to wounds. During

this migration, the cells pick up signals that enable them to release extracellular matrix proteins and multiply. Nonetheless, in comparison to individual fibroblasts in cell culture, they migrate more quickly and with a more pronounced shape in vitro. When fibroblasts migrate into a wound, they usually have a large lamellipodium that extends into the wound, whereas stationary fibroblasts have smaller lamellipodia and are marked by fewer stress fibres within the cells. When fibroblasts are present at wound sites, a variety of growth factors, including as platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), are known to serve as mitogens or chemotactic factors for them. A single fibroblast's migration rate can be tripled by growth factors, and they can even shift the direction of migration [20].

A surgically removed pterygium may leave cicatrix on the cornea, which may encourage the migration of Human Pterygium Fibroblast (HPF) cells to heal the lesion. A multicellular organism's correct structure could only be established and maintained through the process of cell migration. Tissue homeostasis, wound healing, and a robust immunological response were all facilitated by cell migration. Fibroblast cell migration may be seen in vitro when the cells move to the wound site, releasing extracellular matrix (ECM) proteins and enabling fibroblast proliferation. Pterygium excision following surgery would also result in the release of MMP-3, an endopeptide enzyme capable of breaking down all ECM components in connective tissue and cell surface molecules. MMP may alter ECM in the early stages of pterygium invasion. The MMP-3 is highly expressed by apical fibroblasts in pterygium. Due to its potential to activate pro-MMPs including MMP-1, MMP-9, and MMP-13 as well as angiostatin, MMP-3 has a significant effect. Proteolysis, cell migration, and angiogenesis have all been connected to these processes. MMP expression on HPF cells was detected within 48 hours [2].

Epigallocatechin-3-gallate (EGCG) and it's relation to the inhibition of MMP3 expression and the migration of human pterygium fibroblast

Based on different production procedures, teas may be divided into three categories: semi-fermented oolong tea, fermented black tea, and unfermented green tea. The unfermented leaves of the Camellia Sinensis plant are used to make green tea. Because of the early phases of production, green tea maintains the natural structure of its polyphenolic ingredients. Anthocyanins, flavones, phenolic acids, and catechins are some of the polyphenols found in green tea. Green tea extract (GTE) is made by carefully manipulating fresh leaves through time-consuming, meticulous extraction processes. In summary, ethyl acetate and water are often used to extract catechins from green tea leaves, which are then eluted using water/alcohol chromatography [21]. The following are the ingredients found in tea leaves: Tea's constituents are: (1) tea polyphenols, also known as tea catechins; (2) saccharides, like glucose and sucrose; (3) minerals, like potassium, magnesium, calcium, and aluminium; (4) amino acids, like theanine and glutamic acid; (5) caffeine; and (6) insoluble substances, which comprise 62% of the leaves and are composed of polysaccharides, proteins, and pigments. Leaves are the primary component of green tea extract (GTE). It also comprises the following: (-)-catechin gallate (CG), (-)-catechin (EC) (<10%), (-)-epicatechin (EGC) (<10%), (–)-catechin gallate (ECG) (<10%), and (–)-catechin gallate (GCG). These are the other components of it. Out of all the catechins included in green tea, EGCG has demonstrated its accessibility and potential to target the molecular pathways linked to several disease models [22, 23]. Among the green tea catechins, it is also the most powerful component in terms of biological activity. Multiple hydroxyl groups on distinct carbon atom sites define the chemical structure of polyphenols, which may interact with reactive oxidising molecules to prevent oxidative stress. Therefore, there is a strong relationship between green tea's antioxidant activity and the electron-rich properties of polyphenols. The unsaturated 4-oxo group and the 2,3-double bond in the C-ring help to promote electron delocalisation of o-dihydroxyl catechol inside the B-ring [24].

With a stronger ability to bind proteins and nucleic acids than other polyphenolic chemicals found in green tea extract, EGCG is the primary catechin molecule found in the extract. Excreted in urine with ease, the EGCG component is non-toxic and readily dissolves in water. Because there are no negative effects when 30 grammes of EGCG are consumed daily, this substance is harmless. Given their significant potential as anti-inflammatory, antioxidant, anticancer, and other bioactive chemicals, these polyphenolic compounds are given particular attention to EGCG. Apoptosis, necrosis, and autophagy are three ways that EGCG affects cell death pathways and has been shown to suppress inflammatory processes in a variety of different disorders [25, 26].

Through regulating the function of the enzymes that generate reactive oxygen species (ROS), EGCG can lower ROS levels, which are linked to oxidative stress in tissues and can have an impact on the angiogenesis process. Reduced ROS levels can cause damage to cell membranes, which in turn can cause angiogenesis and increase VEGF and bFGF expression. Through the activation of superoxide dismutase (SOD) and the release of reactive oxygen species (ROS) through NADP(H) oxidase (NOX), this process can ultimately lead to a reduction in the

proliferation, migration, and development of vascular tissue [8, 27, 28].

MMP-3, referred to as stromelysin-1, belonged to the family of matrix metalloproteinases (MMPs). Some of the extracellular matrix's (ECM) constituents that were involved in the pterygium's invasion were degraded by MMP-3, including adhesion molecules, growth factors, matrix proteins, and proteases. The proliferating cells in the wound healing phase expressed MMP-3 close to the wound edge. Angiogenesis was driven by the release of growth factors such bFGF and VEGF as a result of ECM degradation, and MMP-3 plays a significant role in angiogenesis by inducing angiostatin. It was believed that MMP-3 was a general inflammatory agent with the ability to produce inflammation throughout the body. MMP-3 alone has the ability to activate pro-MMPs like MMP-1, MMP-9, and MMP-13, enabling them to take part in angiogenesis, proteolysis, and cell migration. [8, 9].

Pterygium tissue, especially at the apex, stimulated fibroblast tissue, which in turn caused fibrillar collagen in the basal lamina to cleave, partially due to MMP-3. Fibroblasts in the apex of the pterygium are highly active and express MMP-3. EGCG reduced MMP3 activity in the culture medium of mice Lewis lung carcinoma-derived cells, with an IC50 value of around 50 μM [29]. Lee et al. found that water extracts of green, white, and black teas reduced UVB-induced skin damage in addition to the decreased expression of MMP3 in a photoaged hairless mouse model [30]. Another research published by Hanis, et al. in 2022 concluded that Due to its capacity to suppress MMP-3 production and impede the migration of human pterygium fibroblast cells, EGCG prevents the formation of human pterygium [2].

EGCG inhibits the pathways of activator protein-1 (AP-1) and mitogen activated protein kinase (MAPK), as well as the formation of MMP1 and MMP3 stimulated by TNF-α [31]. EGCG has the potential to completely inhibit RANTES, ENA-78, and GRO-α synthesis that is stimulated by IL-1b [32]. In particular chondrocytes, EGCG suppresses the mRNA and protein production of MMP1 and MMP13 that is stimulated by IL-1b [33, 34].

A review by Prasanth et al. claims that EGCG can improve the skin's collagen and elastic fibre content, as evidenced by a reduction in the expression of the collagen-breaking enzyme MMP-3 [35]. This indicates that EGCG helps prevent wrinkles on the skin. Using a 3D co-culture model of periodontitis, Morin et al.'s previous study on oral illness discovered that EGCG may reduce the baseline production of MMP-3 level by 27.4% without any stimulation with Aggregatibacter actinomycetemcomitans lipopolysaccharide levels [36].

Role of EGCG in other diseases

EGCG's anti-tumor activity is mediated by a number of mechanisms [37, 38]. One of the main theories for the development of tumours is that tumour promoters block gap junctional intercellular communication and separate preneoplastic cells from the regulatory effect of neighbouring cells. On the other hand, EGCG promotes gap junctional communication between neighbouring cells, shielding them against the growth of tumours. Furthermore, EGCG may reduce chronic inflammatory processes that lead to cell transformation, hyperproliferation, and the start of carcinogenesis, which may explain in part why it has broad anti-inflammatory and antioxidant actions against tumours [39]. Cancer can be initiated and progressed by a variety of proteins and signalling pathways that are also involved in inflammation and cell growth or death.

Recent excellent reviews have shown the benefits of EGCG and its metabolites in neurological disorders [40]. Epidemiological studies carried out in China, Singapore, and Japan have shown a favourable correlation between tea consumption and improved cognitive function or the prevention of cognitive deterioration [41, 42]. The outcomes of other animal investigations corroborated these conclusions. For example, intragastric injection of EGCG for 60 days reduced the buildup of β-amyloid, a key component in Alzheimer's disease, and delayed cognitive decline in senescence-accelerated mice [43]. Moreover, EGCG alters secretase activity and reduces β-amyloid-induced cognitive impairment by inhibiting the ERK and NF-κB pathways [44]. On the other hand, via increasing astrocyte neprilysin production, activation of the ERK and PI3K pathways promotes the EGCG-induced extracellular degradation of the amyloid β-protein. In many mice models of Alzheimer's disease, EGCG reversed a decrease in synaptic proteins and prevented the hyperphosphorylation of tau protein in the hippocampus, which reduced deficiencies in memory and spatial learning [45, 46].

Tea consumption has been associated with a decreased risk of coronary heart disease and atherosclerosis [47, 48]. The Ohsaki National Health Insurance Cohort Study, which comprised 40,530 Japanese individuals aged 40 to 79, discovered a negative correlation between the use of green tea and mortality from cardiovascular disease [49]. Drinking green tea reduced blood pressure and cholesterol in a study done in Norway between the

ages of 35 and 49 that involved 10,233 women and 9856 men without a history of diabetes or cardiovascular disease [50].

There has also been a rise in the usage of EGCG in the treatment of several acute and chronic respiratory problems [51, 52]. For example, in TNFα-induced inflammation, EGCG reduced increases in eosinophil and neutrophil counts in the bronchoalveolar lavage fluid (BALF) and inhibited ICAM-1 expression, oxidative stress, MAPK, and STAT3 activation. In intratracheal LPS-induced pulmonary inflammation, EGCG reduced lung injury and oedema, inflammatory cell counts in the lung, proteinkinase Cα and myeloperoxidase (MPO) activity, TNFα, IL-1β, and IL-6 levels, and enhanced lung regeneration [53].

2. Conclusion

The review concludes that EGCG is a promising agent for inhibiting MMP-3 expression and human pterygium fibroblast migration. Its anti-inflammatory, antioxidant, and anti-angiogenic properties make it a safer alternative to current therapies, offering hope for more effective management of pterygium. To confirm these results and investigate the complete therapeutic potential of EGCG in ophthalmology and other fields, more clinical research is necessary.

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