Curcuma longa aqueous extract: A potential solution for the prevention of corneal scarring as a result of pterygium surgical excision (Review)

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Abstract. Curcumin has been used since ancient times as a treatment for a wide range of pathologies. For centuries, it has been considered to be an effective aid for common human diseases. *Curcuma longa* has been reported to possess various beneficial properties and actions, including anti-inflammatory, proapoptotic, antiangiogenic and cortisone-like actions. Pterygium is a degenerative disorder of the conjunctiva indicative of a strong inflammatory condition that requires surgical treatment, which often results in disfiguring sclerocorneal scars. The delay in the healing of superficial corneal wounds caused by topical administration of light-cortisone results in improved restoration of corneal functions and anatomy compared with physiological healing processes. The present review is focused on the medicinal properties of curcumin, the main component of *Curcuma longa* extract, in particular its strong cortisone-like effect, and its potential use for the prevention and treatment of sclerocorneal scars resulting from pterygium surgical excision.

Contents

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1. Introduction

Curcuma longa is a perennial herb that belongs to the *Zingiberaceae* family (1). It is known by various synonyms, including turmeric and Indian saffron, and has been translated into a number of languages across the world; in Tibetan language it is known as Gaser, whereas in Swahili it is termed Manjano. It is primarily considered to be a coloring agent in the USA, whereas in India it has been used since ancient times as a spice and safe medical remedy, due to its reported beneficial effects in the treatment of dysentery, fever, infections, arthritis and colitis (2). The most notable active components of the herb for medicinal use are curcuminoids; diferuloyl methane represents ~90% of the curcuminoid content in turmeric, followed by demethoxycurcumin and bis-demethoxycurcmin (3-6). For centuries, *Curcuma longa* has been considered to be effective as a treatment for the common cold, urinary tract disease and liver disease, and as a blood purifier (7). Curcumin is extensively used in traditional and alternative medicines, such as Ayurveda, Unani, Siddha and Chinese medicine, for the management of various diseases and conditions, such as wounds, inflammation and cancer (8,9). It was approved as a 'generally safe' compound by the Food and Drug Administration in the USA. In the last three decades, various studies have indicated that curcumin possesses antioxidant, anti-inflammatory, antiangiogenic, and wound-healing properties (10,11). A number of reports indicate potential health benefits of curcumin in the treatment of anterior segment eye diseases (12,13).

2. Pterygium and its treatment

Ocular pterygium is a typically bilateral pathology of the bulbar conjunctiva, generally located on the nasal side and, occasionally, even at the temporal side of the conjunctiva (14). It is characterized by an invasive growth of vascularized connective tissue along with the conjunctival epithelium, resulting in tissue remodeling, fibrovascular proliferation and inflammation (15). Pterygium keratinocytes are tumor-like transforming cells that share features with tumors, such as local invasion, metaplasia, inactivation of tumor suppressor genes and loss of heterozygosity (16). An epidemiological study demonstrated a strong

association between pterygium and UV sunlight exposure, which may damage the DNA; DNA damage has been reported to initiate pterygium development (17). Due to the progressive increase of the ages of populations, the incidence of ophthalmic pterygium is predicted to increase. Despite its benign nature, if untreated, it can grow and invade the cornea, overcoming the corneoscleral junction, impairing visual function and occasionally leading to blindness (18). Although the pathogenesis of the disease is not completely understood, it has been reported that inflammation and fibrosis, angiogenesis and the destruction of the extracellular matrix are factors closely associated with the occurrence of pterygium (19).

At present, surgery is the only effective treatment for pterygium, although relapses are very common; with simple excision techniques, the risk of recurrence has been reported to be >80% (20). The surgical operation consists of the detachment and removal of the pterygium head followed by conjunctival suture, leaving an ample portion of bare sclera or attaching the tissue up to the corneoscleral limbus; it may also be necessary to perform conjunctival reconstruction through the sliding of the tissue or even autologous transplant of the conjunctiva (21). Due to this type of procedure, complications such as infections, conjunctival cysts, or adherent scars limiting ocular movements and impairing visual function may occur (21). A second option for surgical excision of pterygium is the use of amniotic membrane graft, through which a part of the donor's amniotic membrane is fixed to the remaining limbus and bare sclera area after the excision of pterygium (22). The most reliable method is considered to be the use of conjunctival autografts, which involves the removal of the pterygium, essentially leaving an area of bare sclera that is closed by the movement of a free conjunctival transplant from another part of the ocular surface, usually from the superior-temporal part of ocular bulbous (23); however, even this latter method comes with potentially disfiguring corneal complications.

There is no clear-cut single treatment of choice for removing either a primary pterygium or recurrent pterygium; although there are several possible surgical methods (22), there is a high likelihood of sclerocorneal scarring as a result of surgical excision (24). If the scarring extends close to the visual axis, irregular astigmatism and reduced visual function may occur as a disabling complication of the surgery. Moreover, a pterygium that is being removed due to active growth near the visual axis is much more likely to result in some visual loss resulting from scarring near the line of vision (22). The risk is even more accentuated after removal of a recurrent pterygium. Furthermore, recurrences can on occasion be far more aggressive and serious than the original pterygium (25).

Associated with a far lower risk of recurrence is the use of adjunctive pharmacological therapy alongside surgical removal. There are four principal adjunctive therapies of interest: Intraoperative mitomycin; postoperative mitomycin; postoperative β-irradiation; and postoperative 5-fluorouracil (5-FU) (26). Intraoperative and postoperative mitomycin are the most commonly used adjunctive treatments, with mitomycin applied at a dose of 0.2 mg/ml for 3 min during surgery, or for 14 days after pterygium removal, at the same concentration, once daily (27). The recurrence rate is reported to be acceptably low and commensurate with β-irradiation at <10% (28). Nevertheless, there are numerous concerns regarding complications, such as severe pain, corneal and scleral necrosis, and even scleral perforation. With 5-FU, potential complications include cornea opacity, conjunctivitis, sclera granuloma and conjunctiva necrosis (29). Although these complications have been reported rarely, they appear to be most frequently associated with the adjunctive therapies or topical chemotherapy, and may present as a late postoperative issue (26).

At present, there is still no pharmacological treatment of choice for sclerocorneal scarring; cortisone eye drops, which have not led to satisfactory outcomes, are the only existing palliatives. Our recent study reported a proapoptotic effect of *Curcuma longa* on human pterygium keratinocytes (13). Thus, it is hypothesized that curcumin may be an effective topical treatment capable of preventing corneal and scleral scars, and the frequent recurrences following surgical excision of pterygium.

3. Medicinal properties of *Curcuma longa*

Anti-inflammatory properties. It has been suggested that curcumin has a diverse range of molecular targets, supporting the hypothesis that it interacts with multiple cellular signaling pathways and modulates numerous biochemical-metabolic pathways. Both topical and oral administration of curcumin has been found to be as effective as cortisone for the treatment of pain and inflammation (30). Oral intake of *Curcuma longa* substantially reduces inflammatory swelling (4). Furthermore, curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets and cell signaling pathways involved in inflammation, including NF-κB, activated protein-1, STAT, peroxisome proliferator-activated receptor-γ (PPAR-γ) and β-catenin (31). The expression and activation of regulatory proteins such as chemokines, interleukins (ILs), hematopoietic growth factors and transcription factors, which in turn inhibit cellular inflammatory responses and protect cells, has been also reported (31). Of note, *Curcuma longa* is able to inhibit the biosynthesis of prostanoids from arachidonic acid, and curcuminoids inhibit phospholipases, nitric oxide, elastase, hyaluronidase, collagenase, monocyte chemoattractant protein, interferon-inducible protein, tumor necrosis factor and IL-12 (32,33). They also decrease prostaglandin, leukotriene and thromboxane biosynthesis via both cyclooxygenase (COX) and lipoxygenase pathways (34). COX-2 and inducible nitric oxide synthase inhibition by curcumin occur via suppression of NF-κB activation, which occurs by blocking the phosphorylation of IκB (35). Curcumin is an agonist of PPAR-γ, and its activation is associated with the downregulation of NF-κB, which results in a reduction of a number of proinflammatory proteins, such as matrix metallopeptidase (MMP)-9 and MMP-2 (36), both of which play important roles in generating chemotactic stimuli such as vascular endothelial growth factor (VEGF) (37). Curcumin induces anti-inflammatory and proapoptotic effects that may serve beneficial roles in ocular disease (38-40). Furthermore, curcumin induces the downregulation of enzymes such as protein kinase C, which mediates, among other functions, inflammation and tumor cell proliferation (41).

Proapoptotic action. *Curcuma longa* is able to induce apoptotic cell death in pterygium-derived human keratinocytes (13). Evidence suggests that the proapoptotic effects of curcumin are mediated through pro-oxidant pathways (42). Curcumin treatment

leads to the production of reactive oxygen species (ROS) and changes in intracellular glutathione levels; curcumin-induced apoptosis can be inhibited by glutathione (43). Furthermore, the proapoptotic activity of curcumin can be also inhibited by superoxide dismutase and N-acetylcysteine in leukemia cells (42). These findings indicate the involvement of superoxide radicals in the effects of curcumin. The mechanism via which curcumin mediates its pro-oxidant effects is related to mitochondria, which are the major source of ROS in the cell (43). However, it is possible that curcumin activates mitochondrial enzymes, and leads to the production of ROS, which are required for the apoptotic effects of curcumin (44). The generation of ROS induced by curcumin may occur via its interactions with thioredoxin system (45), composed of thioredoxin reductase (TrxR), thioredoxin (Trx), and NADPH, potentially leading to the production of ROS. Curcumin inhibits proliferation and induces apoptosis in cancer cells (46), with minimal effects noted on corresponding non-tumor cell lines. Keratinocytes affected by pterygium exhibit features similar to those of tumors, such as the inactivation of tumor suppressor genes (16), mismatch of the Bax:Bcl-2 homologous antagonist killer protein expression ratio and hypermethylation of the p16 gene promoter (47). These features suggest a possible neoplastic nature of the pathologic condition (48), indicating a basis for potential proapoptotic effects of *Curcuma longa* on these cancer-like cells (13).

Antiangiogenic properties. Angiogenesis is a strictly controlled physiological process regulated by a variety of endogenous angiogenic and angiostatic factors (49). The microvascular system appears capable of responding to physiological demands such as chronic inflammation and wounds with rapid capillary growth (50). VEGF is a prominent proangiogenic growth-promoting hormone, secreted in great quantities in response to hypoxia-inducible factors (51). VEGF upregulates the production of MMPs by endothelial cells in the limbal vascular plexus, stimulating blood vessel formation (52). MMPs and other proteolytic enzymes degrade the extracellular matrix and basement membrane, allowing vascular endothelial cells to enter the sub-epithelial and stromal spaces within the cornea (53). The concentration of VEGF significantly decreases following treatment with curcumin; the inhibitory effects on VEGF synthesis are dose-dependent, with the most potent effect achieved with 80 μmol/l curcumin (54). In addition to effects on VEGF synthesis, Curcumin exhibits direct antiangiogenic activity both *in vitro* and *in vivo* by inhibiting endothelial cell proliferation and corneal neovascularization mediated by fibroblast growth factor (FGF)-2 in a dose-dependent manner (54). Furthermore, curcumin is a strong agonist of PPAR-γ and, according to *in vitro* and *in vivo* models, PPAR-γ ligands exert antiangiogenic effects (55). Finally, curcumin specifically targets the PI3K/Akt/IκB kinase signaling axis, which consequently leads to the suppression of both NF-κB and mTOR pathways, as well as concomitant downregulation of VEGF and activation of caspase pathways (56). These events result in the induction of apoptosis and the prevention of angiogenesis.

4. Curcumin and the cortisone-like effect

The effects of corticosteroids on the corneal epithelium are notable for a number of reasons. Corticosteroids are the most effective drugs for the non-specific suppression of inflammation (57). They prevent corneal neovascularization in clinical and experimental studies (58,59), and are widely used in ophthalmology, but they may delay the healing of corneal stromal wounds (60,61). In fact, the topical application of cortisones decreases the epithelial healing rates compared with a control group treated with placebo (62). It has been shown that the repeated application of 1.0% prednisolone and 0.1% dexamethasone may delay the epithelial wound healing of a superficial epithelium ulcer and markedly reduce the tensile strength of corneal wounds throughout the recovery process (62,63). Unfortunately, the propensity of cortisone, topically administrated in the eye, to raise the intraocular pressure limits its use in the treatment of corneal scars.

Curcumin has been demonstrated to have a potent anti-inflammatory effect and to be as effective as cortisone in cases of chronic inflammation (64). It was observed that the aqueous extract of *Curcuma longa* induces a cortisone-like effect; if applied in the form of eye drops, it is effective in delaying the healing of superficial corneal wounds, with a notable difference in the rate of healing of the superficial corneal wounds when compared with artificial tear eye drops (65). More recently, the anti-inflammatory and analgesic effects of curcumin were attributed to a combination of several properties, namely inhibition of COX, 5-lipoxygenase and glutathione S-transferase (66). It is also notable that curcumin lowers the production of histamine, and increases and extends the action of cortisol, a natural human corticosteroid hormone capable of reducing inflammation and pain (67).

5. Effect of curcumin on the healing of corneal damage

Curcumin has been reported to promote corneal epithelial wound healing, as well as recovery of corneal function (68). A delay in wound healing due to the local application of *Curcuma longa* aqueous extract has been previously observed, occurring in a similar manner to the delayed healing induced by cortisone (69); this contrasts with skin wound healing, in relation to which *Curcuma longa* produces fast wound closure and a short wound healing time (70). It has been reported that the local application of cortisone to corneal wounds delays the rate of healing, reducing the tensile strength of the corneal surface during the healing process (60,63,71). After the use of cortisone eye drops on the cornea surface, ulcer fluorescein staining disappeared after only 80 h (72). Normally, the basal cells of the corneal epithelium form an epithelial plug within 24 h capable of covering the corneal wound, thus restoring the epithelial continuity over the superficial portion of the wound (73). On the basis of studies involving staining the outlines of corneal wounds with fluorescein, it was observed that the fluorescein stain disappeared within 72 h in both superficial and penetrating corneal wounds when placebo eye drops, such as saline solution, were used (65); conversely, the healing of corneal wounds following application of *Curcuma longa* aqueous extract was clearly delayed, as the fluorescein stain did not disappear until 11 days after wound induction. Furthermore, the use of cortisone only resulted in the disappearance of wound fluorescein staining after 128 h (72). Taken together, tensile strength and corneal stretch during corneal wound healing appear to be substantially reduced by the local application of *Curcuma longa* aqueous extract in the

form of eye drops, due to its cortisone-like, anti-inflammatory and wound healing effects, leading to the *restitutio ad integrum* of corneoscleral function. In addition, it has been reported that eye drops formed using an alcoholic extract did not notably delay the rate of healing of corneal wounds, indicating that only some water-soluble factors contained in *Curcuma longa* are responsible for the effect (65).

6. Potential use of *Curcuma longa* aqueous extract as a treatment of scars of the anterior segment of the eye

The primary corneal functions are transmission of incident light, refraction, maintenance of structure, and protection of intraocular structures from pathogens and trauma (74). The transmission and refraction of light through the cornea depends primarily on the transparency of the cornea, which in turn is due to the highly specialized ultrastructure (75). The corneal stroma is a layer rich in extracellular matrix mainly composed of collagen types I and V, proteoglycan fibers, modified fibroblasts and keratocytes, the latter of which account for 2-3% of the stroma volume (76). The transparency of the cornea is due to the collagen fibers arranged in a uniformly equidistant way, arranged in orthogonal lamellae (74). Proteoglycans also play an important role in shaping this unique structure; the leucine-rich proteoglycans present in the stroma are responsible for the precise arrangement of the stromal lamellae by adjusting the interfibrillar distance (77).

Ocular trauma that occurs during surgical pterygium excision often results in scarring and loss of corneal transparency (78). In the event of injury, growth factors play a determining role in stroma repair, as they regulate the organization of the extracellular matrix (ECM) (79). IL-1, transforming growth factor (TGF)-α, TGF-β, FGF-2, insulin-like growth factor 2, epidermal growth factor receptor and connective tissue growth factor, which are mainly produced in the stromal epithelium, tear film and macrophages, induce the production of extracellular matrix-stimulating keratocytes to restore the stromal structure, forming an ordered ECM or scar tissue, depending on their ratios (80). In the early stages of corneal wound healing, actin-containing myofibroblasts synthesize large quantities of collagen, hyaluronic acid and biglicans, and only small amounts of proteoglycan-containing keratin sulfate; this results in the formation of a disorganized and opaque ECM (81). Only in a subsequent phase do myofibroblasts transform into fibroblasts, which, along with keratocytes, synthesize keratan sulfates, collagen type I and collagen type V, thus forming an organized and transparent ECM (82).

During the normal corneal wound healing process, the centripetal contraction movement of the wound edges facilitates the closure of the defect, and results in tensile shrinkage of the corneal epithelium and consequent scar development (83). Based on previously reported studies investigating the anterior segment of the eye (84,85), the use of *Curcuma longa* aqueous extract to prevent disfiguring corneal scarring after surgical excision of pterygium may be a viable treatment option. The extract would be proposed to work by reducing tensile strength of the rapid healing that occurs physiologically after corneal wound scarring (86). Fast wound closure accelerates wound contraction and can exacerbate scar formation (87). It has already been reported in *in vivo* studies that a delay in the healing of superficial corneal wounds caused by topical administration of mild cortisone enables improved restoration of corneal function and anatomy compared with physiological healing (88,89). The use of corticosteroids in the management of corneal scarring has been reported; continued topical use of loteprednol, a mild corticosteroid, for 6 weeks after surgery resulted in the disappearance of leucomatous scars (90). Unfortunately, long-term side-effects of ocular use of cortisone, such as increases in intraocular pressure, glaucoma and cataract, limit its use (91).

Corticosteroids act via the suppression of arachidonic acid formation by producing phospholipase A inhibitory proteins called lipocortins. They temporarily block the exudative phase of inflammation and modulate fibroblast formation during the tissue repair stage. In the acute phase of inflammation, corticosteroids decrease the permeability of capillaries and cellular exudation is reduced (92). Additional mechanisms, such as suppressing leukocyte motility and chemotaxis, and inhibiting inflammatory cytokines, contribute to their action (93). In an *in vitro* study, it was observed that curcumin inhibited human pterygium fibroblast proliferation in a dose- and time-dependent manner (11), potentially leading to reduced tensile strength during wound healing. A delay in wound healing processes allows improved rearrangement of corneal stroma and consequentially complete corneal transparency (94).

During wound healing, free radicals and ROS induce tissue damage and play a major role in the scarring process (95). Several antioxidants have been reported to suppress oxidative damage to these tissues, such as polyphenols, tocopherols and carotenoids (96). Curcumin is a natural phenol that possesses antioxidant activity, inhibiting hydrogen peroxide damage in human keratinocytes and fibroblasts, which may prevent oxidative damage and promote the healing process (97). Topical administration of curcumin was reported to improve all phases of wound repair, including collagen synthesis and maturation, wound contraction and re-epithelialization (69). The current evidence concerning curcumin supports its use in the field of ophthalmology. It is proposed that the topical use of *Curcuma longa* aqueous extract may be an effective approach to facilitate corneal scar healing, and that it is also a viable candidate to prevent pterygium relapse after surgical excision. Additionally, the absence of notable side effects of curcumin treatment in human subjects should also be considered (98). However, further studies may be required for assessing its complete utility.

7. Safety of curcumin

Curcumin appears to be extremely safe and well tolerated in humans, even at high doses. A dose-escalation trial indicated the maximum tolerated dose and safety of curcumin (99). Humans appear to be capable of tolerating high doses of curcumin without notable side effects (100). A phase I study found no adverse effects of curcumin ingestion for 3 months of doses up to 8,000 mg/day: A single dose standardized powder extract of curcumin was administered to 24 healthy volunteers, with the dose ranging from 500-12,000 mg; no curcumin was detected in the serum of subjects administered 500, 1,000, 2,000, 4,000, 6,000 or 8,000 mg curcumin, and only low levels were detected in 2 subjects administered with 10,000 or 12,000 mg curcumin (101). Despite its well-known safety and efficacy, at present curcumin has not been applied

as an ophthalmic therapeutic drug due to its low aqueous solubility (102). Regarding the major limitations of the medicinal use of curcumin, its poor water solubility, stability and bioavailability, there has been considerable progress, including the design of more stable and more potent derivatives, as well as delivery vehicles such as liposomes, microbeads or nanoparticles (103-105). However, as tear fluids wash off eye drops rapidly, topical corneal therapy based on curcumin is still considered a challenge (106).

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All authors contributed to the conception of the study and performed literature searches. GS drafted the manuscript. RDP critically revised the manuscript. All authors read and approved the final manuscript.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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