Potential therapeutic effects of Celastrol on dry eye disease

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Dear Editor

Ocular diseases are a burden on global health. Cataract, diabetes retinopathy, glaucoma, age-related macular degeneration, and dry eyes are common eye conditions [1] and affect the quality of life of patients in terms of physical, emotional, and social activities [2]. Traditional Chinese herbs have been widely used to prevent and treat ocular diseases, including dry eye disease [3]. These are natural and have fewer side effects compared to Western medicines. The potential therapeutic use of a series of traditional Chinese herbs for common eye disorders is an important topic for research [4]. This article describes and discusses the potential role of the traditional Chinese herb, “Celastrol” in treating dry eye disease.

Celastrol is a traditional Chinese herb derived from Tripterygium wilfordii that performs an anti-inflammatory function in managing ocular diseases [5], and several articles on celastrol with eye disorders have been published in recent years [5-12] (Table 1).

A few inflammatory mechanisms are involved in dry eye disease, and comparing them with the anti-inflammatory effects of Celastrol for its therapeutic role in this common eye disease. Interleukin (IL)-8 and IL-6 are inflammatory markers [13-15] that have been proposed in dry eye-related inflammation, and Celastrol reduces IL-8 and IL-6 levels [8, 12]. Tumor necrosis factor-alpha (TNF-α) is elevated in dry eye disease [15], and Celastrol significantly inhibits the TNF-α expression [6, 10, 11]. Inhibition of the nuclear factor kappa B (NF-κB) pathway can attenuate inflammation in dry eye disease [16], with Celastrol exerting an inhibitory effect on NF-κB activation [8, 9, 12]. Matrix metalloproteinase 9 (MMP-9) plays a role in dry eye disease [17, 18]. Celastrol-loaded nanomicelles significantly suppress macrophage-induced corneal neovascularization by inhibiting vascular endothelial growth factor and MMP-9 expressions [10].

Considering the aforementioned in vitro and in vivo evidence supporting the anti-inflammatory properties of traditional Chinese herb, Celastrol could be a possible therapeutic candidate for dry eye disease. However, much more works are required, particularly human clinical studies on dosage and toxicity assessments as well as the development of celastrol nanomedicine in the future.

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### Table 1. Published papers on Celastrol and eye disorders

<table>
<thead>
<tr>
<th>Author (Year of Publication)</th>
<th>Objective</th>
<th>Results</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>Xia et al. (2022) [6]</td>
<td>To identify potential drugs and validate them using bioinformatics in experimental autoimmune uveitis mice considering the unknown pathogenesis of Behçet’s disease</td>
<td>Celastrol significantly inhibited the expressions of TNF and IL-1β in the mice retina.</td>
<td>In Celastrol-treated mice, anterior chamber and retinal inflammations were reduced.</td>
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<td>Li et al. (2021) [7]</td>
<td>To investigate the effect of Celastrol-based nanomedicine on corneal allograft survival</td>
<td>Celastrol inhibited the M1 macrophage and TLR4 expression in corneal allografts through the TLR4/MyD88/NF-κB pathway and significantly decreased the secretion of multiple proinflammatory cytokines to promote corneal allograft survival.</td>
<td>Celastrol-based nanomedicine for corneal allograft rejection was more potent compared to conventional eye drops for ocular anterior segment diseases.</td>
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<td>Zhang et al. (2019) [8]</td>
<td>To investigate the effect of Celastrol on inflammation in human RPE cells and involvement of NF-κB signaling</td>
<td>Celastrol significantly inhibited LPS-induced protein and mRNA expression levels encoding proinflammatory cytokines, IL-6, IL-8, and MCP-1 in HRPE and ARPE-19 cells, which ameliorated LPS-induced inflammation.</td>
<td>Celastrol is a potent anti-inflammatory agent in RPE cells and might be used to prevent and treat age-related macular degeneration.</td>
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<td>Gu et al. (2018) [5]</td>
<td>To investigate the effect of Celastrol on ocular hypertension-induced degeneration of RGCs</td>
<td>Systemic and intravitreal administrations of Celastrol stimulated the survival of RGCs injured by optic nerve crush, and mechanisms underlying Celastrol’s RGC protection effect might be associated with inhibition of TNF-α-mediated cell death.</td>
<td>The number of RGCs increased, and Celastrol mediated neuroprotection against elevated intraocular pressure-induced injury.</td>
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<td>Li et al. (2016) [9]</td>
<td>To investigate anti-inflammatory effects of Celastrol on orbital fibroblasts of patients with Graves’ ophthalmopathy</td>
<td>Expressions of IL-6, IL-8, COX-2, and ICAM-1 were reduced, and IL-1β-induced increase in expressions of IL-6, IL-8, ICAM-1, and COX-2 was inhibited. Suppression of the prostaglandin E2 level in orbital fibroblasts was induced by IL-1β. Attenuation of IL-1β-induced inflammatory responses was associated with inhibiting NF-κB activation.</td>
<td>Celastrol may be a potential treatment for Graves’ ophthalmopathy through attenuation of the inflammatory process.</td>
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<td>Li et al. (2016) [10]</td>
<td>To investigate effects of Celastrol-loaded nanomicelles on activated macrophage-induced CNV and cytokine secretion in rats and macrophages, respectively</td>
<td>Celastrol-loaded nanomicelles significantly inhibited the migration and invasion of human umbilical vein endothelial cells; potently attenuated expressions of VEGF, TNF-α, IL-1β, MCP-1, CINC-3, and MMP-9 protein; and downregulated the ERK1/2, p38 MAPK, NF-κB activations and HIF-1α expression in macrophages. The length and area of CNV were significantly lower in the Celastrol-loaded nanomicelles group than in the control group. After pretreatment with Celastrol-loaded nanomicelles, VEGF and MMP-9 expressions reduced significantly in activated macrophages and corneal tissues.</td>
<td>Celastrol-loaded nanomicelles significantly suppressed macrophage-induced CNV by inhibiting VEGF and MMP-9 expressions. The effect was possibly mediated through attenuation of macrophages via HIF-1α, MAPK, and NF-κB signaling pathways.</td>
</tr>
<tr>
<td>Kyung et al. (2015) [11]</td>
<td>To investigate the effect of Celastrol on survival of RGCs injured by optic nerve crush</td>
<td>Survival of RGCs injured by optic nerve crush in Celastrol-treated animals was better compared to the control group. The TNF-α expression level was decreased in Celastrol-treated animals with or without injury.</td>
<td>Celastrol could exert a RGC protective effect through inhibition of TNF-α-mediated cell death.</td>
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<td>Paimela et al. (2011) [12]</td>
<td>To investigate effects of Hsp70 expression on NF-κB RelA/p65 activity in human RPE cells in vitro using the anti-inflammatory property of Celastrol</td>
<td>Celastrol reduced the IL-6 expression level and activity of phosphorylated NF-κB in LPS-exposed cells. However, silencing the Hsp70 response attenuated the inhibitory effect of Celastrol on NF-κB RelA/p65 activity. No signs of cytotoxicity were detected after administration of anti-inflammatory concentrations of Celastrol.</td>
<td>Celastrol inhibited innate immunity response in RPE cells via the NF-κB pathway and regulation of Hsp70, which is an essential regulator of NF-κB.</td>
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</table>

**Abbreviations:** TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; TLR4, toll-like receptor 4; RPE, retinal pigment epithelium; HRPE, human retinal pigment epithelium; ARPE, animal retinal pigment epithelium; NF-κB, nuclear factor kappa B; LPS, lipopolysaccharide; mRNA, messenger ribonucleic acid; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; RGCs, retinal ganglion cells; COX-2, cyclooxygenase-2; ICAM-1, intercellular adhesion molecule 1; VEGF, vascular endothelial growth factor; CAM-1, intercellular adhesion molecule-1; IL-1α, interleukin-1 alpha; HIF-1α, hypoxia-inducible factors-1α; NF-κB, nuclear factor kappa B; LPS, lipopolysaccharide; mRNA, messenger ribonucleic acid; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; RGCs, retinal ganglion cells; COX-2, cyclooxygenase-2; ICAM-1, intercellular adhesion molecule 1; VEGF, vascular endothelial growth factor; ICAM-1, intercellular adhesion molecule-1; IL-1α, interleukin-1 alpha; CINC-3, Cytokine-induced neutrophil chemoattractant 3; MMP-9, matrix metalloproteinase-9; ERK1/2, extracellular signal-regulated kinase 1/2; p38 MAPK, p38 mitogen-activated protein kinase; HIF-1α, hypoxia-inducible factors-1α; NF-κB signaling pathways.
ETHICAL DECLARATIONS

Ethical approval: Not required.
Conflict of interests: None

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REFERENCES