Therapeutic Efficacy of Nanocomplex of Poly(Ethylene Glycol) and Catechin for Dry Eye Disease in a Mouse Model

Hyesook Lee,1 Whuisu Shim,2 Chae Eun Kim,1,3 So Yeon Choi,1 Haeshin Lee,4,5 and Jaewook Yang1,3

1T2B Infrastructure Center for Ocular Diseases, Inje University Busan Paik Hospital, Busanjin-gu, Busan, Republic of Korea
2Department of Chemistry (BK21 Plus Program), Korea Advanced Institute of Science and Technology (KAIST), Yuseong, Daejeon, Republic of Korea
3Department of Ophthalmology, Inje University College of Medicine, Busanjin-gu, Busan, Republic of Korea
4Department of Chemistry (BK21 Plus Program) and the Graduate School of Nanoscience and Technology, Korea Advanced Institute of Science and Technology (KAIST), Yuseong, Daejeon, Republic of Korea
5InnoTherapy, Inc., Yeongdrungpo-gu, Seoul, Republic of Korea

Correspondence: Jaewook Yang, Department of Ophthalmology, Inje University College of Medicine, 75 Bokjiroro, Busanjin-gu, Busan 47392, Republic of Korea; ocuuloplasty@gmail.com.

HL and WS are joint first authors.

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PURPOSE. We investigated the possibility of the nanocomplex of poly(ethylene glycol) (PEG) and catechin as a new biomedical material to treat dry eye disease.

METHODS. NOD.B10.H2b mice were exposed to an air draft and injected with scopolamine for 10 days. Ten days later, the mice were treated with normal saline (n = 11), 1% catechin (n = 11), 1% PEG (n = 11), and 1% catechin/PEG nanocomplex solution mixture containing catechin and PEG at weight ratios of 1:1 (CP1, n = 11), 1:5 (CP5, n = 11), and 1:10 (CP10, n = 11). All treatments were administered five times a day for 10 days. We estimated the effect of PEG/catechin nanocomplexes on inflammation, tear production, epithelium stabilization, and goblet cell density.

RESULTS. Desiccation stress significantly decreased tear production and increased the corneal irregularity score. Furthermore, desiccation stress markedly increased the detached epithelium and decreased the numbers of conjunctival goblet cells. In addition, the expression of proinflammatory-related factors was markedly induced by desiccation stress in the lacrimal glands. However, the PEG/catechin nanocomplex effectively induced an increase in tear production, stabilization of the corneal epithelium, and an increase in conjunctival goblet cells and anti-inflammatory improvements in a PEG dose-dependent manner.

CONCLUSIONS. In this study, we found that PEG may increase bioavailability of catechin. Therefore, the PEG/catechin nanocomplex can be used as a new biomedical material to treat dry eye disease through stabilization of the tear film and inhibition of inflammation.

Keywords: dry eye disease, poly(ethylene glycol), catechin, tear production, conjunctival goblet cell, inflammation

Dry eye disease is a multifactorial disorder of the tears and ocular surface, including imbalance of tear film, hyperosmolality, and inflammatory damage.1 Inflammation is considered a key factor in the pathogenesis of dry eye caused by a vicious cycle of damage to the ocular surface, including gradual dysfunction and destruction of the lacrimal glands and impairment of the conjunctival epithelium.2,5 Based on this concept, anti-inflammatory agents are the current general trend of therapy for dry eye among the various treatment options.4

Catechin (flavan-3-ol) is a member of the flavonoids and is known as a natural antioxidant found in various fruits, beverages, and tea.5 Catechins have recently attracted much attention with regard to their beneficial effects, including antibacterial, anticarcinogenic, and anti-inflammatory properties.6–9 Previous studies reported that epigallocatechin gallate (EGCG), a derivative of catechin, has therapeutic effects for ocular disease, including dry eye, glaucoma, and various retinal dysfunctions via its anti-inflammatory and antioxidant capacity.10 In 2011, Lee et al.11 demonstrated that EGCG has a beneficial effect on inhibiting proinflammatory mediators in murine dry eye. However, they performed only a clinical observation using fluorescein staining in a dry eye mouse model, and the pathogenesis including inflammation, lymphangiogenesis, and apoptosis was evaluated in vitro in corneal epithelial cells.11 Although catechin is a powerful antioxidant, the utilization of catechin is limited because of its propensity to act as a prooxidant depending on the doses and a low bioavailability attributed to poor solubility in water.9,12 Currently, many investigators have reported that increasing the molecular weight of catechin improved biological properties with a longer circulation time.5,13

Poly(ethylene glycol) (PEG) is a nonionic and hydrophilic polymer widely used in various therapeutic biological drugs as a drug delivery system.14–17 Poly(ethylene glycol)-based copolymers play a potential role as biomedical material for biomedical applications because they are biocompatible, biodegradable, and thermosensitive and have easily controlled properties.18 In 2008, Mok et al.16 reported the applicability of nanocomplexes of PEG and biomacromolecules (such as proteins, DNA, and carbohydrates) for long-acting and sus-
Effect of Nanocomplex of Catechin and PEG for Dry Eye

Materials and Methods

Preparation of the PEG/Catechin Nanocomplex

Catechin and PEG with an average MW = 4600 g per mole were purchased from Sigma-Aldrich Corp. (St. Louis, MO, USA). Methanol was purchased from Merck Millipore (Temecula, CA, USA). Catechin and PEG solutions are prepared separately before preparing the complex. First, catechin was dissolved in methanol at a concentration of 10 mg/mL; PEG was dissolved in distilled and deionized water (DDW) at various concentrations of 2, 10, and 20 mg/mL. Catechin solution and each PEG solution were mixed together at a volume ratio of methanol to DDW of 1:1, 1:5, and 1:10. The resulting solution mixture contained a weight ratio of PEG to catechin of PEG/catechin 1:1, 1:5, and 1:10 and was mixed vigorously for 15 minutes. The solution was then transferred into an evaporator to remove residual methanol from the solution at 50°C for 2 hours. The solution was then filtered with a 0.45-μm filter and lyophilized to obtain powder form. The same procedure was also repeated for pure catechin and PEG. Completely dried PEG/catechin, catechin, or PEG powders contained a weight ratio of PEG to catechin of PEG/catechin 1:1, 1:5, and 1:10.

Preparation of the Complex

For instilling five times per day. The rest were discarded. Thawed each day, and the thawed vial was kept in a refrigerator. The same procedure was also repeated for pure catechin and PEG. Completely dried PEG/catechin, catechin, or PEG powders contained a weight ratio of PEG to catechin of PEG/catechin 1:1, 1:5, and 1:10.

Preparation of the Complex

The resulting solution mixture contained a weight ratio of PEG to catechin of PEG/catechin 1:1, 1:5, and 1:10 and was mixed vigorously for 15 minutes. The solution was then transferred into an evaporator to remove residual methanol from the solution at 50°C for 2 hours. The solution was then filtered with a 0.45-μm filter and lyophilized to obtain powder form. The same procedure was also repeated for pure catechin and PEG. Completely dried PEG/catechin, catechin, or PEG powders contained a weight ratio of PEG to catechin of PEG/catechin 1:1, 1:5, and 1:10.

Animals and Experimental Procedures

Animal care and all experimental procedures were performed in accordance with the Guideline for Animal Experimentation of Inje University Busan Paik Hospital with the approval of the Institutional Animal Care and Use Committee (No. 2016-005) and according to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. A total of 83 NOD.B10.H2b mice (6 weeks old) were obtained from Jackson Laboratory (Bar Harbor, ME, USA) and were adapted for 6 to 10 weeks. Animals were housed in a semi-pathogen-free facility with filter top lids, with food made available ad libitum. Six mice were used for histopathologic analysis at the baseline. Seventy-seven mice were injected subcutaneously with 500 μg/200 μL scopolamine hydrobromide (Sigma-Aldrich Corp.), a muscarin-

Tear Secretion

Tear volume was measured as previously described. Briefly, phenol red-impregnated cotton threads (Zone-Quick; Oasis, Glendora, CA, USA) were placed in the lateral canthus. After 20 seconds, wet threads were turned red by the tears, which we observed through a stereo zoom microscope (SZX7; Olympus Corp., Tokyo, Japan). Tear secretion was calculated using the standard curve with a basic solution (1.5 L of 0.9% saline and 5 mL of 5 N NaOH).

Corneal Irregularities

Corneal irregularities were scored according to the previously described method. The image of a white ring on the corneal surface was acquired using a stereo zoom microscope. The corneal surface was photographed 2 hours after the last scopolamine injection at DS 10d and 1 hour after the last instillation of the catechin and PEG/catechin nanocomplex eye drops. The projected ring was divided into four quarters of 3 clock hours each. The corneal irregularity score was calculated using a 5-point scale based on the number of distorted quarters in the reflected ring: 0, no distortion; 1, distortion in 1 quarter of the ring (3 clock hours); 2, distortion in 2 quarters (6 clock hours); 3, distortion in 3 quarters (9 clock hours); 4, distortion in all 4 quarters (12 clock hours); and 5, severe distortion in which no ring could be recognized.

Corneal Fluorescein Staining

Corneal fluorescein staining was performed according to previous description. One microliter of 5% fluorescein was applied to the lateral conjunctival sac of the mice, and the eyes were examined for fluorescein staining with a slit-lamp biomicroscope (SL-D7; Topcon Medical Systems, Inc., Oakland, NJ, USA) under a cobalt blue light. Punctate staining was recorded in a masked fashion using the standard National Eye Institute grading system, giving a score from 0 to 3 for each of the five areas of the cornea.

Histology

The surgically excised orbits of the mice were fixed in 10% formalin and embedded in paraffin. The tissue was cut with a
Effect of Nanocomplex of Catechin and PEG for Dry Eye

**TABLE.** List of Primary Antibodies Used in Immunohistochemistry

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Type</th>
<th>Dilution</th>
<th>Manufacturer*</th>
<th>Catalog No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICAM-1</td>
<td>MM</td>
<td>1:200</td>
<td>Millipore</td>
<td>MAB2130</td>
</tr>
<tr>
<td>IL-1β</td>
<td>RbP</td>
<td>1:500</td>
<td>Abcam</td>
<td>ab9722</td>
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<td>IL-6</td>
<td>RbP</td>
<td>1:500</td>
<td>Abcam</td>
<td>ab7737</td>
</tr>
<tr>
<td>IL-17</td>
<td>RbP</td>
<td>1:200</td>
<td>Abcam</td>
<td>ab79056</td>
</tr>
<tr>
<td>MMP-2</td>
<td>RbP</td>
<td>1:200</td>
<td>Abcam</td>
<td>ab37150</td>
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<tr>
<td>MMP-9</td>
<td>RbP</td>
<td>1:200</td>
<td>LifeSpan</td>
<td>LS/B2480-50</td>
</tr>
<tr>
<td>TNF-α</td>
<td>RbP</td>
<td>1:200</td>
<td>Abcam</td>
<td>ab66579</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>RbP</td>
<td>1:200</td>
<td>Bios</td>
<td>bs-0920R</td>
</tr>
</tbody>
</table>

* Abcam, Inc., Cambridge, UK; Bios, Inc., Woburn, MA, USA; LifeSpan BioSciences, Inc., Seattle, WA, USA; Merck Millipore Co., Temecula, CA, USA.

**Immunohistochemistry**

The lacrimal glands of the mice were surgically excised, fixed in 10% formalin, and embedded in paraffin. Immunohistochemical analysis was performed according to the previous description. Briefly, 5-μm paraffin sections were deparaffinized, rehydrated, cooked in antigen retrieval solution, and dipped in 3% hydrogen peroxide solution for 30 minutes. The specific primary antibodies were incubated for 1 hour at room temperature (Table) and then washed. The sections were incubated for 40 minutes with secondary antibody obtained from Dako Corp. (Glostrup, Denmark). The sections were visualized with dianobenzidine chromogen and were counterstained with Mayer’s hematoxylin (Sigma-Aldrich Corp.) for 30 seconds. Images of the sections were photographed using a virtual microscope.

**Statistical Analyses**

The data were analyzed with SPSS version 22.0 (SPSS, Chicago, IL, USA) and were expressed as means ± standard deviation (SD). The differences between the groups were analyzed using 1-way ANOVA and statistical significance was defined as $P < 0.05$ by Tukey’s test.

**RESULTS**

**Effect of the PEG/Catechin Nanocomplex on Tear Production**

The tear volume was $0.16 \pm 0.02 \mu L$ at the baseline in the NOD.B10.H2<sup>d</sup> mice, but the desiccation stress significantly decreased tear production to $0.02 \pm 0.01 \mu L$ compared to the baseline ($P < 0.05$, Fig. 1). However, the tear volumes of the catechin group and the CP10 group were markedly increased to $0.13 \pm 0.01$ and $0.15 \pm 0.03 \mu L$ 5 days after treatment compared to the vehicle ($P < 0.05$). In addition, the topical PEG/catechin nanocomplexes gradually increased tear production in a dose-dependent manner. The topical catechin eye drops not only impaired tear production ($0.08 \pm 0.03 \mu L, P < 0.05$) from 3 days after treatment compared to DS 10d, but also increased tear production in a time-dependent manner. Furthermore, the tear volume of the catechin group recovered to the baseline level 5 days after treatment. As shown in the CP1 group, the tear volume significantly increased 5 days after treatment compared to DS 10d, and the levels were similar to the baseline 10 days after treatment ($0.16 \pm 0.03 \mu L$). The CP5 group also showed a marked increase in tear volume ($0.10 \pm 0.02 \mu L, P < 0.05$) compared to DS 10d 3 days after treatment and returned to the baseline level 7 days after treatment ($0.13 \pm 0.01 \mu L$). The tear volume of the CP10 group was statistically different from DS 10d 3 days after treatment ($0.07 \pm 0.02 \mu L, P < 0.05$) and was similar to the baseline 5 days after treatment. However, although the tear production of the PEG group tended to increase, it was not significantly different from that of the vehicle.

**Effect of the PEG/Catechin Nanocomplex on Corneal Surface Irregularities**

The desiccation stress gradually increased corneal irregularities in all groups (Fig. 2A). However, the PEG/catechin nanocomplex groups and the catechin group indicated a circular white ring 7 and 10 days after treatment, respectively. The distorted white ring of the vehicle and PEG groups did not improve after 10 days of treatment. The quantitative data of corneal irregularity scores and the comparison between and within groups are shown in Figure 2B. The irregularity scores following desiccation stress gradually increased to $4.44 \pm 0.62 (P < 0.05)$ compared to the baseline ($0.44 \pm 0.55$). In the CP1, CP5, and CP10 groups, the scores of corneal irregularity significantly decreased to $2.75 \pm 0.29, 2.38 \pm 0.25,$ and $2.25 \pm 0.30$ compared to the vehicle group ($3.65 \pm 0.48$) 7 days after treatment, respectively ($P < 0.05$). However, the catechin group did not statistically differ from the vehicle group 7 days after treatment ($2.88 \pm 0.48$), but catechin markedly impaired corneal irregularity 10 days after treatment ($2.38 \pm 0.47$) $P < 0.05$ versus the vehicle group). Although PEG tended to decrease corneal irregularity, it was not significantly different from that of the vehicle. The corneal irregularity of the vehicle group did not statistically differ from DS 10d.
The Effect of the PEG/Catechin Nanocomplex on Corneal Fluorescein Staining

The fluorescein staining of the corneas was significantly increased to 10.61 ± 0.91 by desiccation stress (Fig. 3). However, the catechin group (6.67 ± 0.58) and the CP10 group (7.33 ± 0.57) were markedly decreased 7 days after treatment and statistically differed from the vehicle group (10.00 ± 1.00). At 10 days after treatment, the corneal fluorescein score was not statistically different between the catechin group (3.67 ± 0.58) and the CP10 group (4.33 ± 0.58). All but the catechin and CP10 groups did not statistically differ from the vehicle group at each time point.
Effect of the PEG/Catechin Nanocomplex on the Desquamation of the Corneal Epithelium

The corneal sections of the mice were stained with H&E at baseline, at DS 10d, and 10 days after treatment (Fig. 4A). The detached epithelial cells were more frequently observed at DS 10d. However, the CP10 group showed a reduction in the number of detached epithelial cells. Figure 4B shows the quantitative data of numbers of detached corneal epithelial cells per 0.1 mm². The desiccation stress markedly increased the detached epithelial cells to 1.60 ± 0.35/0.1 mm² ($P < 0.05$, versus control). In contrast, the desquamated corneal epithe-
Effect of Nanocomplex of Catechin and PEG for Dry Eye

Effect of the PEG/Catechin Nanocomplex on Conjunctival Goblet Cell Population

The inferior fornix conjunctivae of NOD.B10.H2b mice were stained with PAS, and the result showed goblet cells as a strong violet color. As shown in Figure 5B, the numbers of goblet cells were 12.86 ± 0.76/0.1 mm² in the control mice but gradually decreased to 6.19 ± 0.16/0.1 mm² due to desiccation stress (P < 0.05). Nevertheless, the numbers of goblet cells in the catechin, CP1, and CP5 groups significantly increased to 9.71 ± 1.25/0.1, 8.00 ± 0.29/0.1, and 9.24 ± 0.87/0.1 mm² compared with the desiccation stress group, respectively (P < 0.05). However, the levels of goblet cells in these groups did not statistically differ between the groups and did not recover to the control level. The numbers of goblet cells in the PEG group also increased to 8.29 ± 0.28/0.1 mm² and were similar to those in the CP1 group. In contrast, the topical CP10 eye drops markedly increased goblet cells to 13.52 ± 1.67/0.1 mm² (P < 0.05, versus DS 10d), and the levels were similar to the control level. The numbers of goblet cells in the vehicle group did not statistically differ from DS 10d.

Effect of the PEG/Catechin Nanocomplex on Inflammatory Cytokine Expression

Figure 6A shows the sections of the lacrimal glands that were immunostained with antibodies for proinflammatory cytokines. The expression of IL-1β, IL-6, and TNF-α was markedly increased to 2.04-, 3.55-, and 4.02-fold of the control by...
desiccation stress, respectively ($P < 0.05$, Fig. 6B). However, the topical CP5 and CP10 eye drops significantly decreased the expression level to 48.67% and 60.08% on DS 10d, respectively ($P < 0.05$). CP10 gradually suppressed the expression of these inflammatory factors to the control levels. In contrast, the catechin group was not statistically different from DS 10d; the CP1 and PEG groups also had no effect on the expression of proinflammatory cytokines in the lacrimal glands.

**Effect of the PEG/Catechin Nanocomplex on IL-17 Expression**

The desiccation stress gradually increased expression of IL-17 in the lacrimal glands ($15.35$-fold of control, $P < 0.05$; Fig. 7). However, the catechin group and all groups of the PEG/catechin nanocomplex had significantly decreased expression of IL-17 in a PEG dose-dependent manner. The topical CP10 eye drops especially markedly decreased 68% of the expression of IL-16 in the lacrimal glands ($P < 0.05$). Interleukin-6 expression was not affected in the vehicle and PEG groups.

**Effect of the PEG/Catechin Nanocomplex on the Expression of Adhesion Molecules and Matrix Metalloproteinases**

The expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) was significantly increased 2.36- and 6.98-fold of control by desiccation stress ($P < 0.05$). However, the expression of these adhesion molecules in the catechin, CP1, and CP5 groups was not significantly different from DS 10d and the vehicle group. However, the expression of ICAM-1 and VCAM-1 in the topical CP10 group markedly decreased to control levels (1.20- and 1.26-fold of control, respectively). The desiccation stress also gradually increased the expression of matrix metalloproteinase (MMP)-2 and MMP-9 in the lacrimal gland (4.27- and 4.61-fold of control, respectively; $P < 0.05$). All of the groups were not affected by the expression of MMP-2 in the lacrimal gland, whereas only CP10 eye drops significantly decreased the MMP-2 expression to control levels (62.76% of DS 10d). In addition, the expression of MMP-9 was also markedly decreased to control levels as 72% of DS 10d. The expression of MMP-9 in the lacrimal gland was not affected in the vehicle...
and PEG groups. Although the topical catechin, CP1, and CP5 eye drops significantly decreased MMP-9 expression compared to DS 10d, the levels did not recover to the control level.

**DISCUSSION**

In the present study, we evaluated the effects of the nanocomplex of PEG and catechin in the experimental dry eye mouse model and considered the possibility of using this nanocomplex as a therapeutic biological drug for dry eye syndrome. First, we evaluated the effect of catechin, a natural antioxidant, on the stabilization of precorneal tear film, including tear production, corneal epithelium detachment, and goblet cell population in the dry eye mouse model. Second, these results were compared to the effects of adding PEG, a hydrophilic polymer used for drug delivery systems.

Dry eye disease results in potential damage to the ocular surface with symptoms of foreign body sensation, visual impairment, and tear film instability. Therefore, evaluation for damage to the ocular surface is important. Several studies have suggested an evaluation method for damage to the ocular surface in dry eye animal models that included tear volume, fluorescein score, corneal irregularity score, and histologic analysis. In this study, we found that the tear volume significantly decreased in the dry eye mouse model; topical catechin eye drops markedly increased tear production from 5 days after treatment compared to the vehicle (Fig. 1), but did not recover to the baseline. Furthermore, the topical PEG/catechin nanocomplexes gradually increased tear production in a PEG dose-dependent manner. The tear volume of the CP10 group was statistically different from DS 10d 3 days after treatment and was similar to the baseline 5 days after treatment.

Additionally, desiccation stress induced an increasing corneal irregularity score and fluorescein score (Figs. 2, 3). However, topical catechin and CP10 drops markedly decreased corneal irregularity and fluorescein scores; all but the catechin and CP10 groups did not statistically differ from the vehicle group at each time point. Moreover, the amount of desquamated corneal epithelium significantly decreased to the baseline with topical CP10 eye drops, and all but the CP10 group did not statistically differ from DS 10d (Fig. 4). Furthermore, we observed the population of the conjunctival goblet cells that secrete the mucin that stabilizes the tear film and protects the cornea. Goblet cell loss in dry eyes is often associated with a poorly protected and irregular cornea and may lead to sight-threatening corneal ulceration and perforation. In this study, the topical CP10 eye drops markedly increased goblet cells to control levels (Fig. 5). These results corresponded with an improvement in the corneal epithelium desquamation and a decrease in the corneal irregularity score and fluorescein score. Although catechin and CP10 had similar effects including increasing tear production and improvement of corneal irregularities, topical CP10 is more effective in corneal epithelium detachment. These results suggest that adding PEG might overcome the low bioavailability of catechin. CP10 eye drops improved stabilization of the ocular surface through increased tear production, suppression of desquamated corneal epithelium, and improvement of corneal smoothness, including irregularities and fluorescein scores.

Inflammation plays a critical role in the pathogenesis of dry eye. Desiccation stress stimulates the production of proinflammatory cytokines and results in T-cell-activated autoimmune inflammation. Th17-secreted IL-17 was recently shown to disrupt corneal epithelial barrier function, and activation of IL-17 leads to epithelial damage through increased secretion of MMPs and inflammatory cytokines. The inflammation of the ocular surface results in a vicious cycle of damage to the ocular surface, including gradual dysfunction and destruction of the lacrimal glands and impairment of the conjunctival epithelium. Current findings have shown that the lacrimal and submandibular glands are the first affected in the disease process, and MMPs and other proinflammatory cytokines are upregulated in mouse models. In this study, we evaluated the effect of catechin and the PEG/catechin nanocomplex on the production of inflammatory cytokines, expression of Th17-secreted IL-17, and upregulation of MMPs and adhesion molecules in experimental dry eye mice. Our results show that desiccation stress significantly induced the expression of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α in the lacrimal gland, but this elevation was gradually decreased to control levels by topical CP10 eye drops (Fig. 6). In addition, desiccation stress increased not only the expression of IL-17 (Fig. 7), but also the expression of MMPs and adhesion molecules (Fig. 8). However, these inflammatory-related factors were significantly decreased only with CP10 treatment. Therefore, these results suggested that even though...
Topical treatment of catechin alone is ineffective on inflammation, catechin can have an anti-inflammatory effect through the drug delivery system along with PEG.

Overall, we found that the highest PEG-to-catechin weight ratio, CP10, was the most suitable sample for the treatment for the dry eye model. The PEG/catechin nanocomplex effectively induced an increase in tear production, stabilization of the corneal epithelium, increase in conjunctival goblet cells, and anti-inflammatory improvements in this experimental model of dry eye in a PEG dose–dependent manner. On the other hand, without presence of PEG, catechin has poor bioavailability due to insoluble precipitates in the solution, and any further increase in insoluble catechin concentration without PEG could cause strong irritation because of solid precipitates. In conclusion, PEG may increase bioavailability of catechin, and therefore PEG/catechin nanocomplex can be used as a new biomedical material to treat dry eye disease by stabilization of the tear film and inhibition of inflammation.

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Effect of Nanocomplex of Catechin and PEG for Dry Eye

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