Recent advance in natural plant products for treatment of dry eye disease

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Abbreviations
DED, dry eye disease; NO, nitric oxide; SOD2, superoxide dismutase 2; GPx, glutathione peroxidase; Bax, Bcl-2-associated X protein; Polydatin, 3,5,4′-trihydroxyxystilbene-3-β-mono-D-glucoside; PLGA NP, poly(lactic-co-glycolic acid) nanoparticles; CFTR, Cystic fibrosis transmembrane conductance regulator; SM934, β-aminoarteether meleate.

Citation

Abstract
Dry eye disease (DED), a chronic multifactorial illness of the ocular surface with itching, burning, irritation, eye fatigue and ocular inflammation, may result in potential damage, such as cornea and conjunctiva, and even decreased vision. With the global prevalence of DED on the rise, it is crucial to find treatment options with minimal side effects. Natural plant products have shown promise in alleviating DED symptoms and may serve as a potential approach for its treatment. However, their application as instilled drugs is limited by solubility, stability and biological barriers. This review summarizes recent studies (published in the last 5 years) on natural plant products and their derivatives for the treatment of DED, focusing on efficacy, mechanism, drug delivery systems. Meanwhile, their shortcomings are also discussed. By exploring these aspects, we find polyphenol, flavonoid and others natural plant products can effectively improve or treat DED by different mechanisms, and suitable delivery system and structural modification can enhance their therapeutic effect, suggesting they are likely to become candidates for the treatment of DED.

Keywords: dry eye disease; natural plant products; mechanism; polyphenol; flavonoid
**Introduction**

Dry eye disease (DED) with increased tear film osmotic pressure and ocular surface inflammation, is one of the most common factors for ophthalmology visits [1] and can cause various types of symptoms, such as ocular discomfort, instability of tear films and visual disturbance [2, 3]. DED was defined as “a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage” by the Tear Film and Ocular Surface Society Dry Eye Workshop II in 2017 [4]. The causes of DED are multi-factorial, among which tear film instability, ocular surface hypertonic inflammation and injury, and nerve sensory abnormalities play important etiological roles [5]. In terms of its impacts on people, DED not only affects the physical, psychological, and social quality of life of patients, and reduces the patient's productivity, but also may lead to vision damage or blindness without appropriate treatment [6]. The prevalence rate is up to 5%-35% at various ages [1, 7], becoming an increasingly serious health problem [6].

Although no definitive therapy exists, there are various DED treatments or remission modalities, including warm compresses and topical medications, the important of which is the topical application of medications, such as immunosuppressant (such as cyclosporin), artificial tears (such as sodium hyaluronate, methylcellulose), integrin inhibitor (such as lifitigrafst), and secretagogues (such as diquafosol sodium and rebamipide) [8, 9]. However, patient compliance is poor due to delayed efficacy or side effects. Therefore, there is an urgent need to find drugs for treating DED with little or no side effects.

A good source of new drug research and development is natural plants, and its products are usually used to discover and design drug due to good pharmacology or biological activity. Historically, many natural products (secondary metabolites) and natural product derivatives have become our new drugs [10-12]. Moreover, numerous medicinal plants that are used to treat eye diseases have been recorded by different cultures. There are some natural plant products that can be used to treat DED. Because of this, we focus mainly on the articles published in the last 5 years about compounds coming from natural plants in patients with DED and review their research progress to provide guidance for drug discovery of DED in the future.

**DED risk factors and classification**

DED is associated with many risk factors, including environment, lifestyle and health, such as carbon monoxide, nitrogen dioxide, pterygium, excessive multivitamins and caffeine, taking medication, and other diseases [13, 14]. At present, oxidative stress and inflammation are known pathogenic factors of DED [15, 16]. According to the etiology, DED can be divided into “type of decreased lacrimal secretion due to lack of water” and “type of high evaporation due to increased tear film evaporation”, as well as possible mixed cases between the two types [17]. Subcategories can be classified with reference to the different predominant etiologies [4]. For example, based on an abnormal function of gland, eyelid or blink, they can be sub-divided into several subtypes, including lipid anomaly, immune disease, lid surface anomalies and so on [18]. The Chinese Dry Eye Expert Consensus [19] has also established other classifications based on different criteria. These classifications divide dry eye disease according to risk factors into categories such as systemic, eye local, environmental, lifestyle, surgery related factors, etc. They also categorize the DED based on the main components or functional abnormalities of tears, including aqueous tear deficiency, lipid deficiency, mucin deficiency, abnormal tear dynamics and mixed DED. Furthermore, the severity of the disease can be classified as mild, moderate, or severe.

Depending on the cause of the DED, artificial tears, tamponade, warm and pressure, prescription drugs, topical ophthalmic steroids, and mucin secreting agents are used to treat DED or tear film dysfunction. Actually, local Cyclosporin A, autologous serum, and sodium hyaluronate drops are also designed to treat DED, which can play an important regulatory role in inflammation, growth factors, and squamous epithelium of the ocular surface [13].

**Natural plant compounds**

Natural plant products are chemical models and raw materials for treating diseases that are derived from diverse medicinal plants. The reported natural plant products for treating DED are summarized in the Table 1.

**Non-flavonoid polyphenol**

Polyphenols are natural compounds that exhibit antioxidant, anti-inflammatory, and other pharmacological activities due to their structural characteristics. According to reports, polyphenols have the ability to decrease eye inflammation, lessen oxidative stress and apoptosis, regulate tear film and resist damage to the eye surface caused by DED [20]. Polydatin, resveratrol and other natural plant products are primary active phytochemical components of several traditional Chinese herbs and have antimicrobial, antiviral, neuroprotective, anti-inflammatory, and cardioprotective effects [21]. Recently, the effects of polydatin and resveratrol on DED have been mentioned [22-25].

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of administration</th>
<th>Properties</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polydatin</td>
<td>eye drop</td>
<td>Alleviate the symptoms of DED, recover tear volume and goblet cell density, inhibit TNF-α, IL-6 and MMP9, NF-κB, ROS production, NF-κB pathway and NLRP3 inflammasome</td>
<td><img src="image" alt="Polydatin Structure" /></td>
</tr>
<tr>
<td>Resveratrol</td>
<td>eye drop</td>
<td>Alleviate the symptoms of DED, up-regulate SIRT1, induce superoxide dismutase 2 (SOD2) and glutathione peroxidase (GPx), alleviate mitochondrial dysfunction</td>
<td><img src="image" alt="Resveratrol Structure" /></td>
</tr>
<tr>
<td>Gallic acid</td>
<td>eye drop</td>
<td>Improve the symptoms and signs of DED, inhibit oxidative stress and inflammation, impress the apoptosis of corneal epithelial cells, reduce inflammatory factors, protect goblet cells, down-regulate NF-κB, nitric oxide (NO), IL-6 and TNF-α, reduce ROS</td>
<td><img src="image" alt="Gallic acid Structure" /></td>
</tr>
</tbody>
</table>

DED, dry eye disease; NO, nitric oxide; SOD2, superoxide dismutase 2; GPx, glutathione peroxidase.
Table 1 Natural plant compounds used for the treatment of the DED (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of administration</th>
<th>Properties</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechin [26, 27]</td>
<td>Eye drop</td>
<td>Increase tear production and conjunctival goblet cells, stabilize corneal epithelium, inhibit inflammation</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>Xanthohumol [28]</td>
<td>Eye drop</td>
<td>Improve DED pathology, protect human corneal epithelial, increase Nrf2 expression, reduce ocular surface damage and oxidative stress related DNA damage</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
<tr>
<td>Esculetin [29, 30]</td>
<td>Eye drop</td>
<td>Alleviate the symptoms of DED, regulate Bcl-2, Bax and CASP3 expressions, down-regulate inflammatory cytokine and phosphorylated ERK1/2 expressions, scavenge free radicals and activate Nrf2 signal pathway</td>
<td><img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>Quercetin [24]</td>
<td>Eye drop</td>
<td>Protect ocular surface, reduce IL-1α tear concentration and CD4+ T cells, scavenge ROS, inhibit oxidation and inflammation</td>
<td><img src="image4" alt="Structure" /></td>
</tr>
<tr>
<td>Acacetin [31]</td>
<td>Intragastrically administrated</td>
<td>Relieve depression-related DED symptoms, inhibit NLRP3 expression, suppress inflammatory responses, enhance gp78 controlled NLRP3 ubiquitination</td>
<td><img src="image5" alt="Structure" /></td>
</tr>
<tr>
<td>Luteolin [32]</td>
<td>Orally administered</td>
<td>Increase tear secretion, restore corneal defects, decrease IL-1β, IL-6, IL-18 and TNF-α in hippocampi and corneal tissues, regulate SIRT1/NF-κB/NLRP3 signaling pathway</td>
<td><img src="image6" alt="Structure" /></td>
</tr>
<tr>
<td>Anthocyanins [33, 34]</td>
<td>Orally administered</td>
<td>Improve mild-to-moderate DED</td>
<td><img src="image7" alt="Structure" /></td>
</tr>
<tr>
<td>Isorhamnetin [35]</td>
<td>Eye drop</td>
<td>Ameliorate DED symptoms, reduce surface damage and expression of IL-1β, IL-8 and TNF-α, activate CFTR</td>
<td><img src="image8" alt="Structure" /></td>
</tr>
<tr>
<td>β-aminoarteether meleate [36]</td>
<td>Topically administered</td>
<td>Ameliorate DED symptoms, inhibit TLR4/NF-κB/NLRP3 inflammatory pathway</td>
<td><img src="image9" alt="Structure" /></td>
</tr>
</tbody>
</table>

DED, dry eye disease; Bax, Bcl-2-associated X protein; SIRT1, silencing information modulator related enzyme1.
Table 1 Natural plant compounds used for the treatment of the DED (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of administration</th>
<th>Properties</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsanthin [37]</td>
<td>Orally administered</td>
<td>Treat symptoms of DED, increase serum antioxidant levels, inhibit the expression of inflammatory cytokines, suppress vascular cell adhesion molecule and endoperoxide synthase 2</td>
<td><img src="image1" alt="Structure" /></td>
</tr>
<tr>
<td>Pterostilbene [38, 39]</td>
<td>Instillation</td>
<td>Inhibit the oxidation and inflammation, reduce IL-6, IL-1β and TNF-α expressions</td>
<td><img src="image2" alt="Structure" /></td>
</tr>
</tbody>
</table>

DED, dry eye disease.

3,5,4′-trihydroxystilbene-3-β-mono-D-glucoside (Polydatin).
Polydatin, a stilbenoid glucoside, is also called (E)-polydatin and trans-polydatin. Park et al. investigated the protective effect of polydatin on the ocular surface in both in vivo and in vitro DED models [22, 23]. They found that in the in vivo DED models, polydatin restores tear volume, tear film, goblet cell density, and inhibits inflammation, thereby significantly protecting the cornea and conjunctiva after lacrimal gland resection, meanwhile, in the in vitro models, polydatin blocks the NF-κB and NLRP3 inflammasome signaling pathways as well as ROS production, thus suppressing hyperosmolar stress-induced cell cytotoxicity and inflammation. Further, tear volume measurements and tear film breakup time assays also revealed that 0.5% polydatin eye drops significantly recovered the decreased tear volume and reasonably increased the shortened tear film breakup time, separately [22]. In addition, real-time PCR revealed that polydatin significantly inhibits the mRNA expression of TNF-α, IL-6 and MMP9 in a concentration dependent manner [23]. In a word, these research projects displayed that polydatin takes a significant part in restoring the damaged corneal layer and inhibiting the inflammation of the conjunctival epithelium, and may be a promising compound and worthy of deep study in the DED treatment [22].

Resveratrol. Resveratrol, also called 3,5,4′-trihydroxy-trans-stilbene, is derived from natural plants and has various activities against glycation, oxidative stress, inflammation, and neurodegeneration [40]. In 2019, Abengózar-Vela et al. [24] reported that resveratrol can protect the eye surface in experimental DED. Recently, Chen et al. [25] studied the possibility of resveratrol improving DED by restoring mitochondrial function through cell experiments, western blotting, flow cytometry, phenol cotton thread test, periodic acid-Schiff staining, and a DED mouse model. They found that after treatment with resveratrol in DED mice, the numbers of tear and goblet cells increase, the expression of SIRT1 and SOD2/GPx is up-regulated and induced, respectively. In addition, they also found that resveratrol can reverse the mitochondrial dysfunction induced by high osmotic pressure. These phenomena suggested that resveratrol plays a positive role in reducing ocular surface injury and alleviating mitochondrial dysfunction by affecting the expression of SIRT1.

Gallic acid. Gallic acid, a natural polyphenol compound, is derived largely from various plants and exhibits potent anti-inflammatory and antioxidant activity [41]. Gallic acid also has been reported to improve DED syndrome in diabetes mice [42]. Recently, Li et al. [15] discussed the anti-inflammatory and antioxidant effects of gallic acid on experimental DED through in vivo and in vitro studies. In the in vitro experiments, gallic acid not only inhibit inflammation by reducing the activation and nuclear translocation of inflammatory responses, and various inflammatory mediators, such as NF-κB, IL-6 and TNF-α, but also impress ROS production by promoting the activation and nuclear translocation of antioxidant response (such as Nrf2) [15]. At the same time, in the in vivo experiments, after treatment with gallic acid, the apoptosis of corneal epithelial cells was inhibited, inflammatory factors in the cornea and conjunctiva reduced evidently, and goblet cell increased significantly [15]. Taken together, gallic acid is a potential compound to treat DED.

Catechin. Catechin, a polyphenolic compound, belongs to the flavonoids of the flavonoid family and comes from various plants. Catechin can exhibit antioxidant and anti-inflammatory effects by scavenging ROS and regulating other signaling pathways due to its structural characteristics [26, 43]. Previously, it was reported that PEG/catechin nanocomplex can treat DED by stabilizing tear film and inhibiting inflammation, at the same time, bioavailability of catechin is also increased [27]. Recently, Shim et al. used spontaneous hydrogen bonding to make soluble PEG/catechin nanoscale complexes and investigate the therapeutic effect on DED [26]. The results displayed that catechin exhibits better solubility and has therapeutic effect on DED.

Xanthohumol. Xanthohumol, a naturally occurring prenylated chalcone compound derived from Humulus lupulus, exhibits powerful anti-inflammatory and antioxidant ability [28]. Ghosh et al. [16] developed xanthohumol encapsulating poly (lactic-co-glycolic acid) nanoparticles (PLGA NP) and investigated if xanthohumol could protect corneal epithelial cells from DED-associated oxidative stress and the underlying mechanisms. Human corneal epithelial cells were treated with tert-butyl hydroperoxide, and the mice were treated with desiccating stress/scopolamine [16]. The results from this study showed that xanthohumol is able to protect human corneal epithelial against tert-butyl hydroperoxide-induced cell death in a dose-dependent manner by increasing the Nrf2, moreover, xanthohumol encapsulating PLGA NP significantly decreases the damage of oxidative stress in vitro, the injury of ocular surface and oxidative stress associated DNA in vivo, as well as apparently improves DED pathology [16]. The findings from the study suggest that xanthohumol and xanthohumol encapsulating PLGA NP might have the therapeutic potential for DED.

Esculetin. Esculetin, called 6, 7-dihydroxycoumarin, belongs to benzopyrene family, which is isolated mainly from the bark of Praxinus rhynchophylla and has broad spectrum pharmacological activities with various mechanisms, especially powerful antioxidant due to its two hydroxyl groups [44]. It has been shown that esculetin can decrease inflammation and cell death in human retinal pigment epithelial cells induced by lipopolysaccharide-induced [45]. In addition, Jiang et al. [29] used rabbits DED models to observe the therapeutic effects of topical esculetin for DED, and the results show that esculetin is able to relieve the symptoms of DED, as well as downregulated the expressions of the inflammatory cytokine and phosphorylated ERK1/2. Lately, Zhang et al. [30] researched the
effect of esculetin on preventing oxidative damage to corneal epithelial cells and potential molecular mechanism. Conneal epithelial cells and DED model in vivo experiments confirmed that esculetin is able to oppose oxidative injury to corneal cells, and the mechanism is scavenging free radicals and the activating Nrf2 signal pathway. Immediately after, esculetin was also confirmed to exhibit effect on oxidative damage of retinal pigment epithelial cells in vitro [46].

**Polyphenol flavonoid**
Flavonoids are a kind of natural polyphenols coming from plants, which have anti-inflammation and antioxidant activities [29]. Based on these two abilities of flavonoid, combining with the pathogenesis of DED, flavonoid may be a potential drug for treating DED and has received widespread attention in recent years.

**Quercetin.** Quercetin, a natural polyphenol flavonoid, is a type of plant-based chemical widely present in various plants, such as, *Hyperici perforati Herba, Ginkgo Folium* [47]. Quercetin possesses a broad spectrum of bioactivities that include antioxidant, anti-inflammatory, antiviral, antimicrobial, neuroprotection, etc. [48]. Latterly, quercetin is reported to guard the ocular surface in experimental DED [24]. Abengózar-Vela et al. indicated that quercetin reduces IL-1α tear concentration and lowers CD4+ T cells compared to desiccating stress-exposed mice, as well as reducing corneal staining [24]. Soon afterwards, in order to solve the problem of their absorption in the eye, Krtišč et al. [49] explored the effect of the complexes of quercetin, resveratrol and cycloexetrin and the complexes added with hyaluronic acid. This study showed that both complexes can effectively increase the water solubility and stability of quercetin and resveratrol, and can significantly eliminate ROS in cells. This confirmed the potential of quercetin and resveratrol in treating DED.

**Acacetin and luteolin.** Acacetin, also known as 5,7-dihydroxy-4'-methoxyflavone, is a natural flavonoid derived from different herbs, such as *Turnera diffusa* and *Saussurea involucrata Herba* [50]. It has been supported that acacetin exhibits strong antioxidant, neuroproective effects and anti-inflammatory, as well as antidepressant-like efficacy actions [50-52]. Luteolin, a natural polyphenol flavonoid compound, is found in various plants, such as *Chrysanthemi Indici Flos*, etc., and has broad pharmacological activities [52]. In 2022, Xie et al. [51] searched whether acacetin can prevent depression-associated DED. They demonstrated that after administration of acacetin in depression-associated DED mice model, corneal epithelial damage is alleviated, reduction of tear production and loss of goblet cells are improved, and the ubiquitination of NLRP3 is regulated by gp78 signaling, which is one of the potential mechanisms of acetate in preventing depression-associated DED [31]. Immediately after, Xie et al. also used several experiments to prove that luteolin improves the depression-associated DED symptoms in mice based on the SIRT1/NF-κB /NLRP3 signaling pathway [32]. In brief, acacetin and luteolin may have a chance to become leaders in the treatment for depression-associated DED.

**Anthocyanins.** Anthocyanins [53], also known as flavonoid phytochemicals, are naturally planted pigments with water solubility. Anthocyanins have anti-cancer, cardiovascular protection, and eye protection, while anthocyanin oligomers have higher activity than monomeric versions [54]. In previous research, anthocyanin oligomers have been claimed to exhibit potential positive effects in the treatment of DED in a murine DED model experiment [33]. Not long ago, a randomized, double-blind, placebo-controlled study [34] demonstrated that anthocyanin oligomers can improve the tear break-up time and intraocular pressure, relieve ocular surface disease and patient symptomatology, and are safe and effective on treating mild-to-moderate DED. Based on therapeutic effect and safety, the authors suggested that anthocyanin oligomers are important to treat DED and suitable for wider applications.

**Isoharnettin.** Cystic fibrosis transmembrane conductance regulator (CFTR) is an anion channel and has received more attention as a promising target of a new drug for DED [35]. Isoharnettin is a natural flavonoid compound and has anti-inflammatory and antioxidation effects, which is good for chronic inflammatory diseases [55, 56]. In current study, Lee et al. [35] used a cell-based, high-throughput screening to identify whether isharhamettin could ameliorates DED by activating CFTR and increasing ocular tear volume in DED. The authors found that isharhamettin can activate CFTR, increase tear volume and significantly decrease inflammatory mediators, suggesting that isharhamettin is useful for the treatment of DED.

**Others**
In addition to flavonoids and polyphenols, other natural plant products and derivatives with various structures also show efficacy in the treatment of DED.

**β-aminoocteether (SM934).** SM934 meleate is an artemisinin derivative with water solubility and displays quantities of extensively prominent pharmacological activities, involving anti-inflammatory, immunomodulatory and tissue-protective characteristics [36]. To date, Yang et al. [36] investigated the intervention effectiveness of SM934 on DED in different animal models that contain scopolamine hydrobromide-induced rodent model and benzalkonium chloride-induced rat model. This research demonstrated that SM934 can not only preserve the structural integrity of the ocular surface but also prevent corneal and conjunctival inflammation, thus effectively treating DED, which may relate to TLR4/NF-κB/NLRP3 inflammatory pathway and TLR4.

**Capsanthin.** Capsanthin is a carotenoid that has been found in *Capsici Fructus* fruits and shows antiglaucoma activity [57]. In order to enrich pharmacological activities and explore the effect of capsanthin on DED, Shannugham et al. [37] conducted a benzalkonium chloride-induced rat DED model experiment. The results from this study showed that capsanthin is effective against glaucoma, oxidation, inflammatory activity, and inhibits the expression of corneal pro-inflammatory cytokine gene in the rat DED model, suggesting capsanthin is beneficial for managing DED [37].

**Pterostilbene.** Pterostilbene, a naturally occurring stilboid similar to resveratrol, was found in sandalwood and fruits like grapes and blueberries [58]. It has various bioactive properties, including antioxidant, anti-inflammatory, anticancer, and cardioprotective effects, which may help prevent numerous chronic human diseases [38]. As reported previously, in a DED model using human corneal epithelial cells, pterostilbene significantly reduced oxidative stress damage and the expression of IL-6, IL-1β, and TNF-α, suggesting protective effects of pterostilbene on DED [39]. However, its application is restricted by water insolubility and light instability. More recently, Hu et al. [38] created a pterostilbene-peptide amphiphile that could self-assemble into nanomedicine in water to enhance water solubility. They wanted to develop a suitable delivery system for the potential management of DED, which has high solubility and low toxicity. In in vitro study, pterostilbene-peptide amphiphile demonstrated both anti-inflammatory properties and strong ROS scavenging activity, in the in vivo ocular irritation test, pterostilbene-peptide amphiphile showed good ocular tolerance, which could be beneficial in the development of ocular drug.

**Discussion and conclusion**
DED, a multifactorial disease with tear film instability, elevated tear osmolarity and ocular surface inflammation, may cause damage to corneal surface epithelial cells, loss of goblet cells, as well as abnormal mucin secretion, and requires long-term treatment [59]. Considering its serious impact on the quality of life of patients, many treatments are used in the clinical treatment of DED, among them, many drugs only temporarily alleviate symptoms. To date, among the drugs approved by the Food and Drug Administration to treat DED syndrome, only cyclosporine and lifitegrast can inhibit T cell activation and cytokine production [60]. However, currently available therapies still exist limitations [5], therefore, it is necessary to develop new treatment strategies for DED.

As mentioned above, many natural plant products, such as polyphenol and flavonoid, can effectively improve or treat DED in
various ways, and they are likely to become candidates for the treatment of DED. Additionally, local opthalmic medication needs to consider the bioavailability of the drug in the eye, including ocular surface retention times, instillations frequency, stability and strong therapeutic efficacy. Although these natural plant products are effective in the treatment of DED in cell or animal experiments, there are still some limitations. Firstly, aqueous solubility influences ocular bioavailability and ophthalmic formulation [20, 61], but most of the above natural plant products, including flavonoids and polyphenol, are poorly water soluble and may affect the ocular bioavailability and damage ocular surface. Secondly, the release kinetics and stability of majority natural plant products in the eye are not fully studied, and the mechanism also remains uncertain. Besides, the sample size of many studies is insufficient and there is a lack of standardized multicenter, double-blind, randomized, controlled clinical trials, suggesting that their safety in the treatment of DED has not been thoroughly evaluated.

Therefore, it needs to develop advanced drug delivery systems or modify structure. So far, various drug delivery systems are designed to improve the therapeutic effect of DED drugs, such as nanoparticles, microspheres, bioadhesive polymers, etc. [8] Besides topical administration, the nasal spray is expected to be a new way that can quickly and effectively treat DED [62]. For example, varenicline solution nasal spray is approved as therapies for the treatment of DED by Food and Drug Administration in 2021 [63]. Additional molecular modifications also can be used to improve the solubility and therapeutic effectiveness. This study and many others prove that natural plant products have an important potential as a treatment of DED, but it is necessary to conduct an in-depth study on the treatment of DED in the future.

References


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