



Review

Evidence of Polyphenols Efficacy against Dry Eye Disease

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Abstract: Dry eye disease is a multifactorial pathology compromising the quality of life of patients, resulting in significant damage of the ocular surface and discomfort. The current therapeutical strategies are not able to definitively resolve the underlying causes and stop the symptoms. Polyphenols are promising natural molecules that are receiving increasing attention for their activity/effects in counteracting the main pathologic mechanisms of dry eye disease and reducing its symptoms. In the present review, a deep literature search focusing on the main polyphenols tested against dry eye disease was conducted, analyzing related *in vitro*, *in vivo*, and clinical studies to provide a comprehensive and current review on the state of the art. Polyphenols present multiple effects against dry eye diseases-related ocular surface injury. In particular, the observed beneficial effects of polyphenols on corneal cells are the reduction of the pathological processes of inflammation, oxidative stress, and apoptosis and modulation of the tear film. Due to numerous studies reporting that polyphenols are effective and safe for treating the pathological mechanisms of this ocular surface disease, we believe that future studies should confirm and extend the evidence of polyphenols efficacy in clinical practice against dry eye disease and help to develop new ophthalmic drug(s).

Keywords: antioxidants; dry eye disease; epithelial corneal cells; inflammation; polyphenols



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1. Introduction

The definition of dry eye disease (DED) was redefined several times during the last decades. In 1995, the National Eye Institute stated that “Dry eye is a disorder of the tear film, due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with ocular discomfort” [1]. In 2007, the Tear Film and Ocular Surface Society restored the definition in “Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface” [2]. In 2017, the same Society redefined further DED as “a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles” [3]. Data from big observational studies show that prevalence of DED varies greatly among the countries: In the United States, it reaches 6.8% of the population [4], while in India, DED affects 32% of the population [5]. In France, Germany, Italy, Spain, Sweden, and the United Kingdom, the estimated prevalence of DED among patients reporting to ophthalmologists was less than 0.1% [6]. Eyelid anatomy seems potentially implicated in the ethnic differences in the development of DED [7]. It is important to underline that the prevalence of DED is influenced by geographic location, climatic conditions, and patient’s lifestyle, but notably it even depends also on whether the data were generated from patients presenting at

optometry practices/eye hospitals or obtained from general population [5,6]. Though, to date, there is abundant data on DED in adults, minimal literature exists on this ocular surface disease in the pediatric population.

1.1. Pathophysiology of Dry Eye Diseases

The risk factors of DED include age [8], female sex (affecting especially postmenopausal women and women with hormonal replacement therapy [9,10]), autoimmune diseases [11], various types of systemic drugs [12], mood disorders [13], contact lenses use [14], vitamin A and D deficiencies, and a few other conditions [15–17]. Women present a prevalence of DED between 50% and 70% higher than men, which is in large part attributable to the effects of sex steroids as well as to sex-specific autosomal factors, although such differences become more significant with age [17–19]. The interaction effect between sex and pain sensitivity is another element which plays a relevant role in this disease, in particular, DED symptoms gain in women is strictly correlated with remarkable pain sensitivity, which may be a possible reason of greater DED prevalence in women [20]. Prevalence of DED has also increased with the modern office environment that involves intense computer use and air conditioning, factors that desiccate the eyes [21]. All these determinants lead either to reduced secretion of tear fluid defined aqueous-deficient dry eye or higher tear fluid evaporation recognized as evaporative dry eye. These categories are not mutually exclusive and many patients manifest a combination of both these DED pathogenic mechanisms. Both variations have in common tear hyperosmolarity which leads to the downward spiral of DED pathophysiological processes: activation of corneal epithelium's mitogen-activated protein kinase (MAPK) p38 and c-Jun N-terminal kinase (JNK), nuclear factor-kB (NF-kB), and activator protein-1 (AP-1) which are responsible for pro-inflammatory interleukins, matrix metalloproteinases (MMPs), and other chemokines production [8,22]. The core of DED etiology is a vicious cycle, where tear film instability and hyperosmolarity trigger an inflammatory cascade which lead to ocular surface damage and further loss of tear film homeostasis [23]. Tear film instability is at the basis of DED symptoms and, hence, a starting point for inflammation. Tear film hyperosmolarity is linked to cornea and conjunctiva damage, so altering epithelial cells and stimulating resident inflammatory cells [24,25]. In turn, corneal and conjunctival stress stimulates the neurosensory arc, inducing neurogenic lacrimal gland inflammation and altering tear fluid. Furthermore, inflammation, related to an imbalance of ocular homeostasis, is mediated by immune cells [26]. Immune cells release inflammatory cytokines that, in turn, degrade the corneal epithelial barrier and promote apoptosis in the conjunctiva and lacrimal gland. Thus, such processes alter the morphology of the ocular surface, accelerate DED progression, and promote symptoms onset [26,27].

Hyperosmolar conditions, inflammatory and matrix-remodeling factors stimulate ocular oxidative stress. These pathogenic factors are also related to the production of reactive oxygen species (ROS), to the decrement of antioxidant enzymes, such as glutathione peroxidase-1 and superoxide dismutase1 (SOD1), and to the increment of heme oxygenase-1 and cyclooxygenase2 activity, thus disrupting the physiological balance between antioxidative enzymes and ROS [28–32].

Furthermore, the activity of caspases 8, 9, 3, and 7 was enhanced in hyperosmotic conditions inducing apoptotic processes at the corneal/conjunctival level [33–35]. In the conjunctival mucosa, a goblet cell loss, directly related to chronic inflammation and apoptosis processes and induced by tear film hyperosmolarity and epithelial damage, might result in further and important tear film instability [24,25,36]. Moreover, the ocular surface altered by the apoptotic process together with hyperosmolar environment, reduces the stability of the tear film [37] and excites the corneal nerve fibers, which may lead to blinking, stimulation of lacrimal gland, and other DED symptoms [38]. Damage to the conjunctival epithelium significantly impaired mucins production, glycoproteins responsible for binding water and keeping the ocular surface hydrated, resulting in the inability to create a stable and normosmolar tear film [39,40]. In Figure 1, are schematized the key pathogenic factors

contributing to the pathological downward spiral of DED. The ocular surface stresses that can initiate this cycle are variable and innumerable.

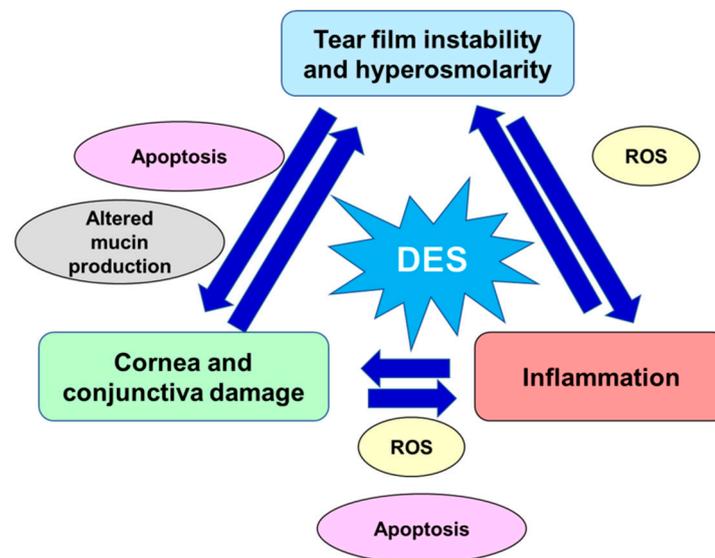


Figure 1. Key pathogenic factors contributing to the pathological vicious circle of dry eye disease. DED: dry eye disease; ROS: reactive oxygen species.

Among the systemic drugs that may cause DED, many are best-selling ones, which may decrease tear production, alter nerve function, induce inflammatory effects on secretory glands without reaching the ocular surface or may have direct irritation effects through secretion into the tears. In fact, the 62% of DED cases in the elderly are secondary to medications, including nonsteroidal anti-inflammatory drugs, diuretics, vasodilators, analgesics/antipyretics, antiulcer agents, sulfonyleureas, cardiac glycosides, anxiolytics/benzodiazepines, anti-infectives, antidepressants/antipsychotics, hypotensive agents, and antihistamines [12,41,42].

DED patients can have the perception of a foreign body in the eye, sore eyes, and reduced visual acuity, compromising the ability of the individual to concentrate, particularly for the ones working at a computer monitor [43,44]. Even if the symptoms are not dangerous, they should not be underestimated, as most of the patients stated an important reduction in quality of life.

1.2. Therapy of Dry Eye Disease

Some of the possible therapeutic strategies for improving symptoms of DED are reducing tear evaporation and absorption, increasing or supplementing tear production, and reducing ocular inflammation and oxidative stress [45]. The first-line treatments for this pathology are tear supplementation, environmental strategies, heat application to soften secretions in obstructed tear glands, correction of eventual eyelid anatomical defects, or discontinuation of DED-inducing drugs [24,46,47]. To date, many randomized clinical trials evaluating DED treatments have been performed searching for transparent diagnostic criteria and standardized outcomes. Laser-assisted in situ keratomileusis (LASIK) is a refractive procedure, which is associated with a 20% of chronic dry eye [48]. This relationship between LASIK and DED makes such patients a valuable population for clinical trials. After a LASIK intervention, the main therapy is the use of artificial tears, which are normally composed of cellulose to maintain viscosity, a spreading agent like polyethylene glycol to prevent evaporation and preservative agents, like benzalkonium chloride, to prevent bacterial and fungus contamination [49]. The artificial tears can contain also aqueous supplementing molecules like carboxymethylcellulose and sodium hyaluronate or polar phospholipids like dimyristoylphosphatidylglycerol [50]. The application of artificial tears

is usually not curative and requires chronic applications, unless a specific etiologic agent is temporary or can be eliminated. Some behavioral attentions, like frequently blinking and avoiding air conditioning, contribute to alleviating the patients' DED discomfort. Conversely, humidifiers in close rooms can sometimes improve the symptom [51]. As reported in the TFOS DEWS II Management and Therapy Report, DED treatment progresses in a stepwise approach, starting with patient education, environmental modification, lid hygiene, and artificial tears application [50]. As previously reported, artificial tears of various types are the mainstay of DED management. Due to the staged management of DED, if the initial steps are inadequate, it is possible to consider other devices (e.g., pulsed light therapy, lifitegrast, topical secretagogues, etc.) which may be used in conjunction with prescription medications [50]. In order to improve tear production, secretagogues agents can be used, like rebamipide, a mucin inducer, or diquafosol tetrasodium [52,53]. Interestingly, also some antibiotics can be used as DED therapy. In particular, tetracycline showed important effects on MMPs, lipases, and pro-inflammatory cytokines [54]; whereas, azithromycin showed empirical secretory effects on Meibomian glands [55]. Other relevant agents against DED are integrin lymphocyte function-associated antigen-1 (LFA-1) antagonist drugs (such as lifitegrast). Lifitegrast acts as a competitive antagonist which blocks the binding between LFA-1 and intracellular adhesion molecule-1 and thereby inhibits T cell migration and inflammatory cascade activation [23,56,57]. In DED non-responding states, the application of corticosteroids or cyclosporin A may be considered. However, corticosteroids should be used only for a short time, as the elevation of intraocular pressure and formation of cataract occur during long-term use [58,59] and cyclosporin A, cyclic polypeptide that prevents T cell maturation, seems low effective and it may induce severe side effects, such as itching, eye redness, and blurred vision [60–62]. Furthermore, due to its' hydrophobic structure, cyclosporin A presents poor biopharmaceutical properties, such as low solubility and permeability, so resulting in difficulties in the formulation and efficient drug delivery [63]. Another possible step-approach against DED is intense pulsed light that seems an effective and safe DED treatment option; in fact, it improves tear film quality and reduces DED symptoms and related discomfort [64].

A new therapy should be quested targeting not only inflammatory biochemical mechanisms, but also oxidative stress, ocular surface injury, and excessive irritation of corneal afferent neurons. In this regard, as described in the following paragraphs, polyphenols represent natural and potent agents potentially effective against DED. In particular, in the present review, was conducted a deep literature search focusing on the main polyphenols tested against DED and analyzing related *in vitro*, *in vivo* studies, and clinical trials (to date just one). In the following paragraphs, the tested polyphenols are introduced and outlined, their currently known effects and mechanisms of action against DED, underlining their therapeutic potential.

1.3. Polyphenols

Polyphenols are natural compounds that originate exclusively as plant secondary metabolites [65,66]. They are characterized by one or more phenol rings on which basis they are classified (Figure 2). Due to their structure, they are effective antioxidant molecules able to decrease the production of free radicals through Fenton reaction [67–69]. Moreover, polyphenols can directly interact with various enzymes, resulting in anti-inflammatory, antimicrobial, anti-viral, anti-aging, anticancer properties and they also show neuroprotective effects [70–75].

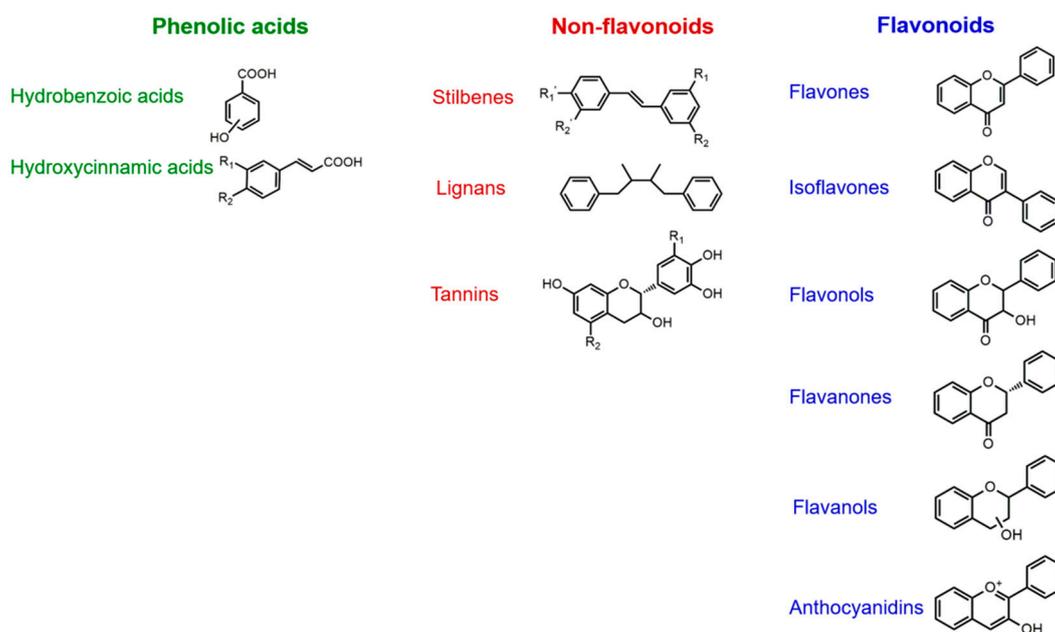


Figure 2. Classification of polyphenols in three classes based on their structure: phenolic acids, non-flavonoids, and flavonoids.

Polyphenols showed therapeutic effects in various fields and the most studied molecules are epigallocatechin gallate (EGCG), resveratrol, quercetin, betaine, pterostilbene, and curcumin [76–79]. Hence, evident therapeutic effects have been confirmed, despite the bioavailability of polyphenols which is, in general, low [80–82]. Notably, the oral administration of polyphenols is safe [83,84]. To date, topical application of polyphenols showed an important potential as treatment of DED [77,85–87].

2. Polyphenols' Effects in DED

Principally, there are two methods for in vitro DED induction: either treatment of corneal cells with interleukin-1 β (IL-1 β) or with tumor necrosis factor- α (TNF- α) or increasing the osmolarity of culture medium using a hyperosmolar medium. The remarkable advantage of in vivo studies, compared to in vitro studies, is the possibility to evaluate not only the biomarkers of DED pathological mechanisms, but also the same parameters which are examined at the ophthalmological visit, such as tear fluid production or fluorescein staining. This last procedure consists of the application of fluorescein solution in the patient's eye, permitting the observation of corneal epithelial defects with the use of a slit lamp [88]. The methods of DED induction to an animal include several topical treatments or the chambers with the desiccating stress conditions. To date, just one clinical trial was performed in DED patients to test the effects of the polyphenol EGCG, but it represents an important starting point to reinforce polyphenols' role in the treatment of DED. However, more clinical trials are needed in the next future, assessing the best combinations and dosages for the patient.

In the following paragraphs, the results and observations from in vitro, in vivo, and human studies about the effects of topically applied polyphenolic compounds against DED are reviewed, underlining their mechanisms of action and beneficial effects against the main DED injuries and related symptoms. In Figure 3, are schematized the polyphenols described in the following paragraphs.

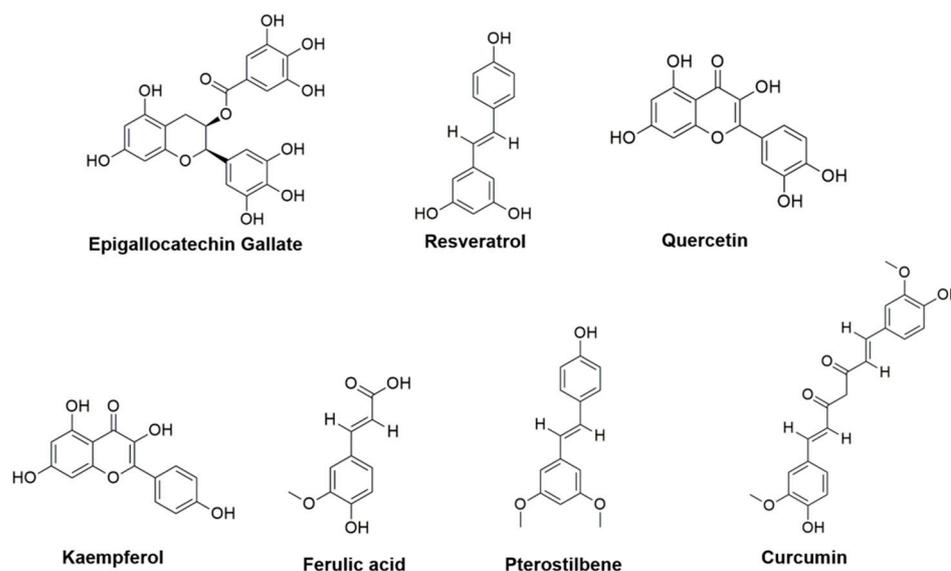


Figure 3. Polyphenols actually tested against dry eye disease: epigallocatechin gallate, resveratrol, quercetin, kaempferol, ferulic acid, pterostilbene, and curcumin.

2.1. Epigallocatechin Gallate

EGCG is the most abundant catechin present in green tea and it is believed to be responsible for most of the biological beneficial effects of tea [89]. EGCG is an active catechin showing antioxidant, anti-inflammatory, epigenetic, low-density lipoprotein cholesterol lowering properties, and also anticancer effects [90–95]. Shim et al. [96] described how this catechin could be solubilized, remedying its poor aqueous solubility.

2.1.1. In Vitro Studies

For evaluating EGCG potential as DED treatment, human corneal epithelial cells (HCECs) were used and dose-dependent inhibition of the inflammatory metabolic pathway was confirmed. Specifically, decrease in pro-inflammatory cytokines was observed after 30 μM of EGCG treatment, even if inhibition of the kinases and transcription factors leading to pro-inflammatory cytokine release (phosphorylation of MAPKs p38 unit and JNK and inhibition of NF- κB and AP-1 activities) already occurred at 3 μM of EGCG. Furthermore, the index of cell viability confirmed no harmful effect of 30 μM EGCG concentration. The EGCG treatment of HCEC lasted for 18 hours [97], less than Luo and Lai [98] who treated cells for 3 days with 0.1% EGCG loaded gelatin polymer and showed normal cell morphology, proliferative capacity, and viability in the control-gelatin group and gelatin-EGCG group. After DED induction followed with EGCG treatment, the authors also observed down-regulation of pro-inflammatory cytokines and chemokines and significant inhibition of ROS. EGCG also inhibited ROS in human corneal limbal epithelium with half-maximal effective concentration (EC₅₀) equaled to 3.41 μM after 60 min of treatment [99].

2.1.2. In Vivo Studies

A mice DED model was treated with 0.1% EGCG after 48 hours of DED induction, observing a significant decrease in fluorescein corneal staining (analyses normally used in clinical practice for detection of foreign bodies in the eye or abrasions of the cornea) and also of pro-inflammatory cytokines and vascular endothelial growth factor. The level of TNF- α was not influenced, but apoptosis of corneal epithelium has been inhibited [100]. In the study of Tseng et al. [101], 0.001% EGCG enriched artificial tears tested on the rabbit DED model were not sufficient to significantly restore a normal tear fluid production after a 3-week application, but the combination with hyaluronic acid reached values comparable to healthy controls. Notably, a significant decrease in inflammatory activity was also described in the group with mixed treatment in comparison with the one treated with hyaluronic

acid alone. Recently, Luo et al. [102] developed a long-acting and functional ophthalmic formulation for the treatment of DED. In detail, the experimental rabbit model of DED was treated with one-time topical instillation of a biodegradable, mucoadhesive, and thermo-responsive hydrogel that provides a sustained release of EGCG and increases the “drug” bioavailability to therapeutic levels for a period over 14 days. Luo et al. [102] observed that this specific formulation in the conjunctival sac could effectively repair corneal epithelial defects through the attenuation of cellular inflammation, oxidative stress, and apoptosis. Interestingly, these findings on a long-acting pharmaceutical formulation underlined the possible management of this complex ocular disease via a simple topical administration route. Luo and Lai [98] studied EGCG loaded gelatin-g-poly(N-isopropylacrylamide). In this form, EGCG was released continuously and, after 6 hours, significantly improved fluorescein and Bengal rose staining scores (a clinically commonly used method to stain damaged conjunctival and corneal cells and thereby identify damages at the ocular surface level). In the group with EGCG in gelatin polymer, the aqueous part of tear film together with epithelial thickness was significantly restored in comparison with the application of either gelatin polymer or EGCG alone. Furthermore, a significant loss of goblet cells, which are responsible for gel-forming mucins secretion in the conjunctiva, was detected in all groups treated with the gelatin carrier alone, EGCG, or EGCG in gelatin polymer. Similarly, Huang et al. [103] studied the gelatin-EGCG nanoparticles coated with hyaluronic acid in phosphate buffer (GEH). The optimal EGCG concentration was defined as 20 µg/mL (0.002%). The formula enabled longer retention on the ocular surface and showed a higher cellular uptake. The rabbit model of DED was treated with GEH twice daily for 3 weeks, showing that the tear secretion was not significantly recovered, but on the other hand, fluorescein staining exhibited lower scores and a lower amount of corneal apoptotic cells were determined. Moreover, inflammatory cytokines significantly decreased after EGCG and GEH treatment.

To further improve drug accessibility to the ocular surface, Li et al. [95] prepared polycatechin-capped gold nanoparticles transporting amfenac, which is part of the family of non-steroidal anti-inflammatory drugs. Catechin and catechin nanoparticles without amfenac topically administrated to rabbit DED models showed significant improvement in corneal thickness, corneal fluorescein staining and Bengal rose staining. Moreover, a reduction in corneal apoptosis was detected together with an increased amount of goblet cells suggesting a therapeutic role of catechin.

2.1.3. Clinical Trial

Nejabat et al. [104] evaluated green tea extract rich in EGCG as topical DED treatment in a double-blind randomized controlled clinical trial with 60 patients involved. Patients followed the treatment for one month. A significant subjective symptom alleviation was recorded in the group with the green tea extract drops. Schirmer test, corneal and conjunctival staining did not show significant differences between the groups, but considerable improvement in tear break-up time (TBUT) test and meibum quality were detected suggesting a progress in tear film stability. Interestingly, EGCG was well tolerated, representing a safe topical treatment against DED.

2.2. Resveratrol

Resveratrol is a natural phytoalexin polyphenol that is found in more than 70 species of plants, herbs, fruits, or vegetables, like mulberries, peanuts, grape, and berry skins [105]. It is well-absorbed and quickly metabolized in the body [106]. Resveratrol is generally known to be beneficial for human health, in fact, several biological effects have been reported, including anticancer activity, anti-inflammatory, antioxidant, cardio- and neuro-protective effects [106–108]. It seems so beneficial for several pathological processes like cardiovascular and neurodegenerative diseases, tumors, pain, tissue injury, and inflammatory-related diseases [109].

2.2.1. In Vitro Studies

Resveratrol is another bioactive polyphenol tested against DED. Using a solution containing 50 μM of resveratrol in the DED cell model for 24 hours, Abengózar-Vela and colleagues [85] observed a significant reduction in the levels of pro-inflammatory cytokines IL-6, -8, and interferon gamma-induced protein-10. Recently, Shetty et al. [110] investigated the role of resveratrol on vitamin D levels and Notch signaling under hyperosmolar conditions. HCECs in hyperosmolar conditions had increased reactive oxygen species levels and decreased vitamin D levels that got restored, most likely through activation of Notch signaling, in the presence of resveratrol. However, an understanding of the molecular basis of corneal epithelial phenotype and Notch signaling modulation to restore corneal surface integrity and health is needed.

2.2.2. In Vivo Study

Abengózar-Vela et al. [111] applied a 0.1% resveratrol solution 3 times a day, starting one day before DED induction, in a mice model. Such treatment improved the fluorescein staining score; however, it did not enhance tears production. On day 6, pro-inflammatory cytokines in the tear fluid were measured and the pro-inflammatory IL-1 α showed a significant decrease together with a notably reversed CD4+ T cells infiltration in the resveratrol treated group.

2.3. Quercetin

Quercetin is a flavonoid abundantly present in a wide variety of fruits and vegetables as well as in tea and red wine [112–115]. It is also found in medicinal botanicals, including Ginkgo biloba, Hypericum Perforatum, and Sambucus Canadensis [116]. In a typical Western diet, the daily intake of quercetin is estimated to be in the range of 0 and 30 mg [112]. Quercetin shows unique biological properties at the basis of potential benefits to overall health and disease resistance, in fact, it exhibits anticarcinogenic, anti-inflammatory, antiviral, anti-hypertensive, and antioxidant effects as well as it may inhibit lipid peroxidation and platelet aggregation and it can stimulate mitochondrial biogenesis [114,116–118].

2.3.1. In Vitro Study

In the last years, the implementation of quercetin as a therapeutic application to the ocular surface has been gaining the attention of the scientific community in the study of DED, keratoconus, and injured cornea [119,120]. Abengózar-Vela et al. [85] evaluated the effects of quercetin or quercetin plus resveratrol treatments obtaining a significant anti-inflammatory and antioxidant effects. Furthermore, quercetin showed a relevant potential in the inhibition of ROS in comparison with other polyphenols, showing an EC50 of 2.98 μM [99].

2.3.2. In Vivo Studies

Oh et al. [120] observed in DED mice, treated with 0.5% quercetin 4 times per day, a significant tear volume restoration to the basal level after 3 days, that interestingly reached the plateau at the 7th day of therapy. Quercetin treatment significantly improved the corneal surface irregularities from the 3rd day of application. Furthermore, it significantly decreased the detachment of corneal cells and increased the number of conjunctival goblet cells. The quercetin protective effect was also shown against TNF- α , MMP-2, MMP-9, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, which were significantly decreased in the group treated with quercetin. On the other hand, Abengózar-Vela et al. [111] used only 0.01% quercetin solution applied 3 times per day starting one day before DED induction to mice and, after 9 days, the positive effects were detected with a significant improvement of the corneal surface, but without enhancement in tear volume.

2.4. Kaempferol and Ferulic Acid

Kaempferol is a ubiquitous polyphenol, present in fruits and vegetables. The richest plant sources of kaempferol are green leafy vegetables, such as spinach, kale, and herbs including dill, chives, and tarragon [121]. This polyphenol shows antioxidant, anti-inflammatory, cardioprotective, and anticancer properties [121–123]. However, still further clinical trials must be carried out to confirm its beneficial effects during clinical application at the aim to manage inflammatory-related diseases [124]. To date, few human studies investigated kaempferol bioavailability and reported that kaempferol glucoside and rutinoid in tea were the most bioavailable forms of this polyphenol.

Ferulic acid is a common polyphenolic molecule most abundantly present in vegetables, like artichokes, eggplants, and in maize bran. Furthermore, it is an effective component of Chinese medicinal herbs such as *Angelica Sinensis*, *Cimicifuga Heracleifolia*, and *Lignisticum Chuangxiong* [125]. Ferulic acid is a polyphenolic compound that possesses excellent antioxidant properties [99,126,127]. However, it is important to underline that this latter is not the only interesting property of this polyphenol, due to various studies, exhibited ferulic acid cytoprotective effects [125,128,129]. To date, ferulic acid shows a poor bioavailability that, together with concerns derived from its pharmacokinetics, may be limit the potential use of ferulic acid in clinical application.

In Vivo Study

Chen et al. [122] studied the combination of two polyphenolic compounds: kaempferol and ferulic acid. The optimal combination has been experimentally set as 100 μM of ferulic acid plus 1 μM of kaempferol. This polyphenolic combination was used in the rabbit DED model, which was treated 3 times per day for 3 weeks. Significant tear fluid restoration was detected together with fluorescein staining improvement as also corneal thickness recovery [122].

To date, there are no specific in vitro studies nor clinical trials about ferulic acid and/or kaempferol against DED.

2.5. Pterostilbene

Pterostilbene is a naturally-derived stilbenoid that structurally resembles resveratrol. It was initially isolated from sandalwood, but is also present in fruits, including grapes and blueberries [130]. The pterostilbene wide range of bioactive properties comprehends antioxidant, anti-inflammatory, anticancer, and cardioprotective effects [131–134], which altogether may contribute to the prevention of various chronic human diseases. Moreover, it seems to improve cognitive performances [135].

In Vitro Studies

In the HCEC DED model, 5 μM of pterostilbene concentration significantly decreased the expression of IL-6, IL-1 β , and TNF- α on both protein and mRNA level. Furthermore, it downregulated some MMPs together with markers of lipid peroxidation and mitochondrial damage. Pterostilbene protected HCECs against ROS overproduction too, and significantly increased the endogenous antioxidant enzymes SOD1 and peroxiredoxin 4 [136]. Recently, Hu et al. [137] designed and synthesized a pterostilbene-peptide amphiphile which could spontaneously self-assemble into nanomedicine in an aqueous solution to improve water solubility. The main objective of this study was to develop a pterostilbene prodrug nanomedicine with improved solubility and reduced toxicity for the potential management of DED. Based on this pilot in vitro study, the synthesized pterostilbene nanomedicine showed both anti-inflammatory effects and potent ROS scavenging activity, which might be promising in ocular drug development.

To date, there are no in vivo studies or clinical trials about pterostilbene against DED.

2.6. Curcumin

Curcumin is one of the most studied polyphenols in the turmeric spice. Curcumin exhibits a broad range of biological and pharmacological activities, including anti-inflammatory, antioxidant, anti-tumor, chemosensitizing, epatoprotective, lipid-modifying, and neuroprotective effects [138–140]. Curcumin and its derivatives may potentially ameliorate the hallmarks of neurodegenerative diseases [141], but further clinical studies are needed. Curcumin presents poor bioavailability and low gastrointestinal absorption which is mainly attributed to water insolubility, rapid metabolism, and excretion [142,143].

2.6.1. In Vitro Study

Chen et al. [144] observed in hyperosmotic-stressed HCECs, that 5 μ M curcumin induced significant anti-inflammatory effects both on mRNA and the protein level. Additionally, downregulation of MAPK and JNK, which regulates inflammatory cytokines production, and NF- κ B transcription factor were observed.

2.6.2. In Vivo Study

Muz et al. [145] evaluated, in a DED animal model, the potential protective effects of an oral formulation composed by lutein/zeaxanthin, curcumin, and vitamin D3 (LCD). The LCD was administered, at different doses, to benzalkonium chloride-induced DED animal model for 4 weeks. LCD formulation significantly limited the inflammatory cascade and oxidative stress, together with ameliorating tear secretion and recovering neurotrophic factors and glyocalyx expression.

To date, there are no clinical studies about treatment with curcumin against DED.

3. Conclusions

A lot of focus has been put on the pathophysiology and possible therapies of DED, but still the current knowledge seems not to be enough to exhaustively help the clinical practice to efficiently manage its symptoms. Polyphenols are natural compounds with high efficacy to suppress oxidative stress and inflammation. They showed high potential in the treatment of neoplastic diseases and did not show important side effects. As their bioavailability is low, application avoiding the gastrointestinal tract is recommended [146,147].

Based on our deep review of the literature, topically applied polyphenols present positive and promising outcomes also against DED (Table 1). Currently, DED is treated with artificial tears, not targeting its pathophysiological mechanisms, or with anti-inflammatory agents that showed important side effects. Polyphenols, targeting the core mechanisms of DED, could be a novel and effective topical treatment against DED. Another interesting and not negligible way to contrast DED symptoms could be by dietetic regimens. Different micronutrients and nutraceutical products showed an important role against ocular surface disease [30] and caloric restriction has been shown to recover age-related functional declines in various organs, including the eye [148]. Although the oral route did not show an optimal absorption, a diet focused on the uptake of polyphenols could show benefits on patients with DED. However, randomized clinical trials are fundamental to affirm definitely the efficacy and safety of a specific dietetic regimen.

Table 1. Evidence of activity of polyphenols against dry eye diseases.

Polyphenoles	In Vitro Studies		In Vivo Studies				Clinical Trial	
	Anti-Inflammatory Effect	Antioxidant Effect	Anti-Inflammatory Effect	Antioxidant Effect	Anti-Apoptotic Effect	Improvement of Ocular Surface Damage	Tear Production	Tear Film Stability
Curcumin	[144]				[145]			
Epigallocatechin Gallate		[97,98]	[95,98,100–103]	[95,98,102]	[95,100–103]	[95,98,100–103]	[95,101,103]	[104]
Ferulic Acid and Kaempferol						[122]		
Pterolstilbene	[136]							
Quercetin	[85]		[111,120]			[111,120]	[120]	
Resveratrol	[85,110]		[111]			[111]		

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