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Review

Nutritional Modulation of Diabetic Dry Eye: Mechanistic Insights and Therapeutic Potential of Dietary Nutrients and Patterns

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Abstract

Diabetic dry eye (DDE) is a common microvascular complication of diabetes that seriously affects quality of life. This review examines the key role of nutrient supplementation and dietary patterns in the prevention and treatment of DDE. This review also focuses on pathological oxidative stress induced by hyperglycemia, which primarily activates the polyol, protein kinase C (PKC), and hexosamine pathways, leading to excessive production of reactive oxygen species (ROS). Excessive ROS, together with pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6), further initiates the NF-κB signaling cascade, upregulates intercellular adhesion molecule-1 (ICAM-1)/vascular cell adhesion molecule-1 (VCAM-1), and activates cellular apoptotic pathways and the unfolded protein response. These events damage ocular surface tissues and induce the pathogenesis of DDE. Indeed, regulating the intake of various nutrients, including macronutrients such as carbohydrates, proteins, and fatty acids; micronutrients including vitamins A, D, C, and E, as well as trace such as elements zinc and selenium; bioactive dietary components such as α-lipoic acid (ALA) and phytochemicals including anthocyanins, resveratrol, quercetin, and carotenoids, may help ameliorate metabolic disorders and inflammatory conditions in ocular surface tissues. The Mediterranean diet, which centers on core foods such as vegetables, fruits, whole grains, olive oil, fish, and nuts, is rich in polyphenols, vitamins, minerals, and unsaturated fatty acids. It is hypothesized to alleviate DDE by regulating oxidative stress, inflammatory responses, and systemic metabolism. Owing to the high antioxidant and anti-inflammatory properties of the Mediterranean diet, these food groups constitute represents an ideal dietary pattern for DDE. Although existing research supports the potential of nutritional interventions, several challenges remain. Future studies should further validate these effects through precision nutrition, interdisciplinary collaboration, and long-term clinical investigations to provide a stronger scientific basis for the prevention and treatment of DDE.

Keywords: diabetic dry eye; dietary patterns; nutrients; hyperglycemia; Mediterranean diet

1. Introduction

Diabetes is a major global public health problem, and its prevalence has continued to rise worldwide over recent decades [1]. Diabetic dry eye (DDE) is a common microvascular complication of diabetes with a high incidence. It causes ocular dryness, discomfort, pain, and even visual impairment, thereby severely reducing patients' quality of life. The reported prevalence of DDE ranges from 15% to 70% across studies and is significantly higher than that in the general population. For instance, it reaches 51.7% among diabetic patients in Saudi Arabia [2,3,4]. The risk of DDE increases significantly with age. DDE differs distinctly from non-diabetic dry eye in terms of etiology, clinical manifestations, and therapeutic responses [4,5] (Table 1, Ref. [2,3,6,7,8,9,10,11,12,13,14,15]).

DDE is primarily induced by persistent hyperglycemia, which leads to tear film instability, corneal epithelial damage, chronic inflammation, and in severe cases, vision loss. It is often exacerbated by diabetic retinopathy and other ocular complications [16]. Current treatments primarily rely on pharmacological agents such as sodium hyaluronate, dexamethasone, and cyclosporine A eye drops; however, long-term application may cause adverse effects. Increasing evidence highlights the potential value of dietary interventions in diabetes and its complications, supporting the need to explore nutritional strategies for DDE prevention and management [17].

Although the association between nutrients and dry eye has been addressed in several reviews, studies specifically examining the association between nutrients and DDE remain limited. Accordingly, this review aims to summarize the impact of nutrient intake and dietary patterns on the development and progression of DDE, which may help develop nutritional strategies for managing diabetic complications. DDE arises from chronic hyperglycemia-induced microvascular damage, neuropathy, and inflammation, accompanied by lacrimal gland dysfunction, decreased oligomeric mucus/gel-forming (MUC5AC), and

Table 1. Pathophysiological and clinical distinctions between DDE and non-diabetic dry eye disease (DED).

Parameter	Diabetic dry eye (DDE)	Non-diabetic dry eye disease (DED)	Reference
Etiopathogenesis	- Chronic hyperglycemia-induced microangiopathy - Accumulation of advanced glycation end-products (AGEs) - Corneal neuropathy with reduced nerve fiber density - Lacrimal gland fibrosis secondary to oxidative stress	- Primary lacrimal insufficiency - Meibomian gland dysfunction - Ocular surface inflammation	[7,8]
Clinical Presentation	- Symptom-sign disparity (asymptomatic early stage) - Progressive corneal complications - Strong correlation with diabetic retinopathy stage	- Symptom-sign correlation - Stable clinical course - Environmental exacerbation patterns	[11,13]
Diagnostic Markers	- Tear film: ↓MUC5AC ↑MMP-9 - AGEs positivity	- Tear hyperosmolarity - Mild elevation of inflammatory cytokines - Alterations in meibum quality	[6,12]
Therapeutic Response	- Requires multimodal intervention - Correlates with HbA1c levels	- Approximately 33 % of patients show resistance to conventional artificial tears - Short-course anti-inflammatories effective - Environmental modification beneficial	[3,15]
Pathological Hallmarks	- Corneal nerve degeneration, Lacrimal gland acinar atrophy - Neurotrophic epitheliopathy	- Conjunctival squamous metaplasia - Meibomian gland dropout - Goblet cell depletion	[2,14]
Management Strategy	- Glycemic control imperative, Neuroprotective agents (e.g., NGF) - AGEs inhibitors - Advanced anti-inflammatory regimens	- Tear conservation approaches - Meibomian gland expression - Mucin secretagogues - Anti-inflammatory pulse therapy	[6,9,10]

Abbreviations: DDE, Diabetic Dry Eye; DED, Dry Eye Disease; AGEs, Advanced Glycation End-products; MMP-9, Matrix Metalloproteinase-9; NGF, Nerve Growth Factor; MUC5AC, mucin 5AC, oligomeric mucus/gel-forming; HbA1c, Hemoglobin A1c; ↓ the downward arrow indicates decreased level of diagnostic biomarker MUC5AC; ↑ the upward arrow indicates increased level of MMP-9.

advanced glycation end-product accumulation. Its severity is closely associated with diabetic retinopathy. In contrast, non-diabetic dry eye typically results from either insufficient tear secretion or excessive evaporation. Clinically, DDE often presents with inconsistent symptoms and signs and carries a high risk of corneal complications; it also responds poorly to conventional artificial tears. In comparison, non-diabetic dry eye shows consistent signs and symptoms and is usually relieved by standard lubrication or short-term anti-inflammatory therapy. Reduced MUC5AC and elevated Matrix Metalloproteinase-9 (MMP-9) in tears further impair tear film stability and complicate the treatment of DDE [6,18,19].

Accordingly, this narrative review aims to summarize the impact of nutrient intake and dietary patterns on the development and progression of DDE, focusing on how targeted nutritional interventions and healthy dietary patterns—particularly the Mediterranean diet—may alleviate DDE. The proposed mechanisms include attenuating hyperglycemia-induced oxidative stress, suppressing chronic inflammation, protecting corneal nerves and lacrimal glands, and improving tear film stability. The findings of this review could help inform the development of nutritional strategies for the management of diabetic complications.

2. Pathogenesis of DDE

The pathogenesis of DDE is primarily associated with oxidative stress and inflammation (OSI) triggered by persistent hyperglycemia. Hyperglycemia remodels glucose metabolism and initiates multiple biochemical pathways that increase reactive oxygen species (ROS) production and promote inflammatory responses. These events synergistically contribute to corneal nerve damage and lacrimal gland dysfunction, ultimately leading to DDE [8].

2.1 Hyperglycemia-Induced Oxidative Stress and Inflammation

Under hyperglycemic conditions, excessive glucose flux activates the polyol, protein kinase C (PKC), and hexosamine pathways, each contributing to oxidative stress. Activation of the polyol pathway depletes Nicotinamide Adenine Dinucleotide Phosphate (NADPH), weakening cellular antioxidant capacity and promoting ROS accumulation in corneal and lacrimal gland epithelial cells. ROS damage intracellular lipids, proteins, and DNA, impairing cellular structure and function [20]. Moreover, hyperglycemia suppresses the activity of critical antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), further amplifying oxidative stress and forming a self-reinforcing cycle. The oxidative microenvironment recruits macrophages and neutrophils, which secrete interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, activating the nuclear factor-κB (NF-κB) pathway and amplifying inflammation. Simultaneously, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are upregulated, facilitating inflammatory cell adhesion and retention on the ocular surface to sustain inflammation. Thus, hyperglycemia-driven oxidative stress and inflammation form a self-amplifying pathological loop, which constitutes the central mechanism of ocular surface damage [9,10,21]. Through these processes, hyperglycemia-induced oxidative stress and inflammation reciprocally amplify each other, driving ocular surface injury.

2.2 OSI-Mediated Corneal Nerve Damage

During oxidative stress, excessive ROS peroxidize unsaturated fatty acids in corneal nerve cell membranes, compromising membrane integrity and disrupting ionic homeostasis and substance exchange. ROS also damage proteins and DNA, interfering with nerve cell metabolism and proliferation and activating apoptotic pathways. Inflammatory cytokines (TNF-α, IL-1β) directly impair nerve cell growth and differentiation and induce apoptosis; they further reduce nerve growth factor (NGF) expression and secretion, disrupting the microenvironment required for corneal nerve maintenance, nutrient supply, and regeneration [11].

2.3 OSI-Induced Lacrimal Gland Dysfunction

Oxidative stress damages lacrimal gland cell organelles, including mitochondria and endoplasmic reticulum, reducing adenosine triphosphate (ATP) production and activating the unfolded protein response, which impairs tear-related protein synthesis and secretion. It also triggers apoptotic pathways, increasing cell death and further reducing secretory capacity. Inflammatory mediators disrupt intracellular signaling in lacrimal glands and inhibit their secretory function. Chronic inflammation alters gland innervation, causing abnormal neurotransmitter release and impaired tear secretion; prolonged inflammatory infiltration and cytokine stimulation ultimately induce lacrimal tissue fibrosis and atrophy, further compromising function [2,12,20,22].

In summary, hyperglycemia initiates a self-perpetuating oxidative stress and inflammation cascade, damaging corneal nerves and lacrimal glands, leading to tear film instability and ocular discomfort characteristic of DDE. The pathogenic mechanisms underlying hyperglycemia-induced oxidative stress and inflammation in DDE are schematically illustrated in Fig. 1.

3. The Effects of Macronutrients

In the management of DDE, various nutrients play distinct and crucial roles, affecting ocular physiology both directly in tissue repair and indirectly by regulating metabolic and inflammatory responses, thereby improving DDE outcomes [23].

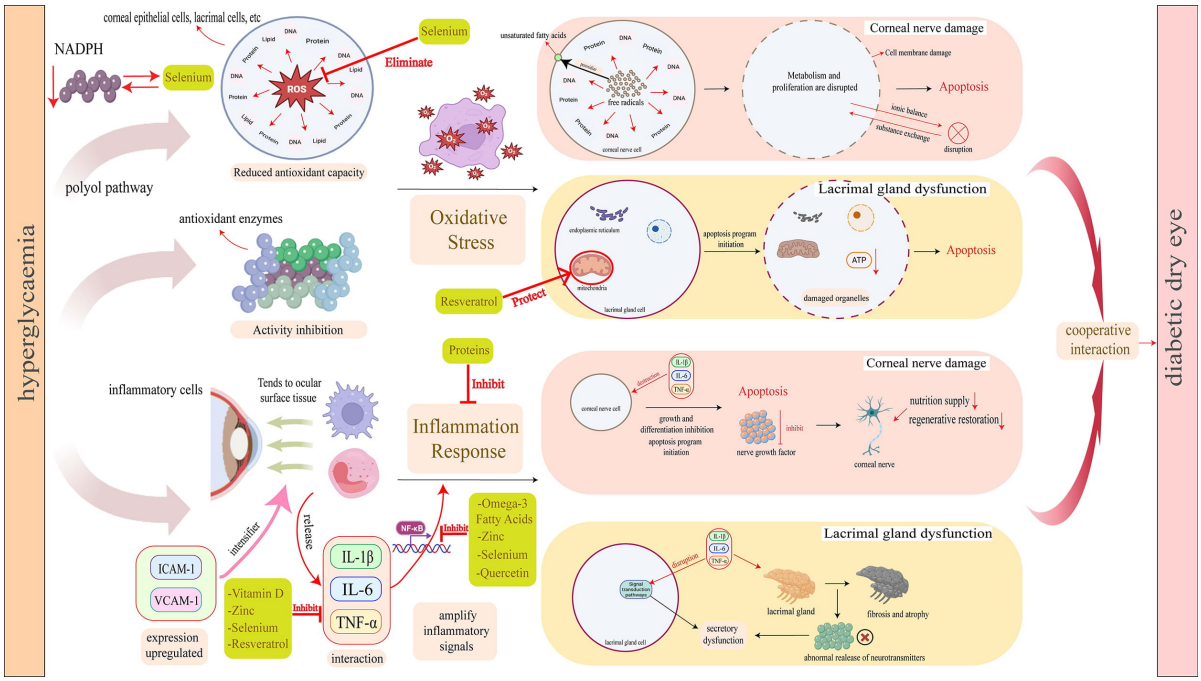

Fig. 1. Pathogenic mechanisms of DDE induced by hyperglycemia and the protective roles of nutritional interventions. This schematic illustrates the interplay between hyperglycemia-induced oxidative stress and inflammatory responses in the pathogenesis of DDE, alongside potential therapeutic targets. 1. Pathological cascade: hyperglycemia activates the polyol pathway and reduces antioxidant capacity, leading to ROS overproduction and mitochondrial dysfunction. Concurrently, upregulated adhesion molecules (ICAM-1, VCAM-1) and inflammatory cytokines (IL-1β, IL-6, TNF-α) trigger an inflammatory cascade via NF-κB signaling. These processes cooperatively induce apoptosis in lacrimal gland cells and corneal nerves, resulting in secretory dysfunction and neurotrophic deficiency. 2. Protective interventions: The diagram highlights specific nutritional agents that attenuate these deleterious pathways. Selenium and Resveratrol mitigate oxidative stress by inhibiting ROS generation and protecting cellular organelles. Furthermore, Selenium, Resveratrol, Vitamin D, Zinc, Omega-3 fatty acids, and Quercetin exert anti-inflammatory effects by inhibiting NF-κB activation and downregulating the expression of adhesion molecules, thereby preserving ocular surface homeostasis against diabetic insults. Abbreviations: DDE, diabetic dry eye; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; IL, interleukin; TNF, tumor necrosis factor; ATP, adenosine triphosphate. Red arrows indicate positive regulation or promotional effects, whereas inhibitory bars denote negative regulation or suppressive effects. Pink/light red areas represent pathological processes or outcomes, pale yellow/beige areas represent physiological mechanisms or protective interventions, and gray areas generally depict cellular structures or molecular complexes.

3.1 Carbohydrates

Within diabetic dietary management, appropriate carbohydrate intake is important for controlling DDE. Complex carbohydrates, such as those in whole grains, are absorbed slowly due to their structural properties, which helps mitigate postprandial blood glucose spikes [24,25]. Oat-derived beta-glucan may slow carbohydrate digestion and absorption, reduce glycemic variability, and protect ocular tissues from hyperglycemia-induced damage [26]. A clinical trial in patients with diabetic retinopathy demonstrated that combined supplementation of beta-glucan and vitamin D significantly reduced C-reactive protein and leptin levels, indicating a protective effect against DDE through inflammation modulation [27].

Dietary fiber from whole grains further benefits ocular health by promoting gut homeostasis, enriching beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, while suppressing peripheral inflammatory markers [28,29]. Gut microbiota imbalance triggers chronic systemic inflammation, which is closely linked to DDE pathogenesis. Moreover, dietary fiber supplementation effectively controls glycosylated hemoglobin, fasting blood glucose and lipid profiles, helping protect ocular vascular and neural function, preserve lacrimal gland secretion, and maintain ocular surface integrity, ultimately reducing DDE risk and alleviating clinical symptoms [30,31]. The Chinese dietary guideline recommends that carbohydrates provide 50%–65% of total daily energy intake, whereas the European Food Safety Authority (EFSA) and the US Dietary Guidelines recommend 45%–60%. The recommended daily dietary fiber intake for adults is 25–30 g/d [32,33,34].

3.2 Protein

High-quality protein contains bioactive substances that maintain the structural and functional integrity of ocular tissues [35]. Functional amino acids and protein derivatives exhibit protective effects against DDE-related inflammation and tissue fibrosis. For instance, glutamine suppresses inflammatory and fibrotic activation of corneal epithelial cells, regulates cell differentiation, and alleviates DDE manifestations.

A preclinical study evaluated a 17-mer PEDF mimetic peptide (Ppx) in diabetic mice with dry eye. After 3–6 weeks of topical administration, mice with impaired corneal sensitivity, decreased tear secretion, epithelial injury and neural degeneration showed significant improvement. Ppx restored tight junction protein ZO-1 expression and corneal epithelial barrier integrity, normalized inflammatory cytokines, parasympathetic nerve markers, and MAPK/JNK pathway activation in lacrimal glands, validating topical protein mimetic intervention as an effective strategy for DDE treatment [36]. For healthy adults, the recommended protein intake is 0.8–1.0 g/kg body weight per day, accounting for 10%–35% of total daily energy. Excessive protein may increase renal burden, risk of osteoporosis, and metabolic disorders [37].

3.3 Fatty Acids

Different fatty acids have distinct chemical structures and roles in metabolic regulation and ocular physiology in DDE patients. Omega-3 polyunsaturated fatty acids (EPA and DHA) are essential for regulating ocular surface inflammation and stabilizing the tear film [38,39]. Mechanistically, EPA and DHA competitively inhibit the arachidonic acid pathway, reducing pro-inflammatory mediators such as PGE_2 and LTB_4, suppress NF-κB activation, and downregulate inflammatory gene transcription. Clinically, omega-3 supplementation improves tear inflammatory biomarkers and alleviates ocular discomfort in DDE patients [39,40,41,42,43].

Omega-3 fatty acids also optimize meibomian gland lipid synthesis, improve tear film lipid composition and properties, and integrate into cell membrane to enhance fluidity, reduce tear evaporation and prolong tear film breakup time. They promote conjunctival epithelial mucin secretion, further stabilizing the tear film and protecting the ocular surface [44].

A 3-month clinical trial in type 2 diabetic patients with moderate to severe dry eye administered daily omega-3 capsules (170 mg EPA + 115 mg DHA). Results showed improved Schirmer I test values, prolonged tear breakup time, reduced conjunctival squamous metaplasia, and lower OSDI scores, confirming the clinical efficacy of omega-3 fatty acids in enhancing tear film function and alleviating DDE symptoms [40].

Dietary sources include deep-sea fish (salmon, mackerel, tuna) for EPA and DHA, and plant sources (flaxseeds, walnuts, chia seeds) for alpha-linolenic acid, which can partially convert to EPA and DHA *in vivo*, though conversion efficiency varies with age, genetics, and diet [45,46].

Monounsaturated fatty acids exert anti-inflammatory and tear film-stabilizing effects. Oleic acid from olive oil modulates inflammatory signaling, inhibits pro-inflammatory enzymes, and reduces ocular surface inflammatory mediator accumulation in DDE patients [47].

For DDE patients, moderate supplementation of omega-3 and monounsaturated fatty acids via fish, vegetable oils and nuts is recommended, whereas saturated fatty acids should be limited to reduce inflammation and optimize metabolism. Medium-chain fatty acids from coconut oil are acceptable for energy supply in moderation. Rational fatty acid allocation helps alleviate DDE symptoms and improve quality of life [48,49,50,51]. The EFSA recommends a safe supplemental DHA intake of 1 g/d, as excessive intake may increase bleeding risk, alter coagulation, and affect glucose, lipid, and immune function. High DHA during pregnancy may adversely affect outcomes [52].

4. The Effects of Micronutrients

4.1 Vitamins

Multivitamins play a crucial role in maintaining eye health and managing diabetic eye diseases, including DDE, through distinct physiological functions, specific mechanisms, and diverse food sources [53].

4.1.1 Vitamin A

Vitamin A (VA), also known as retinoids, is essential for normal ocular physiology. In retinal photoreceptors, retinaldehyde, the active form of VA, is a key component of rhodopsin. Light stimulation triggers photoisomerization of retinal pigment, initiating visual signaling and enabling light perception. VA supports differentiation and metabolism of ocular surface epithelial cells, maintains epithelial integrity, and promotes tear secretion. VA deficiency leads to squamous metaplasia of the ocular epithelium and lacrimal gland dysfunction, contributing to DDE development [53,54].

It also causes conjunctival epithelial chemotaxis, and keratin from the conjunctival stratum corneum mixes with dry rods to form Bitot's spots. VA supplementation may improve DDE by correcting chemotaxis and reducing abnormal keratin-bacteria aggregation. Insufficient retinal retinoid synthesis impairs photoreceptor function, causing night blindness. Animal livers are rich, bioavailable VA sources. Vegetables such as carrots, pumpkin, and spinach, and fruits like mangoes and sweet potatoes, contain β-carotene, converted to retinaldehyde by the body via β-carotene oxygenase [53,55]. The Recommended Dietary Allowance (RDA) of vitamin A is 700 μg retinol equivalent (RE) per day (2300 IU) for adult women, 900 μg RE/d (3000 IU) for adult men, and 770 μg RE/day (2600 IU) for pregnant women. The tolerable upper intake level (UL)

for adults is 3000 μg RE/day (~10,000 IU). Excessive supplementation may cause teratogenicity, hepatotoxicity, and skeletal disorders [56].

4.1.2 Vitamin D

Vitamin D (VD) modulates immune responses and reduces ocular inflammation. Its active form, 1,25-dihydroxyvitamin D_3, binds to VD receptors to regulate immune cell differentiation and function, alleviating ocular inflammation. Because inflammation drives dry eye pathogenesis, VD can effectively mitigate DDE [23,57]. A study comparing 90 children with type 1 diabetes mellitus (T1-DM) to 80 healthy controls found that VD-deficient T1-DM children had lower tear film breakup time, Schirmer test results, and tear meniscus height and area, with higher corneal staining scores. These parameters were also worse in VD-deficient T1-DM children compared to T1-DM children with normal VD levels, indicating that concurrent VD deficiency exacerbates dry eye [58].

Food sources include salmon and mackerel (VD_3), egg yolks, and dairy products. Additionally, 7-dehydrocholesterol in skin converts to VD_3 upon UV exposure, making sunlight an important source [59]. For individuals aged 9–70 years, the RDA of vitamin D is 600 IU (15 μg)/day, with a UL of 4000 IU (100 μg). Even very high long-term intakes generally do not cause adverse reactions, including gastrointestinal symptoms, fatigue, renal dysfunction, or signs of hypercalcemia [60].

4.1.3 Vitamin C

Vitamin C (VC) is a water-soluble antioxidant, may improve DDE through multiple mechanisms. It neutralizes excess free radicals generated under hyperglycemia, reducing oxidative damage to conjunctival goblet cells. VC also mitigates corneal epithelial inflammation by inhibiting vascular endothelial growth factor A (VEGF-A). and promotes collagen synthesis in the corneal stroma, maintaining fiber stability. Animal experiments have confirmed that VC accelerates corneal repair in alkali-burn models [61]. The RDA and optimal intake of VC is 90–100 mg/d, with a UL below 1 g/d. Excessive supplementation may cause gastrointestinal discomfort and increased risk of kidney stones [62].

4.1.4 Vitamin E

Vitamin E (VE) primarily acts as a fat-soluble antioxidant, protecting cell membrane lipids and meibomian gland components from oxidative damage, thereby stabilizing the tear film lipid layer. VE has been reported to reduce diabetes-related neuropathic pain via anti-inflammatory effects and promote corneal innervation recovery when applied topically. Clinical evidence shows that combining VE with coenzyme Q10 eye drops significantly improves tear film stability, but long-term high-dose VE (>800 IU/d) may increase bleeding risk, requiring strict clinical dosage control [63]. The RDA of VE is 15 mg/d (23 IU) for adults, with a UL of 1000 mg/d (1500 IU) for adults, pregnant women, and lactating women. Excessive supplementation may cause gastrointestinal discomfort, fatigue, blurred vision, and other adverse effects [64].

Supplementation with vitamins A, C, D, and E may help alleviate DDE symptoms, providing antioxidant, anti-inflammatory, and ocular surface protective effects. Lutein and zeaxanthin are also beneficial [65]. A balanced diet rich in these vitamins is recommended, with supplementation under physician or dietitian supervision when necessary [38].

4.2 Trace Elements

In the prevention and treatment of DDE, trace elements such as zinc and selenium play crucial roles in regulating glucose metabolism and maintaining ocular surface health due to their unique physicochemical properties. Their effects are closely associated with specific mechanisms and dietary sources [53].

4.2.1 Zinc

Zinc is essential for insulin synthesis, storage, secretion, and structural stability. In pancreatic β-cells, zinc facilitates the conversion of proinsulin to insulin and aids in storing insulin as hexamers within secretory granules, ensuring normal insulin secretion [24,66]. Zinc deficiency reduces the efficiency of insulin conversion, impairs insulin synthesis and secretion, and decreases the tyrosine kinase activity of the insulin receptor, leading to insulin resistance and hyperglycemia [67]. Hyperglycemia and insulin resistance further increase oxidative stress and inflammation in DDE pathogenesis. Zinc acts as a potent antioxidant and is a structural component of Cu/Zn-SOD (copper-zinc superoxide dismutase) and other antioxidant enzymes. It scavenges superoxide anions, hydrogen peroxide, and other reactive ROS, inhibits lipid peroxidation, and protects ocular surface cell membranes, proteins, and nucleic acids from oxidative damage. Furthermore, zinc reduces ocular surface inflammation by regulating the NF-κB signaling pathway and inhibiting inflammatory factor expression [66]. Foods rich in zinc include oysters, beef, lean meat, and eggs. Oysters are particularly high in bioavailable zinc, ensuring adequate absorption [67,68,69]. The RDA of zinc is 8–15 mg/d for adult men and 8–12 mg/d for adult women. The UL is 40 mg/d, and excessive intake may cause gastrointestinal discomfort, impaired immunity, dyslipidemia, and metabolic disturbances [70].

4.2.2 Selenium

Selenium is a key component of the GPx enzymes and plays a vital role in enhancing antioxidant capacity and regulating insulin secretion [71]. In pancreatic islet cells, selenium maintains GPx activity, scavenges excess intracellular ROS, and protects islet cells from oxidative damage, supporting normal insulin secretion and blood glucose

control. In ocular surface tissues, selenium exerts important antioxidant and anti-inflammatory effects [72]. It regulates redox balance in ocular surface cells, inhibits oxidative stress-induced apoptosis, and protects the integrity of ocular surface epithelial cells and lacrimal gland cells [72,73]. Furthermore, selenium inhibiting NF-κB signaling pathway activation, alleviating ocular surface inflammation and improving DDE symptoms [72]. Seafood and animal liver are primary selenium sources, with content varying by species and environment. Animal liver is particularly rich in organic selenium, such as selenomethionine, which has high bioavailability [74]. For selenium, the RDA is 55 µg/d, and the established UL is 400 µg/d, while the EFSA recommends an upper limit of 255 µg/day. Excessive selenium intake may cause hair and nail loss, digestive issues, and joint pain [75].

Overall, these trace elements help improve DDE through mechanisms including glucose regulation, antioxidant activity, and anti-inflammatory effects. Patients may obtain them through a balanced diet under medical guidance, with supplementation as needed [76].

5. The Roles of Bioactive Dietary Components

5.1 α-Lipoic Acid (ALA)

In addition to the macronutrients and micronutrients, other dietary components also exert protective effects on DDE. Recently, ALA, a potent mitochondrial antioxidant, has emerged as a preventive and therapeutic option for DDE due to its multi-target anti-inflammatory and antioxidant properties [77].

ALA directly scavenges superoxide anions and hydroxyl radicals and regenerates endogenous antioxidants such as coenzyme Q10, glutathione, VE and VC, thereby significantly reducing oxidative stress. It can also chelate Fe^{2+} and Cu^{2+}, inhibit the Fenton reaction, and further decreases hydroxyl radical formation. In terms of inflammation regulation, ALA inhibits the activation of NF-κB and weakens T cell-mediated inflammatory responses by downregulating the interaction between nuclear factor of activated T cells 5 (NFAT5) and subunit of nuclear factor-kappa B (p65). Experiments have shown that ALA significantly reduces the expression of matrix metalloproteinase-9 (MMP-9) in corneal epithelial cells, helping to restore tight junction integrity. Additionally, ALA activates factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway, increases antioxidant enzyme levels, enhances adenosine monophosphate-activated protein kinase (AMPK) activity, improves mitochondrial function, and promotes energy metabolism in lacrimal gland cells, collectively conferring antioxidative, anti-inflammatory, and cytoprotective effects [78]. Related clinical evidence supports that human posterior medial corneal (HPMC) morphology and tear breakup time (TBUT) are closely correlated with ocular surface inflammation and oxidative stress status.

A clinical study enrolled 70 DDE patients aged 50–79 years, randomly assigning them to two groups: 35 received eye drops containing 0.1% ALA and 0.3% HPMC, and 35 received 0.3% HPMC alone. Eye drops were administered three times daily for 2 months. After treatment, the ALA group showed greater improvements in TBUT, corneal fluorescein staining, and OSDI scores, with more pronounced tear film morphology recovery [79].

For therapeutic purposes, the routine clinical dose of ALA ranges from 300–600 mg/d, the commonly used dose is 600–1800 mg/d, and the effective therapeutic range spans 200–1800 mg/d. Excessive intake may cause skin rash, gastrointestinal symptoms, or metabolic disturbances [80].

5.2 Phytochemicals

Phytochemicals play a key role in preventing and treating DDE through antioxidant, anti-inflammatory, neuroprotective, and microcirculation-enhancing effects [81].

Polyphenolic compounds with polyphenolic structure, excellent in antioxidant, anti-inflammatory, and immunomodulatory properties. Polyphenols protect cells by activating antioxidant defense systems and regulating immune cells to inhibit inflammatory mediators [13,82,83]. Examples include green tea catechins, red wine resveratrol, and berry anthocyanins, which improve DDE by reducing ocular surface inflammation and oxidative stress and indirectly improving systemic metabolism [84].

Flavonoids, a widely distributed class of polyphenolic compounds in plants, support ocular surface health through ROS scavenging, lipid peroxidation inhibition, and suppression of IL-1β and TNF-α transcription. Dietary sources include citrus fruits, apples, onions, and green tea, with naringin and quercetin absorbed into circulation to act on ocular tissues [85,86,87,88].

5.2.1 Anthocyanins

Anthocyanins activate the Nrf2/HO-1 pathway to alleviate retinal oxidative stress [85]. They also inhibit inflammatory factors and signaling pathways, protect cells from high-sugar damage, and improve ocular microcirculation by dilating blood vessels and reducing blood viscosity to promote nutrient delivery and waste excretion [89]. They are found in dark berries, fruits, vegetables, grains, legumes, dark chocolate, and fresh juices. Fresh, skin-on ingredients are recommended, and a variety should be consumed to obtain different anthocyanins [90]. At usual dietary intake levels, even high doses of anthocyanins or their extracts have shown no negative effects. Nevertheless, the EFSA concluded that the existing toxicological database is insufficient to establish a numerical Acceptable Daily Intake (ADI) for anthocyanins. High-dose anthocyanin concentrates may cause digestive disturbances or, in sensitive individuals, allergic reactions [91].

5.2.2 Resveratrol

Resveratrol enhances antioxidant capacity, increases antioxidant enzyme activity, reduces oxidative stress, scavenges free radicals, restores mitochondrial function, and inhibits apoptosis by upregulating SIRT1. It also downregulates inflammation-related pathways, protects ocular cells from high-sugar damage, regulates the neuroendocrine system to enhance ocular blood circulation and tear secretion, and dilates blood vessels to improve microcirculation [92,93].

Major dietary sources include grapes, dark berries, nuts, and some Chinese herbs, with fresh grapes and nuts preferred over red wine for supplementation [92,94]. Resveratrol is commonly administered at a low dose of 50–500 mg/d, which is the standard dosage for commercial dietary supplements, while a moderate dose of 1000 mg/d is frequently adopted in clinical studies. Excessive supplementation may cause gastrointestinal discomfort, bleeding risk, or hepatic/renal toxicity [95].

5.2.3 Quercetin

Quercetin inhibits xanthine oxidase to reduce ROS, modulates immune cells, suppresses pro-inflammatory cytokines, increases tear secretion, enhances goblet cell density, stabilizes tear film, and protects lacrimal glands and ocular surface integrity via NF-κB inhibition [96,97,98,99].

Sources include dark vegetables, fruits, medicinal plants, grains, and legumes. Fresh or lightly processed foods are preferred, ideally consumed with vitamin C to enhance absorption [100]. Quercetin is generally recognized as safe (GRAS) by the FDA at an oral dose of 500 mg/d. Oral intake exceeding 1000 mg/d may cause gastrointestinal discomfort and headaches, while intravenous administration above 1400 mg/m^2 can lead to dyspnea, vomiting and nephrotoxicity [101].

5.2.4 Carotenoids

Carotenoids are natural fat-soluble pigments divided into carotenes (α-carotene, β-carotene, β-cryptoxanthin) and xanthophylls (lutein, zeaxanthin, meso-zeaxanthin, lycopene, astaxanthin). Sources include carrots, leafy greens, citrus, dark vegetables, fruits, and aquatic products [102,103].

As natural fat-soluble antioxidant pigments, carotenoids exert multiple functional mechanisms in the potential intervention of DDE [102]. In terms of neuroprotection, carotenoids can maintain the level of brain-derived neurotrophic factor (BDNF), prevent neuronal degeneration, protect corneal nerve function, and thus may improve reflex tear secretion. In addition, β-carotene can be converted into vitamin A, which is essential for maintaining the health of ocular surface epithelium. They also preserve inner and outer retinal nuclear layer thickness and reduce apoptosis [104].

Existing research evidence has confirmed that carotenoids have definite protective effects against diabetes retinopathy (DR) and age-related macular degeneration (AMD). Their antioxidant and anti-inflammatory mechanisms are highly consistent with the pathological basis of DDE [105]. However, direct DDE-specific clinical studies are limited, and optimal dosage, treatment duration, and formulations require further research.

Dietary intake recommendations per 2023 Chinese DRIs: lutein SPL 10 mg/d (UL 60 mg/d); lycopene SPL 15 mg/d (UL 70 mg/d). National intake reference figures also differ by country. It should be noted that the US/Canada have not established an official DRI for lutein, and average US adult lutein+zeaxanthin intake is only about 1.7 mg/d (NHANES 2011–2012) [33,106].

Phytochemicals improve DDE through antioxidant, anti-inflammatory, and immunomodulatory effects. Patients may increase intake of phytochemical-rich foods, but due to individual variability, physician or dietitian supervision is advised for safety and efficacy [23,88].

A comparison of the role of phytochemicals in DDE is shown in Table 2 (Ref. [93,95]).

5.3 Synergistic Effects of Combined Nutritional Components

Different nutrients may exert synergistic effects, and their combined use can achieve stronger preventive and therapeutic effects against DDE.

It has been reported that the synergistic action of VC and VE significantly improves DDE. Combined VC and VE supplementation increase Schirmer values by 30%, prolongs TBUT, and elevates goblet cell density in diabetic patients [107]. VC regenerates oxidized VE, and their complementary solubility covers ocular surface microenvironments to scavenge ROS, reduce oxidative damage, and form a complete antioxidant defense network [108].

Jikang Mingmu Eye Drops (JMD), a traditional Tibetan medicine rich in phytochemicals (silymarin, quercetin, gallic acid, etc.), has shown therapeutic potential in DDE. In db/db diabetic mice, JMD dose-dependently increased tear secretion, reduced corneal fluorescein staining, improved conjunctival epithelial morphology, enhanced goblet cell density, and decreased conjunctival IL-6 and IL-17α levels. Effective concentrations were 0.25–1 g/mL, but clinical efficacy and mechanisms in humans remain to be clarified [109].

Combinations of omega-3 fatty acids and antioxidants exhibit strong synergistic potential in DDE. Clinical trials show that combined supplementation improves TBUT, Schirmer values, and OSDI scores while reducing inflammatory factors in diabetic and glaucoma-complicated dry eye patients [17,40,110].

However, large-sample, double-blind, placebo-controlled trials specifically targeting DDE are still lacking. The dose–response relationship, long-term safety,

Table 2. Comparison of the role of phytochemicals in DDE.

Chemical classification	Representative compound	Structural features	Core mechanisms	Best food sources	Reference
Polyphenols·Flavonoids					[93]
·Flavonols	Quercetin	C6-C3-C6 structure, 3-OH	·Inhibits NADPH oxidase ·Upregulates occludin protein	Onions, apple peel, buckwheat	
·Anthocyanins	Cyanidin	Flavonoid cation structure, glycosylated	·Activates Nrf2/ARE pathway ·Inhibits VEGF	Blueberries, blackcurrants, purple sweet potatoes	
Polyphenols·Non-Flavonoids					[95]
·Stilbenes	Resveratrol	Stilbene structure (C6-C2-C6)	·Activates SIRT1/PGC-1α ·Mitochondrial protection	Grape skin, peanut testa	
·Phenolic acids	Gallic acid	Benzoic acid derivative	·Direct electron transfer antioxidant	Green tea, gallnuts	

and mechanisms of omega-3 fatty acids and ALA on tear lipid metabolism and meibomian gland microbiota remain unclear. Overall, omega-3 fatty acids combined with antioxidants exert synergistic effects in four aspects: anti-inflammation, antioxidation, tear film lipid layer repair, and meibomian gland function enhancement, representing a highly promising adjuvant therapy for DDE [43].

The summary of core mechanisms and literature evidence by which some key nutrients regulate DDE is shown in Table 3. As summarized in Table 3 (Ref. [32,33,34,36,40,53,58,61,63,66,72,79,90,93,99,104]), the strength of evidence for nutritional interventions in DDE varies considerably. Omega-3 fatty acids, α-lipoic acid (ALA), and combined VC/VE have been validated in human interventional studies. Vitamin D deficiency is consistently associated with worse dry eye indices in diabetic patients [40,58,79,108]. In contrast, evidence for protein and certain phytochemicals such as JMD remains limited to animal models and awaits clinical confirmation [36,109]. Well-designed randomized controlled trials are needed to optimize dosage, duration, and combinations.

6. The Impact of Dietary Pattern

The Mediterranean diet features high intake of vegetables, fruits, whole grains, olive oil, fish, and nuts, which are abundant in polyphenols, vitamins, minerals, and unsaturated fatty acids. It may alleviate DDE by regulating oxidative stress, inflammatory responses, and systemic metabolism [11,90,111,112]. Vitamins and minerals synergistically strengthen antioxidant defenses, while fatty acids serve as precursors of anti-inflammatory mediators and work with polyphenols to reduce ocular surface inflammation. Fatty acid composition and cooking methods largely influence nutrient bioavailability, which warrants further investigation [113].

Although direct clinical studies of the Mediterranean diet for DDE are limited, evidence from metabolic outcomes suggests benefits. A meta-analysis of seven RCTs including 1371 type 2 diabetes patients found that the Mediterranean diet reduced HbA1c by –0.39% (95% CI: –0.58 to –0.20, $p < 0.001$) and fasting plasma glucose by –15.12 mg/dL (95% CI: –24.69 to –5.55, $p = 0.002$) compared to control diets [114]. Since DDE prevalence is closely linked to glycemic control, these improvements may help alleviate dry eye symptoms [115].

Clinical studies also indicate that Mediterranean diet patterns rich in omega-3 fatty acids, polyphenols, and antioxidants can improve ocular surface inflammation and tear film stability. However, most evidence relies on intermediate metabolic endpoints rather than direct DDE outcomes, highlighting the need for well-designed, long-term clinical trials measuring DDE-specific parameters. Early dietary intervention is recommended to maximize benefits and prevent irreversible ocular surface damage. The Mediterranean diet can be integrated with glycemic control, blood pressure management, and regular ophthalmic monitoring for optimal efficacy [116,117,118].

7. Future Directions

7.1 Precision Nutrition and Biomarkers

Future nutritional intervention for DDE is expected to advance toward precision nutrition tailored to individual metabolic and genetic characteristics, moving beyond generalized supplementation strategies. Further investigations should focus on identifying specific, non-invasive biomarkers in tear fluid and serum that can effectively predict individual responses to nutritional interventions in DDE patients. Potential targets include metabolic indicators associated with oxidative stress, fatty acid metabolism, and advanced glycation status, which could act as early warning signals or dynamic efficacy markers for personalized nutri-

Table 3. Summary table of core mechanisms and literature evidence for key nutrients regulating DDE.

Nutrient category	Proposed mechanisms	Evidence type	Clinical relevance	Recommended intake and safety considerations	Reference
Carbohydrates	Slow glucose absorption, modulate inflammation, regulate gut microbiota, stabilize metabolism	-	Reduce DDE risk, relieve symptoms, stabilize diabetic metabolic status	Carbohydrates: 50%–65% total energy (Chinese Dietary Guidelines); 45%–60% total energy (EFSA / US Dietary Guidelines); dietary fiber: 25–30 g/d; safe at recommended intake	[32,33,34]
Proteins	Inhibit inflammation and fibrosis processes of CECS and regulate CDT	Animal	Reverse DDE pathology, restore tear secretion and corneal function	0.8–1.0 g/kg body weight/d; excess increases renal burden and osteoporosis risk	[36]
Omega-3 fatty acids	Reduce the synthesis of PGE_2 and LTB_4, and inhibit the activation of the NF-κB signaling pathway.	Clinical	Improve tear film function, alleviate DDE discomfort	Supplemental DHA: ≤1 g/d; moderate intake; excess increases bleeding risk	[40]
VA	Maintain ocular epithelium integrity, promote tear secretion, support visual function	-	Prevent and improve DDE, avoid ocular surface dysfunction	RDA: 700–900 μg RE/d; UL: 3000 μg RE/d; excess causes teratogenicity, hepatotoxicity	[53]
VD	Regulate immune responses and promote the secretion of anti-inflammatory cytokines.	Clinical	VD deficiency exacerbates DDE; adequate intake alleviates severity	RDA: 600 IU/d; UL: 4000 IU/d; excess causes hypercalcemia, renal dysfunction	[58]
VC	Antioxidant, inhibit corneal inflammation, promote corneal repair	-	Alleviate ocular oxidative injury, facilitate corneal repair	RDA: 90–100 mg/d; UL: <1 g/d; excess causes GI discomfort, kidney stone risk	[61]
VE	Antioxidant, stabilize tear film, promote corneal innervation recovery	-	Improve tear film stability, alleviate DDE and neuropathic pain	RDA: 15 mg/d; UL: 1000 mg/d; high dose increases bleeding risk	[63]
Zinc	Regulate insulin function, antioxidant, inhibit ocular inflammation	-	Ameliorate DDE-related oxidative stress and inflammation	RDA: 8–15 mg/d; UL: 40 mg/d; excess causes GI discomfort, immune impairment	[66]
Selenium	Antioxidant, protect pancreatic and ocular cells, inhibit inflammation	-	Alleviate ocular inflammation, improve DDE symptoms	RDA: 55 μg/d; UL: 400 μg/d (US/Chinese standards), 255 μg/d (EFSA); excess causes selenosis	[72]
ALA	Scavenges ROS, chelates metal ions, inhibits inflammatory signaling, and activates the Nrf2/HO-1 and AMPK pathways.	Clinical	Improve DDE indicators, repair corneal epithelium	200–1800 mg/d (therapeutic effective range); 300–600 mg/d (clinical dose); 600–1800 mg/d (commonly used dose); excess causes skin rash, GI symptoms	[79]
Anthocyanins	Antioxidant (Nrf2/HO-1 pathway), anti-inflammatory, improve ocular microcirculation	-	Alleviate ocular oxidative stress, assist DDE relief	No numerical ADI (EFSA); low allergic risk, no obvious excess harm	[90]
Resveratrol	Antioxidant, anti-inflammatory, improve ocular blood circulation	-	Protects ocular cells, potentially relieves DDE symptoms	50–500 mg/d (supplement); 1000 mg/d (clinical dose); excess causes GI reaction, bleeding risk	[93]
Quercetin	Antioxidant, inhibit ocular inflammation, stabilize tear film	-	Reduces ocular inflammation, improves tear secretion	Safe ≤500 mg/d; excess causes GI discomfort, headache	[99]
Carotenoids	Antioxidant, convert to VA, protect retinal neurons	-	Protects ocular tissues, potential DDE relief via systemic support	Lutein: 10 mg/d (UL 60 mg/d);lycopene: 15 mg/d (UL 70 mg/d); safe at recommended intake	[104]

CECS, corneal epithelial cell sheet; CDT, cell death triggering; PGE_2, prostaglandin E_2; LTB_4, leukotriene B_4; DHA, docosahexaenoic acid; VA, vitamin A; RDA, Recommended Dietary Allowance; VD, vitamin D; UL, Tolerable Upper Intake Level; RE, retinol equivalent; GI, glycemic index; VC, vitamin C; IU, International Unit; VE, vitamin E; ALA, α-linolenic acid; HO-1, heme oxygenase-1; AMPK, adenosine monophosphate-activated protein kinase; EFSA, European Food Safety Authority; ADI, Acceptable Daily Intake.

tional strategies. In addition, functional genetic variants that regulate nutrient metabolism and utilization warrant in-depth exploration and validation as key stratification biomarkers. Polymorphisms in fatty acid desaturase genes *FADS1*/*FADS2* may determine the conversion efficiency of plant-derived ω-3 polyunsaturated fatty acids, while variations in the vitamin D receptor gene *VDR* may alter ocular tissue sensitivity to vitamin D [119,120]. Elucidation of these genetic features will support precise adjustment of nutrient types and dosages, thereby improving the effectiveness and safety of nutritional interventions. Integrated multi-omics strategies combining metabolomics and genomics should be established to develop individualized predictive models, enabling early and targeted nutritional prevention before obvious clinical symptoms of DDE appear.

7.2 Integrated Clinical Management

Given the multifactorial and chronic characteristics of DDE, future research should prioritize the systematic integration of nutritional interventions into routine clinical management as a valuable adjuvant therapy. Further studies are urgently needed to establish standardized clinical protocols for combining nutritional supplements, including ω-3 polyunsaturated fatty acids, combined antioxidants, and bioactive phytochemicals, with conventional DDE treatments such as artificial tears, topical anti-inflammatory eye drops, meibomian gland physiotherapy, and systemic glycemic control medications [121]. Related directions include exploring whether nutritional supplementation can reduce the dosage or long-term side effects of topical medications, improve the low response rate of DDE patients to conventional artificial tears, and define appropriate timing and intensity of nutritional interventions based on DDE severity, corneal nerve damage status, and tear film function indices. By constructing a comprehensive multimodal management framework, nutritional therapy can exert synergistic effects with conventional treatments to achieve sustained improvement of ocular surface health and long-term stabilization of DDE symptoms.

7.3 Synergistic Nutritional Interventions

Future investigations should also move beyond single-nutrient studies to systematically explore synergistic interactions among multiple nutrients. Rational combinations of antioxidants, ω-3 fatty acids, vitamins, and phytochemicals deserve intensive screening and optimization to achieve stronger anti-inflammatory, antioxidant, and tear film-stabilizing effects. The molecular mechanisms underlying nutrient–nutrient interactions in the hyperglycemic ocular surface microenvironment require further clarification to support rational design of compound nutritional products. Safe and standardized nutritional formulations suitable for long-term clinical use in DDE patients should be developed with clear dose setting, administration routes, and safety profiles.

7.4 Clinical Validation and Long-Term Safety

Current evidence for nutritional interventions in DDE remains limited, and long-term and high-quality clinical evidence is needed to support clinical translation. Future studies should conduct large-sample, multi-center, double-blind, placebo-controlled randomized trials specifically designed for DDE populations to clarify the efficacy, optimal dose, intervention duration, and long-term safety of nutritional interventions. The *in vivo* mechanisms by which nutrients improve lacrimal gland secretion function, promote corneal nerve repair, and regulate meibomian gland lipid metabolism remain to be fully elucidated [122]. The actual clinical value of representative dietary patterns such as the Mediterranean diet in DDE prevention and management also needs to be verified by long-term prospective studies. Completion of the above research will provide robust scientific support for translating nutritional strategies into routine clinical care and ultimately improve the prognosis and quality of life of DDE patients.

8. Conclusions

This review comprehensively summarizes the critical roles of various nutritional components and dietary patterns in the management of DDE. The existing evidence strongly demonstrates that appropriate nutritional interventions, including rational intake of macronutrients, micronutrients, and bioactive phytochemicals, effectively target hyperglycemia-induced oxidative stress, chronic inflammation, and tear film instability, thereby protecting corneal nerves, improving lacrimal gland function, and alleviating DDE symptoms. The Mediterranean diet is a balanced and sustainable dietary pattern rich in antioxidants anti-inflammatory compounds and unsaturated fatty acids. It notably has great potential to improve metabolic status and ocular surface health in diabetic patients and serves as a safe and feasible strategy for DDE prevention and adjunctive therapy.

Collectively, nutritional modulation serves as a promising, non-invasive, and clinically translatable approach for DDE care. Although further large-sample, long-term clinical trials and mechanistic studies are still needed to optimize application regimens, current findings provide robust scientific support for implementing nutrition-based strategies in clinical practice. This review underscores the value of nutritional interventions as an integral component of comprehensive DDE management and offers clear directions for future research toward precision nutrition, combined interventions, and integrated clinical care.

This review emphasizes DDE-specific nutritional interventions, integrating nutrients, dietary patterns, and pathological mechanisms, providing actionable directions for future research, precision nutrition, and combined interventions.

Limitations include small sample sizes, observational studies, and a lack of individualized nutrient metabolism

considerations. Synergistic mechanisms of nutrients and dietary patterns remain unclear, and study heterogeneity prevents definitive causal conclusions.

Author Contributions

QL: design and drafting; YC, WY, YG, WL: conception and design; LC: literature screening, collation and analysis of published data, drafting; KW, HX, SW: interpretation of literature-derived data, revising; DP: collation and analysis of published data, revising; LY: literature screening, collation and analysis of published data, drafting; GS: analysis and interpretation of data, revising. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

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