Review

The Protective Effect of Polyunsaturated Fatty Acids against Dry Eye Disease: A Literature Review

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Abstract: Dry eye disease (DED) is a common disease, and have an adverse effect the physical, functional, and psychological quality of life. It is a multifactorial disorder characterized by the loss of tear film homeostasis, in which self-perpetuating vicious cycle leads to deterioration of function and inflammation of the lacrimal functional unit. Hence, treatment strategies should be aimed at the interruption of the vicious inflammatory cycle and alleviation of ocular surface inflammation. Anti-inflammatory therapies have been shown to improve the signs and symptoms of the disease. Evidence indicates that polyunsaturated fatty acids (PUFAs) may contribute to reinforcement of innate anti-inflammatory mechanisms, and systemic and topical administration of PUFAs may help modulate ocular surface inflammation. In the present review, the authors will introduce the results of clinical and experimental studies to elucidate the mechanism, efficacy, and safety of systemic and topical supplementation with PUFAs as an alternative therapeutic strategy for DED. This review will also include discussion regarding current perspectives, including evidence-based recommendations and possible side effects of PUFAs supplementation. The review of the literature suggests that PUFAs supplementation can be a viable option for the treatment of DED, although further studies are needed for establishment of treatment guidelines.

Keywords: dry eye; dry eye disease; essential fatty acids; ocular surface; omega-3; polyunsaturated fatty acids

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1. Introduction

Dry eye disease (DED) is a multifactorial ocular surface disorder characterized by the loss of tear film homeostasis, i.e., hyperosmolarity and instability of tear film [1]. In addition to inflammation and damage of ocular surface, neurosensory dysfunctions can contribute to ocular symptoms [1], such as ocular discomfort, grittiness and pain foreign body sensation, and blurry vision [2], which can cause interference of activities of daily living (e.g., using digital devices, reading and driving) [2]. Thus, the disease can result in serious impairment of physical, functional, and psychological quality of life [2,3]. It is one of the most common diseases with a prevalence of 5% to 50% worldwide [4–7]. It has also become a major public health problem in terms of economic burden, with high indirect costs caused by the substantial loss of productivity [8]. Aging is associated with an increasing prevalence of DED [9–11], as we have reported that the prevalence of 33.2% in a Korean population aged 65 years or older [5]. Female sex, Asian ethnicity, contact lens wear, medical comorbidities, such as diabetes mellitus and Sjögren's syndrome, psychological conditions, such as depression and stress, systemic medications (e.g., antihistamines, antidiuretics, and diuretics), and environmental conditions (e.g., air pollution, low humidity, and prolonged use of digital devices) can also increase the risk of DED [4,7,12–14].

A vicious cycle of inflammation involving the lacrimal functional unit is thought to be a major role in the pathogenesis of DED [6,12,13]. Disruption of the tear film

homeostasis caused by ocular surface desiccation triggers the activation of an inflammatory cascade involving the ocular surface epithelium and residing immune cells: promotion of the production of innate inflammatory mediators, such as matrix metalloproteinases (MMPs), cytokines (e.g., tumor necrosis factor (TNF- α) and interleukin (IL)-1 β) and chemokines (e.g., C-X-C motif ligand (CXCL) 9 (monokine induced by gamma interferon [MIG]), CXCL10 (Interferon gamma-induced protein [IP]-10) and C-C motif ligand (CCL) 20 (Macrophage Inflammatory Protein [MIP] 3 α)); activation of inflammatory cells (e.g., CD4+ T cells); maturation of dendritic cells, which may initiate a vicious self-perpetuating inflammatory cycle that eventually leads to further deterioration of ocular surface inflammation and damage [6,12–14].

Hence, the treatment approaches focused on breaking the vicious inflammatory cycle can conceivably be effective for DED [6]. Artificial tears can relieve ocular surface inflammation by reducing tear osmolarity and diluting inflammatory mediators on the ocular surface, although they may not be the definitive treatment for the self-perpetuating inflammation on the ocular surface [6]. Systemic and topical and systemic administration of anti-inflammatory drugs, such as cyclosporine A, corticosteroids, and lifitegrast have been applied for the alleviation of the ocular surface symptoms and signs [6].

Therapeutic approaches aimed at reinforcing the endogenous anti-inflammatory and immunomodulatory mechanisms may also be helpful [14]. Previous studies have shown that oral and topical administration of omega-3 (ω 3) and omega-6 (ω 6) polyunsaturated fatty acids (PUFAs) can decrease the concentrations of inflammatory mediators associated with DED, improve dry eye symptoms, restore tear film homeostasis, and facilitate corneal nerve regeneration, suggesting that supplementation with these PUFAs can be alternative treatment for DED [15–26].

In this literature review, we aim to introduce the studies regarding the influences of ω 3 and ω 6 PUFAs on DED and discuss the potential underlying mechanisms of PUFAs in the treatment of the disease.

2. Pufas and Modulation of Inflammation

Fatty acids consist of a carboxyl group at one end, a hydrocarbon backbone in the middle, and a methyl group at the other end [27]. PUFAs are fatty acids that have more than one double bond in their hydrocarbon backbone [27]. The ω 3 and ω 6 PUFAs have their first double bond at the third- or sixth-carbon from their methyl end, respectively [27]. Because humans and mammals lack the ability to synthesize ω 3 and ω 6 PUFAs in vivo, these PUFAs, also referred to as “essential” fatty acids, must be obtained from dietary sources or supplements [16,28].

The ω 3 PUFAs include short-chain forms, such as, α -linolenic acid (ALA) and long-chain forms, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [16]. Short-chain ALA can be further converted to long-chain forms in the human body by alternative desaturation and chain elongation [16]. ALA is richly contained in plant sources, e.g., spinach, green beans, broccoli, chia seed, flaxseed oil, and walnuts [16]. EPA and DHA derive largely from marine-based sources, e.g., salmon, mackerel, herring, sardines, tuna, anchovies, and prawns [16].

Linoleic acid (LA), an ω 6 PUFA usually obtained from vegetable oils (e.g., palm, soybean, and canola oils), can further be metabolized to γ -linolenic acid (GLA), dihomo- γ -linolenic acid (DGLA) and the end-product, arachidonic acid (AA) [16,29]. GLA is richly contained in borage and primrose oils, while AA is predominantly derived from animal products, e.g., poultry, egg yolk, and meat [16].

PUFAs can be precursors for eicosanoids [30]. AA, the major ω 6 end-product, produces pro-inflammatory eicosanoids, i.e., prostaglandins (PG), leukotrienes (LT), and thromboxanes (TX) [15], which promote the inflammatory cascade and can result in various inflammatory diseases and cardiovascular problems [31]. However, a few DLGA-derived eicosanoids, such as, PGE1 and TXA1, can have anti-inflammatory properties that may complicate the association between ω 6 PUFAs and inflammation [32].

Omega-3 PUFAs can be precursors for anti-inflammatory molecules. For instance, PGE3 and LTB5, which are EPA-derived eicosanoids, have anti-inflammatory effects [32]. EPA and DHA, which are ω 3 metabolites, compete with AA as a substrate for lipoxygenases and cyclooxygenases [30], which can lead to the inhibition of the synthesis of pro-inflammatory eicosanoids and the resolution of inflammation [15,33]. EPA and DHA can also be precursors of four families of anti-inflammatory molecules: resolvins, protectins, lipoxins, and maresins [15,16]. Experimental studies revealed that resolvin D1 inhibited the synthesis of pro-inflammatory cytokines in corneal epithelial cells and enhanced the secretion of goblet cell mucin that can protect the ocular surface [34,35]. An animal study using a Sjogren's syndrome-like mouse model also reported that aspirin-triggered resolvin D1 restored saliva secretion and reduced the number of T-helper cells within submandibular gland lymphocytic infiltration [36]. It also inhibited the expression of inflammatory cytokine genes and proteins in submandibular glands from female mice [36]. Pham et al. [37] recently demonstrated that application of DHA plus pigment epithelium-derived growth factor (PEDF) facilitated corneal epithelial wound healing and nerve regeneration and increased tear production by enhancing the synthesis of resolvin D6 stereoisomer and neuroprotectin D1 (NPD1), a member of protectin family that acts in neural tissues, in an animal model of corneal nerve damage. They also showed that resolvin D6 stereoisomer can promote regeneration of corneal epithelial cells and nerves and attenuate neuropathic pain by modulating a specific transcriptomic signature in the trigeminal ganglion [38]. Topical administration of resolvin E1 facilitated corneal epithelial recovery, increased conjunctival goblet cell density, decreased macrophage infiltration of the ocular surface and increased tear secretion [39,40]. NPD1 and Lipoxin A4 was also shown to accelerate corneal re-epithelialization [41]. Gao et al. [42] revealed that acute oral supplementation with DHA prevented the exacerbation of DED in a DHA-deficient mouse model by enhancing lymph node lipoxin A4 formation, decreasing helper T (Th) 1 and Th 17 cells and increasing regulatory T cells. These results suggest that PUFAs may modulate ocular surface inflammation, which might be protective against DED [42].

Although an ideal ω 6: ω 3 ratio of dietary intake has not been established, a low ratio appeared to be desirable [43]. Dietary ω 6: ω 3 intake of $\leq 2:1$ is shown to be beneficial for perinatal development [44]. A balanced ω 6: ω 3 intake of $\leq 4:1$ might be desirable for the competitive inhibition of the synthesis of AA-derived inflammatory eicosanoids by ω 3 PUFAs, i.e., EPA and DHA [15]. Higher ω 6: ω 3 ratio may be associated with an increased risk of the development of diverse pathologies, e.g., inflammatory, autoimmune, and cardiovascular diseases, whereas a lower ω 6: ω 3 ratio with increased ω 3 PUFAs consumption can be protective against these diseases [16]. In DED patients, the ω 6: ω 3 ratio in the tear samples had correlation with tear film breakup time (TBUT) and the Schirmer and corneal staining scores, suggesting that an increase in the ω 6: ω 3 ratio in tears may be associated with the aggravation of ocular surface inflammation in DED [45]. The study also demonstrated that AA-derived PGE2 correlated with low tear osmolarity, the corneal staining score and meibomian gland plugging [45]. In 2005, the Women's Health Study, an epidemiologic study including 32,470 women demonstrated the association between reduced intake of ω 3 PUFAs and the risk of DED [2]. The study reported that a higher dietary ω 6: ω 3 ratio ($>15:1$ versus $<4:1$) was related to a 2.5-fold increased risk of DED [2]. They also revealed that each additional gram of ω 3 PUFA intake a day was associated with a 30% decrease in the risk of the disease. Cermak et al. [46] revealed that the energy-adjusted intake of ω 3 PUFAs was significantly lower in female patients with Sjogren's syndrome compared to age- and sex-matched controls.

3. PUFAS Supplementation and DED

3.1. Experimental Studies

An in vitro study by Hampel et al. [47] reported that EPA and DHA supplementation showed anti-inflammatory effects on cultured human meibomian gland epithelial cells by inhibiting cyclooxygenase-2 gene expression, decreasing production of pro-inflammatory

cytokines, such as TNF- α , IL-6, and interferon (IFN)- γ , and facilitating the production of anti-inflammatory molecules, such as resolvin D1 [47]. A study using a rat model revealed that supplementation with ω 3 (EPA and DHA) and ω 6 (GLA) elevated the concentrations of the PUFAs in phospholipids in both the lacrimal gland and the plasma, suggesting that the PUFAs intake may help modulate inflammation in the lacrimal gland and preventing DED [48]. In a pharmacologically induced rat DED model, the intake of EPA, DHA, and GLA for 28 days resulted in the incorporation of the PUFAs into the phospholipids in the extraorbital lacrimal gland, and inhibited the elevation of intraglandular concentrations of both PGE1 and PGE2 [49]. The combined oral supplementation also prevented damage of corneal epithelial cells, reduction in mucin production and the overexpression of MHC II molecules in the conjunctival epithelial cells [49]. Andrade et al. [50] also showed that oral supplementation with ALA increased the lacrimal peroxidase activity and improved lacrimal secretion in a rat DED model [50].

3.2. Oral Supplementation of ω 6 PUFAs for DED

In a randomized trial, Barabino et al. [51] reported that oral supplementation with LA and GLA for 45 days resulted in improvements in dry eye symptoms, ocular surface inflammation and corneal staining in patients with inflammatory DED [51]. In patients with Sjögren's syndrome, the oral intake of LA and GLA for 30 days improved dry eye symptoms, alleviated ocular surface inflammation, and increased the concentrations of PGE1, an anti-inflammatory eicosanoid, in tears [17]. This indicated that supplementation of ω 6 PUFAs may have influence on the lacrimal functional unit [17]. In patients with DED associated with contact lens wear, oral GLA supplementation in the form of evening primrose oil for 6 months led to an alleviation of symptoms of DED and discomfort associated with contact lens wear and an increase in tear meniscus height [18] (Table 1).

Table 1. Summary of the studies on the efficacy of ω 6 PUFAs on DED.

Study	Design	Level (of Evidence) *	Sample Size	Daily Dose	Duration	Objective and Subjective Study Outcomes
Barabino et al. [51] (2003)	Randomized controlled trial (RCT)	I	26	57 mg LA + 30 mg GLA	45 days	Reduced ocular surface inflammation, Improved dry eye symptoms.
Aragona et al. [17] (2005)	RCT	I	40	224 mg LA + 30 mg GLA	30 days	Increased tear PGE1 levels, Improved signs and symptoms of DED
Kokke et al. [18] (2008)	RCT	I	76	300 mg GLA	6 months	Alleviated dry eye symptoms, Improved contact lens comfort

* The level of evidence was rated according to the guidelines of the American Academy of Ophthalmology, based on the scale introduced by the Oxford Centre for Evidence-Based Medicine [52].

3.3. Oral Supplementation of ω 3 PUFAs for DED

Wojtowicz et al. [21] reported that oral supplementation with fish oil (EPA + DHA) and flaxseed oil for 90 days resulted in increased tear production, although there was no significant influence on the tear evaporation rate or meibum lipid composition. Kawakita et al. [20] also showed that the supplementation of EPA and DHA in the form of fish oil for 12 weeks improved dry eye symptoms, corneal staining score and TBUT. Kangari et al. [19] revealed that short-term (for 30 days) administration of EPA and DHA resulted in the improvement of symptoms of DED and tear film stability [19]. Olenik [53] reported that the intake of EPA and DHA for 12 weeks led to the improvement of ocular surface symptoms and contact lens tolerance [53]. Bhargava et al. [23] also showed that oral supplementation of EPA and DHA for 6 months improved symptoms of DED, contact lens discomfort, and conjunctival epithelial metaplasia associated with contact lens wear [23]. Oral supplementation with EPA and DHA for 3 months was helpful for improving symptoms of DED, increasing tear stability, and restoring conjunctival metaplasia in patients with DED associated with visual display terminal (VDT) use [25]. Short-term (45 days) supplementation with EPA and DHA also resulted in improved dry eye symptoms, tear stability and conjunctival epithelial changes in patients with VDT-associated DED [24].

Chinnery et al. [54] revealed that oral administration of EPA and DHA for 90 days provided neuroprotection for the corneal sub-basal nerve plexus in correlation with a restoration of tear homeostasis [54]. For DED associated with type 2 diabetes mellitus, oral ω 3 PUFA supplementation improved the symptoms of DED, Schirmer score, TBUT, and restored conjunctival epithelial metaplasia [55].

In comparison between two forms of ω 3 supplements, Deinema et al. [56] revealed that the phospholipid form (krill oil) might be more advantageous than the triacylglyceride form (fish oil) with additional improvements in ocular surface symptoms and the reduction of tear inflammatory cytokine IL-17 α levels, although both forms resulted in improved tear osmolality and stability [56].

Goyal et al. [57] reported that oral ω 3 supplementation (1.2 g of a triglyceride formulation) improved the Schirmer score in DED after laser in situ keratomileusis. The intake of ω 3 PUFAs also accelerated epithelial healing, improved TBUT, and facilitated visual recovery after photorefractive keratectomy [58]. Oral supplementation of ω 3 PUFAs was associated with additional improvements in tear stability and osmolality as well as symptoms associated with DED after phacoemulsification surgery [59]. Park et al. [60] demonstrated that oral supplementation of EPA and DHA for 2 months might improve ocular surface symptoms and inflammation, rather than tear secretion, in DED after cataract surgery.

However, the Dry Eye Assessment and Management (DREAM©) study reported that oral supplementation of EPA and DHA for 12 months failed to show superior outcomes than olive oil placebo [61], and discontinuation of the ω 3 supplementation for an additional 12 months had no influence on the outcomes [62] (Table 2).

A systematic review concluded that a beneficial effect on symptoms of DED might exist when oral ω 3 supplementation was provided in addition to conventional treatments, such as, artificial tears, steroid eye drops, and warm compresses compared with conventional treatment alone [27]. Smith et al. [63] suggested that a protocol comprising daily warm compress and oral ω 3 supplementation for 30 days could improve dry eye symptoms, corneal staining score and TBUT.

3.4. Combined Oral Supplementation of ω 3 and ω 6 PUFAs for DED

A clinical trial showed that the oral intake of 2000 mg of sea buckthorn oil, containing both ω 3 and ω 6 PUFAs, for 3 months improved dry eye symptoms and tear osmolality during the cold season [64].

A clinical trial reported that the oral intake of 2000 mg of sea buckthorn oil, containing both ω 3 and ω 6 PUFAs, improved symptoms of DED and tear osmolality during the cold season [64]. Creuzot-Garcher et al. [26] reported that oral administration of Nutrilarm® capsules (Laboratoires Thea, Paris, France), a combined ω 3 (EPA + DHA) and ω 6 formulation (GLA + LA), for 6 months showed an additional therapeutic effect in improvement of ocular fatigue and TBUT [26]. Another randomized trial revealed that oral intake of combined ω 3 and ω 6 PUFAs (EPA + DHA + borage oil) can attenuate the expression of HLA-DR, an inflammatory marker, in the conjunctival epithelium in DED patients [13]. Sheppard et al. [65] also demonstrated that supplemental GLA and ω 3 PUFAs alleviated ocular irritation, restored ocular surface smoothness, and inhibited HLA-DR expression and dendritic cell maturation in the ocular surface in patients with postmenopausal keratoconjunctivitis sicca, indicating an improvement in ocular surface inflammation [65]. A balanced supplementation with ω 3 and ω 6 PUFAs combined with application of topical cyclosporine was also shown to be effective for the treatment of contact lens-related DED [66] (Table 3).

Meta-analyses revealed that the combined ω 3 and ω 6 supplements showed minimal amount of improvement in tear stability, although no influence on tear production was observed [27,33]. A systematic review concluded that the combination of ω 3 and ω 6 supplements can be beneficial in patients with DED associated with certain pathologies, such as contact lens wear or intensive VDT use [33].

Table 2. Characteristics of clinical trials on the efficacy of ω 3 PUFAs on DED.

Study	Design	Level	Sample Size	Daily Dose	Duration	Objective and Subjective Study Outcomes
Wojtowicz et al. [21] (2011)	RCT	I	36	450 mg EPA + 300 mg DHA + 1000 mg flaxseed oil	3 months	Increased tear production and tear volume
Kawakita et al. [20] (2013)	RCT	I	27	1245 mg EPA + 540 mg DHA	3 months	Decreased eye pain, Improved BUT and corneal stain score
Kangari et al. [19] (2013)	RCT	I	73	360 mg EPA + 240 mg DHA	1 month	Increased tear secretion, Decreased tear evaporation, Improved dry eye symptoms
Olenik [53] (2014)	Non-comparative Interventional study	III	905	127.5 mg EPA + 1050 mg DHA	3 months	Decreased dry eye symptoms, Improved contact lens tolerance
Bhargava et al. [23] (2015)	RCT	I	496	720 mg EPA + 480 mg DHA	6 months	Improved dry eye symptoms and contact lens comfort, Restored conjunctival metaplasia
Bhargava et al. [25] (2015)	RCT	I	478	720 mg EPA + 480 mg DHA	3 months	Improved dry eye symptoms, Decreased tear evaporation, Improved conjunctival metaplasia
Bhargava et al. [24] (2016)	RCT	I	522	1440 mg EPA + 960 mg DHA	45 days	Alleviated symptoms of DED, Improved tear stability and conjunctival metaplasia
Chinnery et al. [54] (2017)	Prospective comparative study	II	12	1000 mg EPA + 500 mg DHA	3 months	Protection of the corneal nerve plexus, Normalization of tear osmolarity
Georgakopoulos et al. [55] (2017)	Non-comparative interventional study	III	36	510 mg EPA + 345 mg DHA	3 months	Improved tear stability and dry eye symptoms
Deinema et al. [56] (2017)	RCT	I	60	krill oil; 945 mg EPA + 510 mg DHA/fish oil; 945 mg EPA + 510 mg DHA	3 months	Improved tear stability (both form) Additional benefit in phospholipid form (krill oil), with improved dry eye symptoms and decreased basal tear levels of interleukin 17 α
Goyal et al. [57] (2017)	Prospective, open-label study	II	60	720 mg EPA + 480 mg DHA	13 weeks	Improved Schirmer score
Ong et al. [58] (2013)	Prospective comparative study	II	18	450 mg EPA + 300 mg DHA	45 days	Improved corneal wound healing, Improved tear stability and visual recovery
Mohammadpour et al. [59] (2017)	RCT	I	48	540 mg EPA + 360 mg DHA	1 months	Improved tear stability, Improved dry eye symptoms.
Park et al. [60] (2020)	Prospective comparative study	II	66	1680 mg EPA + 506 mg DHA	2 months	Improved symptoms of DED, Reduced ocular surface inflammation
DREAM study [61] (2018)	RCT	I	535	2000 mg EPA + 1000 mg DHA	12 months	No superior outcomes than placebo

Table 3. Summary of the studies on the efficacy of $\omega 3$ and $\omega 6$ PUFAs on DED.

Study	Design	Level	Sample Size	Daily Dose	Duration	Objective and Subjective Study Outcomes
Larmo et al. [64] (2010)	RCT	I	86	2000 mg sea buckthorn oil (149 mg $\omega 3$ + 245 mg $\omega 6$)	3 months	Prevented elevation of tear film osmolarity
Creuzot-Garcher et al. [26] (2011)	RCT	I	181	28 mg EPA + 392 mg DHA + 82 mg GLA and 126 mg LA	6 months	Improved ocular fatigue, Increased TBUT
Brignole-Budouin et al. [13] (2011)	RCT	I	121	427.5 mg EPA + 285 mg DHA + 15 mg $\omega 6$	3 months	Improved dry eye symptoms. Reduced expression of conjunctival inflammatory marker
Sheppard et al. [65] (2013).	RCT	I	38	126 mg EPA + 99 mg DHA + 710 mg LA + 240 mg ALA	6 months	Improved ocular irritation. Inhibited conjunctival dendritic cell maturation
Wang et al. [66] (2016).	Prospective cohort study	II	360	Various ratios of $\omega 3$ and $\omega 6$	3 months	Alleviation of contact lens-related DED

3.5. Topical Application of PUFAs

The topical administration of PUFAs might be an intriguing option as it can avoid accumulation of extra calories as well as gastrointestinal side effects caused by oral PUFAs intake [16]. PUFAs may be able to penetrate into the lipid layer of the tear film and exert influence on the structure and physicochemical properties of the lipid layer [67].

In a murine DED model, topical ALA application alleviated corneal epithelial damage and ocular surface inflammation reflected by the expression of inflammatory cytokines (e.g., IL-1 α and TNF- α), and an increase in CD11b(+) cells [68]. Combination of topical 0.2% $\omega 3$ PUFA and artificial tears provided significant additional effect for a restoration of corneal epithelial integrity and regularity and a reduction in the levels of conjunctival inflammatory cytokines (e.g., IL-10 and IL-17) and oxidative stress markers (e.g., 4-hydroxynonenal) in a mouse DED model [69].

The topical application of PUFAs may be beneficial for DED associated with corneal damage after keratorefractive surgery [16]. Topical treatment with DHA combined with nerve growth factor (NGF) stimulated regeneration of corneal epithelium and nerve after PRK in a rabbit model [70]. The application of DHA/PEDF combination eye drops stimulated synthesis of NPD1 and promoted recovery of corneal epithelial cells and nerve plexus, and restoration of corneal sensation after corneal stromal dissection in a rabbit model [71,72]. The corneal epithelial cells released PEDF in response to injury, and the addition of DHA resulted in the stimulation of the NPD1 synthesis through an autocrine mechanism [73]. The DHA/PEDF combination eye drops also inhibited the production of LTB₄, a pro-inflammatory cytokine, which subsequently attenuated the inflammation associated with corneal damage [73].

A clinical trial showed that the addition of trehalose and flaxseed oil to artificial tears facilitated recovery after ocular surface damage with fewer adverse effects [74]. A recent study showed that $\omega 6$ LA at low concentrations (20 mol%) in topical preparations enhanced the spreadability and stability of the tear lipid layer, which can be beneficial for stabilization of tear film in DED patients [75].

3.6. Supplementation of PUFAs for MGD

An experimental study demonstrated the influence of PUFAs on the quantity and quality of lipids in human meibomian gland epithelial cells, indicating the possible association between PUFAs and meibomian gland dysfunction (MGD) [76]. Pinna et al. [77] reported that oral supplementation with LA + GLA and eyelid hygiene synergistically alleviated lid margin inflammation and dry eye symptoms in MGD [77]. The administration of flaxseed oil (contains 55% ALA and 15% LA; 6000 mg per day) for 12 months in patients with obstructive MGD and blepharitis led to improvements in TBUT and dry eye symptoms [78]. The supplementation was also associated with reductions in saturated fatty acids in the meibum and improvements in the meibum score, indicating its direct influence on the meibomian gland [78].

Bhargava et al. [79] revealed that oral supplementation of EPA and DHA resulted in an improvement in symptoms of DED, and the benefit appeared to be more marked in MGD. Administration of EPA and DHA for 6 months significantly improved the symptoms of DED, the Schirmer and the meibomian gland scores and TBUT in patients with rosacea [22]. Olenik et al. [80] showed that ω 3 PUFAs intake improved dry eye symptoms, Schirmer score, tear film stability, meibomian gland expression and lid margin inflammation in patients with MGD [80]. Epitropoulos et al. [81] also demonstrated that the supplementation with EPA and DHA resulted in an improvement in ocular surface symptoms, TBUT, tear osmolarity and MMP-9 positivity in patients with MGD. Korb et al. [82] showed that the combination treatment comprising ω 3 supplements, lipid emulsion eye drops and lid wipes improved meibomian gland function and ocular surface symptoms in patients with evaporative DED (Table 4). Ziemanski et al. [83] reported that diet with high ω 3 and moderate ω 6 might be protective against MGD in postmenopausal women, although supplementation with ω 3 and ω 6 showed no beneficial effect on DED [83]. A systematic review concluded that a moderate daily dose of ω 3 may have a protective effect against MGD [84].

Table 4. Summary of the studies on the efficacy of ω 3 PUFAs on MGD.

Study	Design	Level	Sample Size	Daily Dose	Duration	Objective and Subjective Study Outcomes
Pinna et al. [77] (2007)	Prospective comparative study	II	57	15 mg GLA + 28.5 mg LA	6 months	improved symptoms of MGD, Reduced lid margin inflammation
Macsai et al. [78] (2008)	RCT	I	38	6000 mg flaxseed oil (3300 mg ω 3)	12 months	Decreased symptom score of DED, Improved TBUT and meibum score
Bhargava et al. [79] (2013)	RCT	I	518	650 mg EPA + 350 mg DHA	3 months	Decreased dry eye symptoms, Improved tear stability
Bhargava et al. [22]. (2016)	RCT	I	130 (Rosacea)	720 mg EPA + 480 mg DHA	6 months	Improved symptoms, tear stability and meibomian gland score
Olenik et al. [80] (2013)	RCT	I	64	127.5 mg EPA + 1050 mg DHA	3 months	Improved signs and symptoms of MGD, Improved tear stability
Epitropoulos et al. [81] (2016)	RCT	I	105	1680 mg EPA + 560 mg DHA	3 months	Improved tear stability, Decreased score of dry eye symptoms
Korb et al. [82] (2015)	RCT	I	26	2000 mg ω 3	3 months	Improved meibomian gland, functionality, and dry eye symptoms

4. Current Perspectives

Evidence accumulated from studies conducted within the past decades indicates that supplementation with PUFAs, particularly ω 3, may help the treatment of DED [85].

The report of the 2007 dry eye workshop (DEWS) indicated increased dietary ω 6: ω 3 ratio and decreased consumption of ω 3 PUFAs as risk factors for DED [86]. The DEWS II report in 2017 also listed low PUFA intake as a probable risk factors for DED [7]. A consensus panel for clinical guidelines recommended oral ω 3 PUFA supplementation for the management of moderate DED [87]. The recommendation by the Practicing Ophthalmologists Curriculum from the American Academy of Ophthalmology also included systemic ω 3 PUFA administration as the treatment of MGD and blepharitis [88]. The daily intake of a moderate dose of ω 3 was also shown to have beneficial effect against MGD [84]. Meanwhile, the safety profiles of PUFAs have not been paid much attention to, as studies regarding the PUFAs supplementation in patients with DED have rarely reported adverse effects of the PUFAs [85].

However, no formal consensus has been established for the optimal protocol of PUFA supplementation, which comprises the composition and dose of the supplements and the duration of treatment [89]. This has been attributed to the following reasons. (1) Clinical trials have had considerably heterogeneous compositions, doses, and durations, making it difficult to establish guidelines [85]. (2) There are few well-controlled long-term clinical trials involving a large population.

An epidemiological study indicated that over 80% of adults in developed countries may have ω 3 PUFAs deficiency [90], and the American Dietetic Association (ADA) recommended the daily intake of 500 mg of ω 3 PUFAs [91]. PUFAs are also suggested to

be able to lower the risk of coronary stroke, mainly by reducing blood cholesterol level, and also have shown promising effects against cancer, diabetes, and depression [92]. The American Heart Association (AHA) recommended diet with at least two servings of fish a week and consumption of foods containing high amount of ω 3 PUFAs for the prevention of cardiovascular diseases, which is also conceivably beneficial for the prevention of DED [93]. High doses of ω 3 PUFAs of 200–2200 mg per day were shown to be beneficial for the improvement of psychological symptoms, including anxiety and depression [94,95]. These findings indicate a high dose of oral ω 3 PUFA supplementation can also be advantageous for the patients with DED [96].

However, an adequate consumption of EPA + DHA is not easily achievable with dietary intake alone [29], because the processing and cooking of food results in a substantial loss and denaturation of the PUFAs [97]. In addition, only a small fraction of PUFAs can be converted to anti-inflammatory molecules during in vivo metabolism [29]. Hence, oral supplementation using an extract formula, such as compound capsules, may be more effective for achieving the therapeutic dose of ω 3 PUFAs [29,96].

The intake of fish oil capsules, the most common formula for ω 3 PUFA supplements, can sometimes cause adverse effects, including nausea, regurgitation, and fish-tasting aftertaste [93]. Fish allergy may be a contraindication for fish oil supplements [88,93]. Vegetable sources of PUFAs, including primrose or flaxseed oil, can be recommended for these patients [88,96].

Despite the potential health benefits, precautions are necessary because the administration of high-dose ω 3 PUFAs (over 2000 mg EPA + DHA per day) can be associated with several health risks [89]. The intake of an excessive amount of ω 3 PUFAs can be associated with an increased risk of hemorrhage due to its potential antithrombic effect, and it may be contraindicated in patients with a bleeding tendency [31,89]. Therefore, medical advice is necessary for patients with hematologic disorders and liver and cardiovascular diseases before commencing ω 3 PUFAs supplementation [89]. High blood levels of long-chain ω 3 PUFAs, i.e., EPA and DHA, could be associated with a higher risk of prostate cancer [89,98]. As fish oils are also rich in fat-soluble vitamin A, long-term supplementation with an excessive dose of fish oil capsules can lead to hypervitaminosis A, which can cause hypercalcemia and osteoporosis due to increased bone turnover [96]. Both the FDA in the USA and the National Health and Medical Research Council in Australia have recommended that the consumption of up to 3000 mg (3 g) of ω 3 PUFAs per day, derived both from dietary intake and supplements, may be safe [89,93].

It should also be noted that seafood can be affected by ocean pollution, and coldwater fish, the main source of ω 3 PUFAs, can accumulate toxins (e.g., mercury and dioxins) in their body as they are located at the upper levels of the food chain in the ocean [88]. Hence, FDA has recommended that the intake of a large amount of fish that may contain increased levels of toxins including mercury, e.g., swordfish, marlin, shark, king mackerel, and bigeye tuna, should be avoided [88]. Nonetheless, FDA recommends the consumption of ≥ 8 ounces (227 g) of seafood every week for American adults, and also advises that the consumption of seafood containing relatively low levels of mercury, e.g., salmon, sardine, herring, cod, haddock, anchovy, oyster, scallop, shrimp, and canned light tuna, up to 12 ounces (340 g) per week may be safe [88]. Although this literature review has a limitation that systematic analysis or meta-analysis of the results of the studies were not performed, we believe this review may provide readers with new information as the results of the studies recently reported was introduced [34,36–38,42,60–62,74,75,83,85]. This review also included the results of experimental studies [47–50].

For the evaluation of the influence of PUFAs on DED, conventional objective tests, such as TBUT, Schirmer test, and corneal stain score and subjective tests, such as questionnaire for dry eye symptoms have been commonly used. However, these tests show limited reproducibility, which might influence the inconsistency of the outcomes among the studies with similar designs [99]. Discrepancy between sign and symptoms often observed in DED might also be associated with contradictory outcomes [99,100]. More reproducible and

reliable tests, such as tear osmolarity, tear cytokine level, impression cytology, and in vivo confocal microscopy have been introduced for assessment of DED, which may be helpful for more accurate evaluation of the influence of PUFAs on DED [24,54,56,64,65]. Newly developed objective test methods for DED, such as anterior segment optical coherence tomography, non-invasive tear breakup time, interferometry, tear film imager, meibography, and thermometry are shown to allow more reproducible and accurate measurement of biomarkers of DED, such as tear volume, thickness, height and stability, meibomian gland function, thickness of tear muco-aqueous and lipid layers, and ocular surface temperature [101]. Therefore, application of these devices is expected to enable the evaluation of the real efficacy of various PUFAs on DED [101].

In conclusion, this review showed that supplementation with PUFAs, particularly ω 3 PUFAs, may be an effective treatment strategy for DED, although consensus for treatment guidelines on the composition, dose, and treatment duration has not yet been established. Further well-controlled clinical studies with large populations are therefore required for evaluation of the efficacy and safety of PUFA supplementation for the treatment of DED and the establishment of an optimal regimen including the composition, dose, mode of administration, and duration [16,88].

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