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Review

Role of Lutein Supplements in the Management of Dry Eye Syndrome: A Systematic Review

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Abstract

Background: Dry Eye Disease (DED) significantly impacts global populations, causing discomfort and vision problems. This review explores the effects of lutein supplementation on DED symptoms and signs. **Methods**: A systematic review was conducted following PRISMA guidelines, examining clinical trials from databases including PubMed, Web of Science, EMBASE, and the Cochrane Library. Six randomized controlled trials (RCTs) involving 584 subjects were included. Meta-analysis was not conducted due to heterogeneity in study designs, dosages, and outcome measures. **Results**: Lutein dosages ranged from 3 mg/day to 20 mg/day, with treatment durations from 4 to 12 weeks. Improvements were observed in subjective symptoms, with significant reductions in Ocular Surface Disease Index (OSDI) scores in some studies. Objective measures also showed positive results: tear break-up time (TBUT) increased significantly in some trials. However, other studies reported no significant differences between treatment and control groups, reflecting heterogeneity in outcomes. Schirmer's test and corneal-conjunctival staining results varied, with some showing significant improvements and others not. **Conclusions**: Lutein supplementation may benefit DED patients by improving symptoms and tear film stability. However, due to study heterogeneity, larger, well-designed RCTs are needed to establish standardized dosing and confirm these findings.

Keywords: dry eye; lutein; nutritional supplements; tear film; oxidative stress

1. Introduction

Dry eye disease (DED) is a common global condition, often leading to consultations with eye care professionals. Individuals with moderate to severe dry eye often experience significant discomfort and limitations in daily activities. According to the statement of Dry Eye Workshop II (DEWS II) by the Tear Film & Ocular Surface Society (TFOS) launched in March 2015, the definition of dry eye disease [1]. "Dry eye is 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".

The symptoms and signs of dry eye are varied and can significantly impact the quality of life. The primary symptom of DED is a dry, gritty, or sandy sensation in the eyes. Other common symptoms include asthenopia (eye strain), characterized by eye pain, fatigue, discomfort, tearing, light sensitivity, and difficulty keeping the eyes open. Individuals with DED may also experience fluctuating or blurred vision, particularly during activities that require sustained focus, such as reading or computer use. Signs of DED include reduced tear film stability, as evidenced by decreased tear break-up time (TBUT). Corneal and conjunctival staining (KC staining) can reveal areas of epithelial damage. Changes in meibomian gland function (MGD), such as abnormal secretion or morphology, can contribute to DED. A low tear meniscus height and decreased Schirmer's test (ST) results may indicate tear deficiency. Increased tear osmolarity is a hallmark of DED and signifies tear film instability [1].

The core mechanism of dry eye is evaporation-induced tear hyperosmolarity, which is the defining feature of the disease. This instability can arise from insufficient tear production, excessive tear evaporation, or an abnormal tear composition. Elevated osmolarity exacerbates harm to the ocular surface and sets off inflammatory responses, leading to a cascade of damaging event. This inflammation prompts the release of pro-inflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs). Inflammatory mediators further perpetuate tissue damage, creating a vicious cycle of inflammation and epithelial dysfunction [1,2]. The oxidative stress also plays a role in dry eye disease. The oxidative stress can cause cellular damage and apoptosis of ocular surface cells, contributing to the corneal and conjunctival epithelial cells damage, and to the loss of goblet cells, which are critical for mucin production in the tear film [3–5]. An imbalance between the systems that neutralize radicals and the production of free radicals within the tear film, meibomian gland, and mitochondria may lead to tissue inflammation, damage, and accumulation of reactive oxygen species (ROS) [3]. Meibomian gland dysfunction (MGD) refers to changes in the quality

and quantity of meibum secretion, which alters the tear film lipid layer. These changes may be caused by inflammation and oxidative stress, leading to increased tear evaporation [6]. Mitochondria are particularly susceptible to oxidative stress, and their dysfunction is a critical factor in cell death and disease progression. In DED, oxidative damage to mitochondria can impair cellular energy production and contribute to the pathological processes on the ocular surface [3].

The management of dry eye disease is complicated and individualized. The aim of treatment is to restore the hemostasis of the ocular surface and tear film, through break the vicious cycle of inflammation. Stepwise use of topical lubricant such as artificial tears, anti-inflammatory agent, and/or physical containment such as eye shield, therapeutic contact lens, even surgical intervention can be applied according to the severity of dry eye. As a key factor in the pathogenesis of DED, oxidative stress is regarded as an effective target for its treatment. Antioxidant therapy such as Visomitin (SKQ1) [7], N-acetylcysteine eye drops [8], fibroblast growth factor [9], hyaluronate acid [10] were used in the clinical trial, with improving symptoms and signs of dry eye disease.

Lutein is a xanthophyll, which is a lipid-soluble primary carotenoid that humans obtain from their diet such as dark green vegetables and egg yolk [11]. Lutein acts as an antioxidant and protects the plants from the damage of photo-induced free radicals [12]. It is recognized for its antioxidant and anti-inflammatory health advantages, including the prevention of heart attacks, metabolic syndromes, and macular degeneration [13–15]. To date, several studies were conducted on lutein and dry eye in preclinical studies [16,17]. Lee *et al*. [16] used lutein to treat rats with PM 2.5 induced dry eye disease, which improved the tear secretion. Liu *et al*. [17] develop oral deliverable dectin-1 specific lutein nanoparticles which alleviating dry eye disease in rats. A limited number of randomized controlled trials have investigated the association between lutein supplementation and dry eye syndrome [18–23]. However, the supplements were not only pure lutein but combined with other components. The difference in study material needs a summary-generating systematic review of the literature.

2. Materials and Methods

The aim of this article is to evaluate the association of lutein supplementation and dry eye in human studies. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) reporting guidelines. A comprehensive literature review was conducted to identify published articles on the topic using database searches from PubMed, Web of Science, EMBASE, and the Cochrane Library indexes. We retrieved all relevant publications reporting findings on the association between dry eye (dry eye and/or tear) and lutein (lutein and/or xanthophyll) prior to 4 April 2024. The initial results from publications were screened based on specific selection criteria and further reviewed according to their titles and abstracts. Only articles in English were included.

2.1 Selection Criteria

Preclinical studies were excluded because we wanted to focus on the effects of lutein on human dry eye.

Prospective randomized clinical trials satisfying the following criteria were included in this review: (1) interventional studies assessing the effects of lutein supplementation on clinical endpoints in human; (2) human with subjective-reported dry eye syndrome or diagnosed with dry eye disease; and (3) peer-reviewed original research.

2.2 Data Extraction

We extracted detailed information from the selected studies after screening the articles. The following data were extracted: the first author's name, publication year, countries of the study conducted, sample size, study population, the subjective or diagnosed dry eye, the type of intervention, the concurrent therapy of dry eye, the follow-up duration, the evaluation methods and the main outcomes.

2.3 Literature Quality Assessment

The quality of the RCTs was assessed using Cochrane Collaboration's tool [24] for the risk of bias assessment, which including through 6 aspects: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data attrition bias); and (6) selective reporting (reporting bias).

3. Results

Initially, 255 citations were screened. After excluding duplicates, non-English articles, and clearly irrelevant studies, 17 articles remained for further review. Of these, preclinical studies, the studies not involving oral lutein supplements, those not addressing of lutein supplements and dry eye, and those without full text available were excluded. Ultimately, six studies were included in the systematic review (Fig. 1). The studies were regarding the oral lutein supplements and the symptoms/signs of dry eye.

Six randomized controlled trials (RCTs) examined the effect of lutein supplementation on patients with self-reported or diagnosed dry eye, which involving a total of 584 subjects (Table 1, Ref. [18–23]). The test group received quantified dietary supplementation, including lutein, for periods ranging from 4 weeks to 12 weeks, while the control group received a placebo. Study outcomes included scores from subjective questionnaires such as the Ocular Surface Disease Index (OSDI) [25], the Dry Eye-related Quality of Life Score (DEQS) [26] and Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED) [27],

Table 1. The characteristics of included randomized controlled trials.

Study	Country	Number of participants (N)	Participant Characteristics	Daily Components of the supplement	Amount of lutein/day	Other therapies	Duration
Kan *et al*. [21] (2020)	China	360	VDT use >6 hrs/day Self-reported eye fatigue	Lutein ester 12 mg, 20 mg, 28 mg; Zeaxanthin 1.2 mg, 2.0 mg, 2.8 mg; Chrysanthemum extract 75 mg, 125 mg, 175 mg; Goju berry extract 75 mg, 125 mg, 175 mg; Backcurrant extract 100 mg, 167 mg, 233 mg	1: placebo (N = 76); 2: 6 mg lutein (N = 76); 3: 10 mg (N = 75); 4: 14 mg (N = 76)	?	90 days
Kawabata *et al*. [22] (2011)	Japan	20	VDT use >4 hrs/day Self-reported dry eye	Lutein 17.5 mg; DHA 783 mg, EPA 162 mg; Anthocyanidin 59 mg	1: placebo (N = 9); 2: 17.5 mg Lutein (N = 11)	N	4 weeks
Kawashima *et al*. [23] (2016)	Japan	40	Subjective symptoms of dry eye	Lutein 3 mg; DHA 54 mg, EPA 81 mg; Vitamin C 40 mg, Vitamin E 8 mg, Zinc 7 mg; Enterococcus faecium WB2000 10 mg, Lactoferrin 135 mg, GABA 0.5 mg	1: placebo (N = 20); 2: 3 mg (N = 20)	?	8 weeks
Kizawa *et al*. [19] (2021)	Japan	44	Subjective symptoms of eye fatigue during VDT use	Lutein 5 mg, Astaxanthin 3 mg; Anthocyanin 36 mg	1: placebo (N = 20); 2: 5 mg (N = 20)	N	6 weeks
Liu *et al*. [18] (2021)	China	60	MGD related dry eye	Lutein 10 mg, Zeaxanthin 2 mg; 250 mg DHA, 30 mg EPA; Aronia extract 50 mg; Vitamin C 100 mg, Vitamin E 20 mg; Zinc 20 mg, Selenium 25 ug, Taurine 50 mg	1: placebo (N = 30); 2: 10 mg (N = 30)	Y*	12 weeks
Radkar *et al*. [20] (2021)	India	60	Mild to moderate DED	Lutein 20 mg, Zeaxanthin 4 mg; Curcuminoids 200 mg; Vitamin D3 600 IU	1: placebo (N = 30); 2: 20 mg (N = 29)	Y**	8 weeks

VDT, Visual Display Terminal; hrs, hours; DHA, Docosahexaenoic Acid; EPA, Eicosapentaenoic acid; GABA, Gamma-aminobutyric acid; MGD, meibomian gland dysfunction; DED, dry eye disease. ?, not mentioned; Y, yes; N, No.

*Concurrent therapy with warm compression once daily per night, eyelid margin applied with tobramycin and dexamethasone ophthalmic ointment once per night for the first 2 weeks, followed by levofloxacin ophthalmic gel once per night for the next 10 weeks, 0.1% sodium hyaluronate 4 times a day for 12 weeks.

**Concurrent therapy with artificial tears (hydroxypropyl methylcellulose, 0.70% w/v) as rescue.

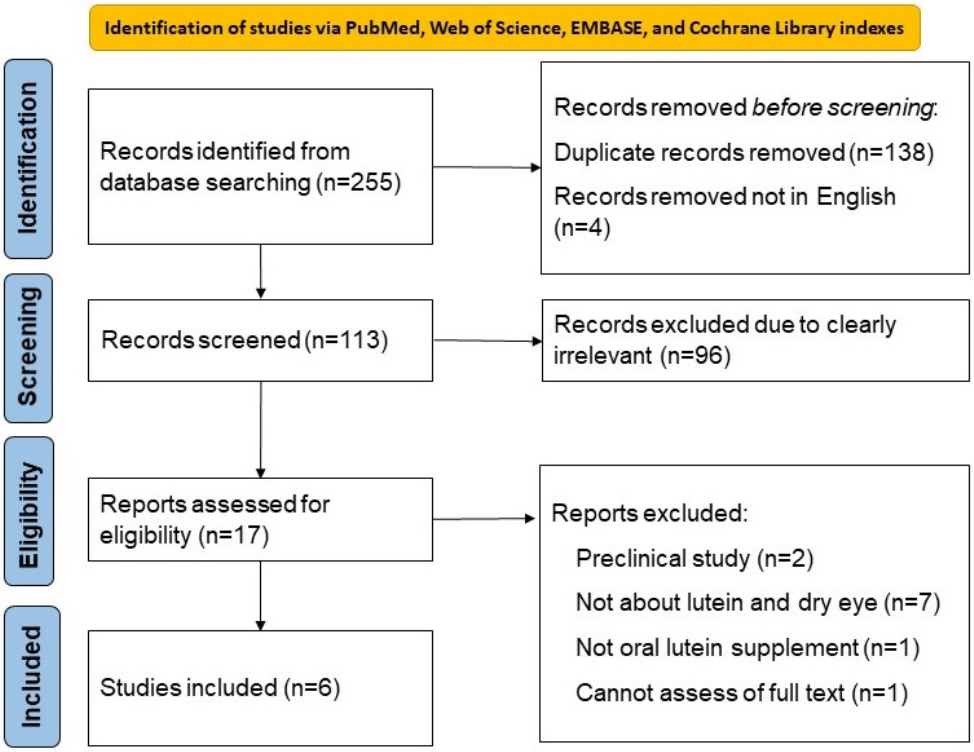

Fig. 1. Flow diagram of study selection process.

as well as objective measurements like Schirmer's test (ST) values, tear break-up time (TBUT), and corneal-and-conjunctival staining (KC staining) levels. Table 2 (Ref. [18–23]) presents the results of the risk of bias assessment. According to the Cochrane Collaboration's tool, two studies were rated as having a low risk of bias [19,20], two studies had unclear risk of bias [22,23], and two studies had a high risk of bias [18,21]. Four studies mentioned randomization and allocation to the placebo or supplement group but did not report the methods of random sequence generation and allocation [18,21–23].

The lutein dosage in the test groups ranged from 3 mg/day to 20 mg/day. The other components are listed in the Table 1.

The evaluation methods and main results are listed in the Table 3 (Ref. [18–23]). In the five studies that evaluated objective measurements, all assessed TBUT [18–21,23], four evaluated ST [19–21,23], and three evaluated KC staining [18,20,23]. Among them, three studies [18,20,21] demonstrated significant improvement in objective measurements while two studies [19,23] found no significant difference between the test and control groups.

Regarding subjective symptoms, different questionnaires were used in the five studies. The OSDI was employed in two studies of diagnosed dry eye [18,20], while the SPEED [20], the DEQS [23], and other regionally limited questionnaires [19,21,22] were used in the remaining studies.

4. Discussion

This systematic review examined existing randomized controlled trials evaluating oral lutein supplements for dry eye. Given that asthenopia (eye fatigue, pain, and tearing) is a significant symptom of dry eye, studies including healthy individuals with self-reported eye fatigue were also considered.

The classification of DED includes the aqueous deficient, evaporative and mixed type [28]. The traditional method to DED classification requires patients to fit the criteria (such as an OSDI score of 13 or higher, ST results of less than 10 mm, TBUT of less than 10 seconds) [29]. These criteria have high sensitivity and specificity but may exclude patients whose signs and symptoms were inconsistent [30].

According to DEWS II, the diagnostic tests for DED include assessment of symptoms and homeostasis markers [28]. Subjective symptomatic evaluation, such as the questionnaire of Dry Eye Questionnaire-5 (DEQ-5) with a score of 6 or higher, or an OSDI score of 13 or higher. Additionally, one of the following objective findings must be present: TBUT less than 10 seconds, tear osmolarity greater than 308 mOsm/L, or positive for ocular surface staining. Evaluating the morphology of meibomian gland, abnormal lipid layers, and low tear volume can also help subclassify the DED. Therefore, in the studies evaluating dry eye, combining both subjective and objective tests is more appropriated. In the selected studies in our systemic review, five

Table 2. Risk of biases determined by the Cochrane Collaboration tool.

	Liu *et al*. [18] (2021)	Kizawa *et al*. [19] (2021)	Radkar *et al*. [20] (2021)	Kan *et al*. [21] (2020)	Kawabata *et al*. [22] (2011)	Kawashima *et al*. [23] (2016)
(I) random sequence generation (selection bias)	?	-	-	?	?	?
(II) allocation concealment (selection bias)	?	-	-	?	?	?
(III) blinding of participants and personnel (performance bias)	+	-	-	-	-	-
(IV) blinding of outcome assessment (detection bias)	+	-	-	-	-	-
(V) incomplete outcome data (attrition bias)	?	-	-	-	-	-
(VI) selective reporting (reporting bias)	-	-	-	+	-	-
Risk of bias	High	Low	Low	High	Unclear	Unclear

-: Low risk of bias; +:High risk of bias; ?: Unclear risk of bias.

studies included both subjective and objective evaluation [18–21,23], while one study only included subjective evaluation [22].

Regarding the TBUT value, Kan *et al*. [21] reported a significant increase in TBUT from 7.97 sec to 8.69 sec in the 6 mg lutein supplement group ($p < 0.05$). Kizawa *et al*. [19] and Kawashima *et al*. [23] found no significant difference between two groups. Liu *et al*. [18] discovered that TBUT was longer in both groups, being significantly longer in the supplement group. Radkar reported an increase in TBUT the supplement group, while it decreased in the placebo group [20].

Regarding the Schirmer test (ST), Kan *et al*. [21] found the increasing percentage of subjects with more than 10 mm in the supplement groups. Kizawa and Kawashima *et al*. [19,23] found no significant difference between the two groups. Radkar reported a significant increase the treatment group [20].

In terms of corneal or conjunctival staining (KC staining), Kawashima and Liu found decrease staining in both groups without a significant difference between them [18,23]. Radkar reported a significant decreased in staining in the supplement group, but no difference in the placebo group [20].

Subjective symptoms were assessed by questionnaires. Liu *et al*. [18] and Radkar *et al*. [20] utilized the OSDI, and Kawashima employed DEQS [23]. These are two of the main questionnaires used globally for evaluating dry eye symptoms. Kan *et al*. [21] and Kawabata *et al*. [22] used the regional limited questionnaire, whereas Kizawa used a Likert scale for specific questions [19]. Despite the use of different questionnaires, subjective improvement in dry eye symptoms was observed in the supplement groups, except for the study conducted by Kizawa *et al*. [19].

The lutein dosage in the test groups ranged from 3 mg/day to 20 mg/day, which is not exceeding the threshold established by the Council for Responsible Nutrition (CRN) [31]. In the pre-clinical studies mentioned above, the pure lutein supplements improved tear production and alleviate dry eye. None of the studies reviewed used pure lutein supplements for dry eye, and the components of the oral supplements varied.

The other components of the oral supplements containing omega-3 fatty acids such as eicosapentaenoic acid (EPA) and (docosahexaenoic acid) DHA [22,23]; Phytochemicals, such as crysanthemum flavonoids, anthocyanin from the plant extracts (Goju berry, backcurrant, aronia), and curcumins [21,22]; carotenoids such as zeaxanthin and astaxanthin [19–21]; and various vitamins such as vitamin C, E and minerals such as zinc and selenium.

The omega-3 fatty acids have been reported to regulate the body's inflammation by attenuating pro-inflammatory mediators and were thought to have positive effects on dry eye disease including typical dry eye and meibomian gland dysfunction [32–34]. Anthocyanin, a kind of flavonoids, may enhance antioxidant capacity by scavenging free radicals and upregulating antioxidant enzymes in ocular tissue, and they have been found to alleviate dry eye related symptoms [35,36]. Zeaxanthin, an isomer of lutein, and astaxanthin, another type of carotenoids, possess antioxidant and anti-inflammatory function. The compounds have been found to improve the symptoms and signs of mild-to-moderate DED [37,38]. Theses supplements often contain additional components with antioxidant and anti-inflammatory functions, alongside lutein. This makes it difficult to isolate the specific effects of Lutein on dry eye symptoms.

Table 3. The evaluation methods and main results of the included randomized controlled trials.

Study [23]	Objective Signs		Subjective symptoms	
	Evaluation Methods	Main results	Evaluation methods	Main results
Kan [21] (2020)	ST, TBUT, TM	Increased frequency of ST ≥10 mm in 10 mg and 14 mg groups	CFDA approved questionnaire	Dry eye significantly decreased in the supplement groups and in the higher doses.
Kawabata [22] (2011)		-	Modified Nakamura's asthenopia questionnaire	Significant improvement of dry eye, frustration, stuffy head in the supplement group
Kawashima [23] (2016)	ST, TBUT, KC staining	All improve but no significant difference in two groups	DEQS	Significant decrease of dry eye symptoms in the supplement group
Kizawa [19] (2021)	ST, TBUT	No significant difference in two groups	Likert scale method	No significant difference in two groups
Liu [18] (2021)	TBUT, KC staining, MG morphology and quality	Significant improvement of TBUT, MG morphology and quality in the supplement group	OSDI	Significant improvement of OSDI in the supplement group
Radkar [20] (2021)	ST, TBUT, KC staining, tear osmolarity, MMP-9, AT use	Significant improvements for ST, TBUT,KC staining scores, tear osmolarity, MMP-9 level, reduced artificial tear use and its frequency of use in the supplement group	OSDI, SPEED	Significant improvements (p = 0.0001) for OSDI and SPEED compared to placebo

ST, Schirmer's test; TBUT, Tear break up time; TM, tear meniscus; KC staining, keratoconjunctival staining; MG, meibomian gland; MMP-9, Matrix metalloproteinase-9; CFDA, China Food and Drug Administration; DEQS, Dry Eye-related Quality of Life Score; OSDI, Ocular Surface Disease Index; AT, Artificial Tears; SPEED, Standard Patient Evaluation of Eye Dryness Questionnaire.

There are some limitations of this study that should be mentioned. First, the study enrolled the studies with subjectively reported eye fatigue syndrome, which might cause potential bias and confounding effects. Second, the types of dry eye were not strictly distinguished due to the limited information in the literation. Third, the evaluation tool for dry eye of each study were different, which might cause difficulties in comparing. Furthermore, the direct evaluation of the lutein supplements for dry eye was challenging due to the complex composition of the oral supplements. This complicates the ability to pinpoint the exact effects of lutein on dry eye. Despite these limitations, the study made efforts to clarify the association between oral lutein supplements and dry eye.

5. Conclusions

The primary goal in managing DED is to break the cycle of tear film instability, inflammation, and oxidative stress. Current treatment approaches, including artificial tears, anti-inflammatory eye drops, warm compresses, and in some cases, surgery, aim to stabilize the ocular surface. This systematic review analyzed six randomized controlled trials involving 584 participants, with lutein doses ranging from 3 mg to 20 mg per day over periods of 4 to 12 weeks. While some studies showed improvements in tear break-up time and Schirmer's test results with lutein supplementation, the presence of additional ingredients in the supplements makes it challenging to isolate the specific effects of lutein. Although lutein may offer some benefits in alleviating symptoms and stabilizing the tear film, further research is needed to confirm its efficacy. Future studies should use pure lutein supplements or measure blood lutein levels to provide more definitive conclusions.

Availability of Data and Materials

Not applicable.

Author Contributions

YC and CH contributed to the conceptualization, drafting, wrote the main manuscript text and prepared tables. CH reviewed, corrected and approved the manuscript. 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

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR36626.

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