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THE ANALYSIS STUDY OF INTERVENTIONS FOR DRY EYES: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Introduction: *Dry eye disease (DED) results from dysregulated ocular inflammation, causingpersistent ocular surface dysfunction, with a global surge in prevalence, especially among children andadolescents, due to increased technology use. Beyond significant ocular morbidity, DED's association with systemic autoimmune disorders, impact on quality of life, and links to psychological and sleep disorders underscore its extensive repercussions. This systematic review aims to comprehensively explore an integrated approach to managing DED, emphasizing preventive and promotive strategies across various levels of healthcare.*

Method: *The researchers in this study followed the 2020 PreferredReporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure that their work met the required standards. This was done to ensure the precision and reliability of the conclusionsderived from the research.*

Result: *This systematic review investigated final 15 articles. After looking at the titles and summaries, we found 6 papers that fit our criteria. At first, we excluded several articlesbecause they were written in review style and case reports. But after reading the full papers carefully, we included four papers in our final analysis. These papers included a retrospective observational study,prospective study, and double-blind, randomized, placebo-controlled trial, and prospective interventional pilot study.*

Conclusion: *In summary, a study suggests that OPT-IPL (Optilight Intense Pulse Light) treatment enhances tear film lipid layer (TFLL) and improves signs and symptoms of dryeye disease (DED) by enhancing meibomian gland function. The phase 3 trial with NOV03 provides compelling evidence of reduced DED signs and symptoms over 8 weeks, demonstrating statistical andclinical significance, with good tolerability. Additionally, the ESSENCE-2 trial highlights the efficacyof a water-free cyclosporine solution in improving ocular surface staining associated with DED, showcasing potential advantages over existing therapies. Our study revealed promising and safe outcomes for dietary supplementation, which preserved tear production in a rat dry eye model and showed significant improvements in both objective parameters and subjective dry eye symptoms. However, further data is needed to validate its widespread use as a common intervention.*

Keywords: *Cyclosporine, dietary supplement, dry eyes syndrome, intense pulse light, NOV03,perfluorohexyloctane, tear film lipid layer*

INTRODUCTION

Dry eye disease (DED) is a complex condition stemming from dysregulated ocular inflammation, leading to persistent dysfunctionof the ocular surface. Its global prevalence has surged across all age groups, particularly in children and adolescents, exacerbated by the digital revolution and heightened reliance on video display units (VDUs).[1,2] The chronic nature of DED poses challenges for individualswith pre-existing conditions, while the continuous influx of new cases amplifies the overall disease burden. Advanced stages of DED result in a formidable ocular surface disease, posing intricate challenges in management and carrying substantial economicimplications.[2]

Beyond the substantial ocularmorbidity associated with DED, its links tosystemic autoimmune disorders add an additional layer of concern, potentially impacting life-threatening conditions. Patients grappling with DED often endure role limitations, pain, and compromised general health, significantly diminishing their quality oflife (QoL) comparable to individuals dealing with serious medical conditions such as chronickidney disease and severe angina.[3] Moreover, DED has been correlated with psychological and sleep disorders, contributing to extensive economic, social, and psychological repercussions for affected individuals.[4]

Given the evolving epidemiological landscape marked by a transition from communicable to non-communicable chronic diseases, recent studies project a substantial and continuing increase in the annual incidence andprevalence of DED.[5] Therefore, it is imperative for healthcare providers to recognize that sustainable disease control necessitates not only effective treatment but also the implementationof robust preventive strategies. As efforts persist in treating existing DED cases, it iscrucial to concurrently focus on preventive measures to mitigate the overall impact of the disease. This systematic review aims to comprehensively explore an integrated approach to managing DED, emphasizingpreventive and promotive strategies across various levels of healthcare.

METHODS

PROTOCOL

The researchers in this study followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure that their workmet the required standards. This was done to ensure the precision and reliability of the conclusions derived from the research.

CRITERIA FOR ELIGIBILITY

For inclusion in the study, published articles had to meet particular requirements.They had to be research papers written in English, focusing on interventions for dry eyes.The studies had to meet the following criteria: articles need to have been published after 2016but within the applicable timeframe for this systematic review. Articles falling into categories like editorials, lacking a DOI, reviewarticles that were already published,or duplicating previously published journal papers were excluded from the assessment.

SEARCH STRATEGY

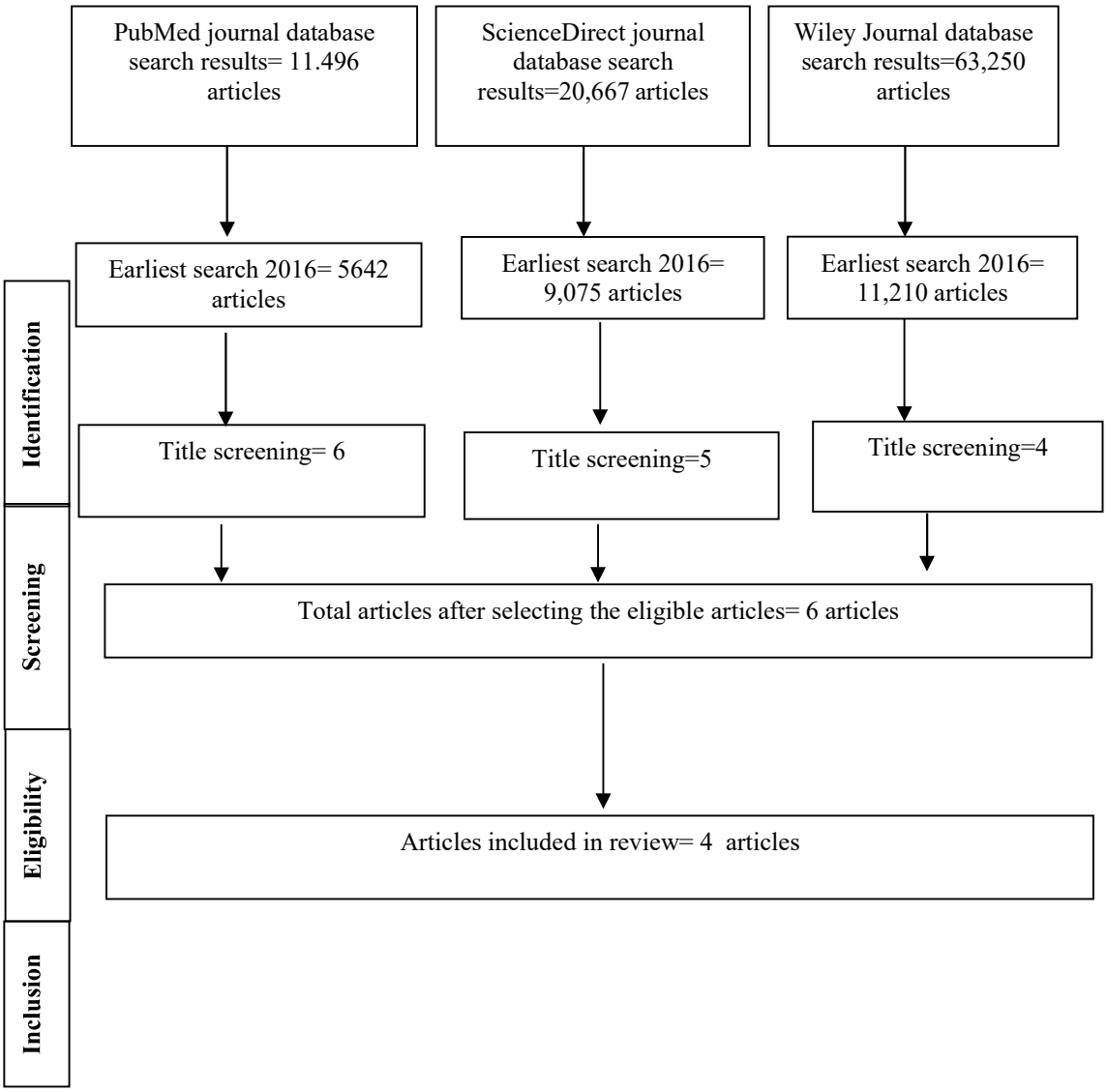
We conducted a comprehensive literature search using PubMed, Wiley Journal Database, and ScienceDirect focusing on studies published from 2016 to 2024. The search terms employed were as follows (("intervention s"[All Fields] OR "interventions"[All Fields] OR"interventive"[All Fields] OR"methods"[MeSH Terms] OR "methods"[AllFields] OR "intervention"[All Fields] OR "interventional"[All Fields])AND("keratoconjunctivitis sicca"[MeSH Terms] OR ("keratoconjunctivitis"[All Fields] AND "sicca"[All Fields]) OR "keratoconjunctivitissicca"[All Fields] OR ("dry"[All Fields] AND "eyes"[All Fields]) OR "dry eyes"[All Fields] OR "dry eye syndromes"[MeSH Terms] OR

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria for the studies were as follows: (1) original research that assesses interventions for dry eyes; (2) Randomized Controlled Trials (RCTs) or observationalstudies (cohort or case-control studies); (3) availability of relevant data. Exclusion criteria were as follows: (1) ongoing studies or studies without available data; (2) duplicate publications. In cases of duplicate publications,the most recent article was chosen; (3) Non- English language studies were excluded ("dry"[All Fields] AND "eye"[All Fields] AND"syndromes"[All Fields]) OR "dry eye syndromes"[All Fields])) AND (2016:2024[pdat]). Moreover, we performed cross-referencing of relevant articles to reveal additional research. The evaluation of studyquality, methodology, interventions, and resultswas undertaken independently by theresearchers, resolving any differences through discussion and agreement. Furthermore, both researchers collected and compared discoveriesfrom all studies, considering the potential for conducting a meta-analysis if deemed feasible.

DATA RETRIEVAL

The authors conducted a thorough examination of relevant studies, specifically selecting those that met precise inclusion criteria. They focused on original, unpublishedpapers in English to ensure a refined and high- quality selection. The analysis covered essential information, such as study particulars,authors, publication dates, locations, and research methodologies, aligning with thestudy's objectives.



RESULT

Our search produced 15 results. Afterlooking at the titles and summaries, we found 6papers that fit our criteria. At first, we excludedseveral articles because they were written inreview style and case reports. But after readingthe full papers carefully, we included fourpapers in our final analysis. These papersincluded prospective randomized examiner-masked sham- controlled study included eight-week, phase 3,multicenter,randomized,double-masked, saline-controlled study, aphase 3, multicenter, randomized, double-masked, a preliminary study in a rat model and a prospective, randomized, double-blind,placebo-controlled study in humans were conducted.

Song et al.'s research adhered to the guidelines of the Institutional Review Board atHe Eye Specialist Hospital in Shenyang, China.Participants were recruited consecutively fromthe outpatient department and providedinformed written consent. The IPL (Intense Pulsed Light) group included 45 participants (26 females, 19 males) with a mean age of 28.16 ± 3.59 years, while the sham group included 41 participants (23 females, 18 males)with a mean age of 28.07 ± 3.71 years. Both groups showed symptoms and signs of Dry EyeDisease (DED) related to Meibomian Gland Dysfunction (MGD), with no significant difference in baseline clinical parameters ($P > 0.05$).[7]

Author	Origin	Method	Sample Size	Result
Song et al., 2021.[7]	China	Prospective randomized examiner-masked sham-controlledstudy included	86 participants (142eyes) with DED.	At 3-month, TFLL, NITBUT, MG drop-out, MG quality, MG expressibility, FS and OSDI improved significantly (P < 0.05) in the IPL group, while the sham group had no significant improvements. Except for Meibo-score and FS, all parameters significantly correlatedwith the improvement in TFLL following IPL treatment. Additionally,artificial tears usage was significantly less in the IPL group from D-42 onwards.
Tauber eet al., 2023.[8]	USA	Multicenter, randomized, double-masked, saline-controlled study.	Of the 599 patients randomized, 597 were treated (NOV03, n ¼ 303; saline, n ¼ 294).	At week 8, improvement from baseline was significantly greater (P < 0.001) with NOV03 versus saline for tCFS (least square [LS] mean treatment difference, e0.97; 95% confidence interval [CI]: e1.40, e0.55)and VAS dryness score (e7.6; 95% CI: e11.8, e3.4). Improvement from baseline also significantly (P < 0.01) favored NOV03 on all keysecondary end points: LS mean treatment difference (95%CI) was e4.7(e8.2, e1.2) for VAS dryness score at week 2, e0.6 (e0.9, e0.2) for tCFSat week 2, e5.5 (e9.5, e1.6) for VAS burning or stinging score at week8, and e0.2 (e0.4, e0.1) for cCFS at week 8. Most ocular adverse events (AEs) were mild in severity; no serious ocular AEs occurred. One patient discontinued NOV03 because of an AE (eye irritation).
Akpek EK et al., 2023.[9]	USA	A phase 3, multicenter, randomized, double-masked.	A total of 834 studyparticipants wererandomly assigned to cyclosporine(423 [50.7%]) or vehicle (411 [49.3%]) groups at 27 sites.	Participants treated with cyclosporine solution had greater improvement in tCFS (−4.0 grades) than the vehicle group (−3.6 grades) at day 29 (change [Δ] = −0.4; 95%CI, −0.8 to 0; P = .03). The dryness score showed treatment benefits from baseline in both groups: −12.2 points for cyclosporine and −13.6 points for vehicle (Δ = 1.4; 95%CI, −1.8 to 4.6; P = .38). In the cyclosporine group, 293 participants (71.6%) achieved clinically meaningful reductions of 3 grades or higher in tCFS vs 236 (59.7%) in the vehicle group (Δ = 12.6%; 95% CI, 6.0%-19.3%; P < .001). These responders showed greater improvement in symptoms at day 29 including dryness (Δ = −4.6; 95%CI, −8.0 to −1.2; P = .007) and blurred vision (Δ = −3.5; 95%CI, −6.6 to −4.0; P = .03) compared with nonresponders.
Motoko et al., 2016.[10]	Japan	a prospective,randomized, double-blind, placebo-controlledstudy	Forty Japanese volunteers aged 22 to 59 years.	Supplementation dose-dependently mitigated the decrease in tear production in rats. Among subjects with confirmed dry eye, clinical symptoms improved at weeks 4 and 8 more significantly in the supplementation group than in the placebo group (P<.05). The rate of increase in the Schirmer value was greater in the supplementation group. No adverse events occurred.

The Meibo-score, evaluatingMeibomian Gland (MG) dropout, MG quality, and expressibility, significantly improved in the IPL group at day-21, day-42, and 3-month compared to the sham group. Fluorescein Staining (FS) scores in the IPL group remainedunchanged at day-21 and day-42 ($P > 0.05$) andonly showed significant improvement at 3- month compared to the sham group. The Overall Dry Eye Symptoms and Impact (OSDI)score significantly improved at day-42 (18.97 ±6.71 vs. 35.00 ± 9.49) and 3-month (19.02 ± 6.70 vs. 35.13 ± 9.41) in the IPL group compared to the sham group. Artificial tear usage significantly decreased in the IPL group at day-21 and day-42 compared to the sham group. [7]

A total of 599 patients were randomized, with 597 receiving treatment(NOV03, n = 303; saline, n = 294). Of these, 289 in the NOV03 group (95.4%) and 279 in the control group (94.9%) completed the study.Apart from DED, prevalent ocular medical history included cataracts, intraocular lens implantation (13.9%), vitreous detachment, andblepharitis. This phase 3, multicenter, randomized, double-masked, saline-controlled trial was conducted across 26 U.S. sites from December 2019 to March 2021. Due to NOV03being a single chemical entity, a vehicle controlgroup was not feasible. Common nonocular medical history included hypertension, postmenopause, and hypercholesterolemia,each in over 20% of patients.[8]

NOV03 showed statistical superiority for all four key secondary endpoints. The LS mean treatment difference was -4.7 (95% CI:8.2, -1.2) for VAS dryness score change from baseline at week 2 ($P = 0.009$), -0.6 (95% CI: -0.9, -0.2) for tCFS score change from baseline (study eye) at week 2 ($P = 0.001$), -5.5 (95% CI: -9.5, -1.6) for VAS burning or stinging score change from baseline at week 8 ($P = 0.006$), and -0.2 (95% CI: -0.4, -0.1) for conjunctival Corneal Fluorescein Staining (cCFS) score change from baseline (study eye) at week 8 ($P< 0.001$). [8]

The ESSENCE-2 trial was a randomized, double-masked, vehicle- controlled study assessing the efficacy, safety, and tolerability of cyclosporine solution over 4weeks. A total of 1879 patients were screened across 27 sites, with 834 enrolled. Of these, 423(50.7%) were assigned to the cyclosporine group and 411 (49.3%) to the vehicle group. Asignificant majority, 817 participants (98.0%), completed the study, with 17 participants (2.0%) discontinuing treatment (8 in the cyclosporine group, 9 in the vehicle group). Both participants who withdrew due to adverseevents were from the cyclosporine group (one with instillation site burning, the other withcholelithiasis).[9]

There were 21 major protocol deviations, including issues with study visits, inclusion/exclusion criteria, concomitant medication, study drug assignment, andnoncompliance. At day 29, the cyclosporinegroup showed a more significant improvementin total Corneal Fluorescein Staining (tCFS) compared to the vehicle group (Δ = -0.4; 95% CI, -0.8 to 0; P = .03). Both groups showed improvement in dryness score from baseline, with no significant difference between them (Δ = 1.4; 95% CI, -1.8 to 4.6; P = .38). [9]

All secondary endpoints, includingcentral CFS, central CFS responders,conjunctival staining, and tCFS at day 15, showed better outcomes with cyclosporine compared to the vehicle. Cyclosporine responders demonstrated significant improvements in symptoms at day 29 comparedto nonresponders, indicating clinical relevance of a 3-grade or higher improvement in corneal surface staining. [9]

Reductions in blurred vision score wereobserved in both groups, with no significant difference. A post hoc analysis of participants with high central CFS scores at baseline showed greater reductions in blurred vision score in the cyclosporine group compared to thevehicle group at day 29.[9]

Forty participants were enrolled andrandomly assigned to either the placebo or supplementation group (n=20 per group). Efficacy analyses included 20 subjects in the placebo group and 19 in the supplementation group, with one subject excluded due to insufficient data. Baseline characteristics showed no instances of meibomian dysfunction, and no significant differences were found between the groups.[10]

Objective dry eye parameters revealed an increase in Tear Film Break-Up Time (TFBUT) at weeks 4 and 8 from baseline in both groups, with no significant intergroup differences. Fluorescein staining scoressignificantly decreased from baseline at week 8in both groups without significant differences. The Schirmer test value increased from baseline, showing a significant intergroupdifference, with a greater trend in the supplementation group, though not statisticallysignificant.[10] Subjective dry eye symptoms assessedvia the DEQS total score showed significant decreases at weeks 4 and 8 in both groups. Participants with confirmed dry eye showed a significantly greater decrease in DEQS total score in the supplementation group compared to the placebo group at weeks 4 and 8, with notable improvements in specific ocular symptoms, particularly ocular fatigue.[10]

DISCUSSION

This study assessed the effectiveness ofOPT-IPL therapy on Tear Film Lipid Layer (TFLL) patterns and its impact on Dry Eye Disease (DED). Significant correlations ($P < 0.05$) were found between ΔTFLL and improvements in ΔNITBUT, ΔMG quality, ΔMG expression, ΔOSDI score, and ΔAT usage, while ΔMG dropout and ΔFS showed nosignificant correlation ($P > 0.05$). A decrease inartificial tear usage aligned with reduced OSDIscores, attributed to enhanced TFLL and tear- film stability. No significant differences were observed in Best-Corrected Visual Acuity(BCVA), Epithelial Cell Count (ECC), and Intraocular Pressure (IOP). No adverse effects like depigmentation, swelling, blistering, redness, or hair

loss were reported, and no ophthalmic complications were observed post- OPT-IPL treatments. [7]
Intense Pulsed Light (IPL) treatment, commonly used in dermatology, demonstrated safety in enhancing meibomian gland function, stabilizing the tear film, and reducing ocular surface inflammation in evaporative DED. IPL's photobiomodulation effect involves light-induced photochemical reactions, promoting wound healing, tissue regeneration, increased circulation, and reduced inflammation. The tearfilm lipid layer's critical role in maintaining tearfilm homeostasis and understanding DED pathophysiology was emphasized. IPL treatment is recommended around the periorbital area to reduce telangiectasias, erythema, and inflammatory markers.[7]

This study underscored the tear film lipid layer's pivotal role in the etiology and treatment of Dry Eye Disease (DED). The complex structure and function of lipids,including nonpolar and polar lipids, are crucialfor the tear film lipid layer. Meibomian gland dysfunction disrupts this lipid layer, leading to tear film instability. While the precise mechanism of NOV03's action is not fully understood, it is believed to form a durable, antievaporative barrier on the ocular surface, preventing evaporation of the aqueous tear filmcomponent and reducing DED signs andsymptoms. Additionally, it may reduce frictionduring blinking. Animal studies have shown improvements in the tear film lipid layer qualityfollowing NOV03 administration, with evidence of penetration into meibomian glands.The inclusion of patients with varying MGD severity underscores NOV03's potential effectiveness, even in cases with minimal functional meibum production. Ongoing research aims to explore NOV03's precise mechanisms further.[8]

Administered four times daily for 8weeks, NOV03 exhibited a favorable safetyprofile and high tolerability. Only one adverse event (AE), severe eye irritation, led to NOV03discontinuation, with no serious AEs reported in the NOV03 group. Blurred vision, the most common ocular AE, occurred in 3.0% of NOV03 users, characterized as mild andtransient, typically resolving within minutes. The preservative-free nature of NOV03 drops likely enhances tolerability, as evidenced by thelow rate of instillation site reactions, contrasting with preservatives that mayexacerbate DED signs and symptoms.[8]
In the ESSENCE-2 (CYS-004) study, aphase 3 clinical trial, aimed to validate theefficacy, safety, and tolerability of a water-free0.1% cyclosporine ophthalmic solution for treating Dry Eye Disease (DED) compared to its vehicle. The study included patients with moderate to severe, predominantly aqueous-deficient DED, characterized by low Schirmer tear production scores, high corneal staining, and ocular symptom scores. Notably, 35% of participants had concurrent cataracts, highlighting the importance of managing DEDto ensure accurate measurements before and after cataract surgery. [9]
The study confirmed the superiority ofcyclosporine over the vehicle in improving totalCorneal Fluorescein Staining (tCFS) by day 29,with a significant effect seen as early as day 15.This rapid onset of efficacy surpasses that of other DED treatments. A responder analysis defined significant clinical improvement as a 3-grade or more enhancement on the NEI scale. The cyclosporine group had a higher proportion of responders (71.6%) compared to the vehiclegroup (59.7%), and these improvements were associated with significant symptom relief.[9]

Our investigation revealed that mixed components in a dietary supplement significantly preserved tear production in a rat dry eye model. In a double-blind, randomized controlled study involving individuals with dryeye symptoms, 8 weeks of daily supplementation led to notable improvements in both objective parameters and subjective dryeye symptoms, especially in participants with confirmed dry eye, compared to the placebo group.[10]

In terms of tear production, the rate of increase was generally higher in the supplementation group compared to the placebo group, supporting outcomes observed in the initial rat model. Previous research demonstrated accelerated oxidation of protein, fat, and DNA at the ocular surface in the rat model, suggesting oxidative stress involvementin ocular surface cell degeneration and lacrimalgland dysfunction. Increased free radicals havebeen linked to lacrimal dysfunction and dry eye.[10]
The dietary supplement's composition was designed to counteract oxidative stress,including components like Vitamins C and E, zinc, lutein, and EPA/DHA, known for their antioxidant and anti-inflammatory properties. Lactic acid bacteria, specifically the E. faeciumWB2000 strain from traditional Japanese medicine (Strong Wakamoto), were included for their oxidative stress-reducing abilities. Previous studies have associated EPA/DHA with reduced dry eye incidence and benefits in treatment, while oral lactoferrin consumption has been linked to increased tear volume and improved symptoms. These results suggest a potential reduction in oxidative stress through supplementation, with further details on molecular mechanisms to be reported in a forthcoming study. [10]

CONCLUSION

Our study suggests that OPT-IPL treatment significantly enhances the tear film lipid layer (TFLL) and improves signs and symptoms of dry eye disease (DED) through better meibomian gland function. The phase 3 study with NOV03 in DED patients associatedwith meibomian gland dysfunction (MGD) shows statistically significant and clinically meaningful improvements over 8 weeks, demonstrating NOV03's efficacy and tolerability. The ESSENCE-2 trial furthersupports the efficacy of a water-free cyclosporine solution in improving ocularsurface staining associated with DED, with rapid and significant improvements in corneal epithelial damage.

Additionally, our investigation indicates that dietary supplementation preserved tear production in a rat dry eye modeland showed significant improvements in both objective parameters and subjective dry eyesymptoms in a double-blind, randomized controlled study, especially in participants withconfirmed dry eye. This suggests the supplement's potential in

alleviating dry eyethrough its antioxidant and anti-inflammatory components, which reduce oxidative stress andimprove tear production. Further clinical practice insights would enhance understandingof these treatments' potential.
While our study on supplementation asa therapy for dry eye symptoms and objective ocular changes indicates promising and safeoutcomes, additional data are necessary to validate its widespread use as a common intervention for DED.

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