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Enhancement of Macular Pigment Optical Density and Contrast Sensitivity following Supplementation with Supercritical Fluid Extraction-based Lutein Ester Products: Evidence from a Randomized, Double-Blind, Placebo-Controlled Study in Healthy Adults

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ABSTRACT:

Introduction: Macular pigment optical density (MPOD) is an important marker of macular carotenoid status and visual function. Although lutein supplementation can increase MPOD, comparative clinical evidence on different lutein-ester delivery formats remains limited. This study compared three supercritical fluid extraction (SCFE)-based lutein ester formulations: a conventional lutein ester preparation (LE), a true oil solution of lutein ester (LETOS), and a self-emulsifiable lutein ester formulation (LEU).

Methods: In this randomized, double-blind, placebo-controlled, parallel-group study, 128 healthy adults with baseline MPOD values of 0.20–0.35 were randomized equally to LE, LETOS, LEU, or placebo for 90 days. MPOD was assessed by heterochromatic flicker photometry at baseline and Days 15, 30, 60, and 90 at 0.25°, 0.5°, and 1° eccentricities in both eyes. Secondary outcomes included contrast sensitivity, visual processing speed, intraocular pressure, and Schirmer test results. Serum lutein concentration was assessed on Day 15 as an exploratory outcome.

Results: All three lutein ester groups showed significant improvements in MPOD compared with placebo from Day 30 onward ($p < 0.05$), with Day 90 increases ranging from approximately 28.5% to 45.1%. Contrast sensitivity also improved in the active groups, whereas no consistent treatment-specific effect was observed for visual processing speed or intraocular pressure. LETOS showed the largest observed improvement in MPOD among the active formulations.

Conclusion: Ninety days of supplementation with the tested lutein ester formulations increased MPOD and improved contrast sensitivity in healthy adults with relatively low baseline MPOD. LETOS produced the largest observed MPOD response, although direct

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formulation comparisons should be interpreted in the context of the different lutein-equivalent doses used. No clinically meaningful safety concerns were identified during the study.

1. INTRODUCTION

Macular pigment optical density (MPOD) is a key biomarker of retinal health and visual performance, primarily determined by the concentration of the xanthophyll carotenoids within the macula. These carotenoids act as blue-light filters and potent antioxidants protecting the retina from photo-oxidative stress and age-related degeneration of photoreceptor cells [1,2]. Higher MPOD levels have been associated with improved contrast sensitivity [3], visual processing speed [4], and glare recovery [3], and a reduced risk of age-related macular degeneration (AMD) [2,5].

Although lutein and zeaxanthin are obtained from dietary sources such as green leafy vegetables and egg yolk, typical dietary intake is often insufficient to achieve optimal macular concentrations. Consequently, nutritional supplementation has become an effective strategy for enhancing macular pigment and supporting visual performance in both healthy and at-risk populations. Lutein is a fat-soluble carotenoid; therefore, its intestinal absorption is enhanced when consumed with dietary fat [7]. Free lutein is susceptible to degradation when exposed to light, heat, and oxygen, reducing its stability. In contrast, lutein esters exhibit greater chemical stability, improved shelf life, and better retention of potency in finished products, and may not need to be taken along with a fatty meal for absorption [7,8].

Several randomized trials and meta-analyses have shown that lutein supplementation can increase MPOD and improve selected measures of visual performance [8,9]. However, clinical response is influenced by formulation, lipid matrix, and bioavailability. Lutein esters require hydrolysis before absorption, and newer delivery approaches, including true oil solutions and self-emulsifying systems, are intended to improve dispersion, micelle formation, and intestinal uptake [8,10]. Despite these developments, head-to-head randomized clinical evidence directly comparing different SCFE-based lutein ester delivery formats under the same study conditions is limited, particularly in healthy adults with relatively low baseline MPOD. This evidence gap makes it difficult to determine whether formulation technology meaningfully influences the magnitude or timing of retinal lutein response.

The present study therefore compared three SCFE-based lutein ester products likely LE (Xanthogreen®), LETOS (Xanthogreen® TOS), and LEU (Xanthogreen® Ultra) with placebo. The primary objective was to evaluate change in MPOD over 90 days. Secondary objectives were to assess contrast sensitivity, visual processing speed, intraocular pressure, dry eye measures, acceptability, and safety. Serum lutein concentration on Day 15 was evaluated as an exploratory outcome.

2. MATERIALS AND METHODS

2.1. Ethical Considerations

This multicenter clinical study was conducted after written informed consent was obtained from all participants and after approval by the ACE Independent Ethics Committee and the Vagus Institutional Ethics Committee. The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guideline (ICH-GCP E6 R2), the Declaration of Helsinki, and applicable Indian Council of Medical Research ethical guidelines. The trial was prospectively registered with the Clinical Trials Registry–India on 30 November 2023 (CTRI/2023/11/060356).

2.2. Study Design

This was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical study with 90 days of supplementation. Participants attended five study visits: baseline/Day 0, Day 15, Day 30, Day 60, and Day 90. Eligibility, demographic information, medical and surgical history, concomitant medication use, physical examination, and baseline ocular assessments were completed at screening/baseline. MPOD, visual processing speed, contrast sensitivity, intraocular pressure, and dry eye assessments were performed at the scheduled efficacy visits. Test-product acceptability was assessed on Day 90 and serum lutein concentration on Day 15. Vital signs were assessed at each visit; haematology, blood chemistry, urinalysis, and

pregnancy testing in women of childbearing potential were performed at baseline and Day 90. Adverse events and serious adverse events were monitored throughout the study.

2.3. Participants

Participant recruitment was conducted from 18/12/2023 to 24/12/2023. Healthy adults aged 18–50 years of either sex were eligible if MPOD was 0.20–0.35 by heterochromatic flicker photometry, visual acuity was 20/20 or corrected to normal, no clinically significant ocular pathology was present, written informed consent was provided, and the participant agreed to attend scheduled visits and maintain the usual balanced diet during the study.

Baseline ocular eligibility assessment included visual acuity using a Snellen chart, slit-lamp biomicroscopy (Topcon 2L-26), and dilated fundus examination using an ophthalmoscope and 78-dioptre lens. These examinations were performed to confirm normal ocular status and exclude clinically significant pathology before randomization.

Exclusion criteria included MPOD <0.20 or >0.35; age-related macular degeneration, colour blindness, glaucoma, mature cataract, pan-retinal degeneration, or other clinically significant ocular disease; only one functional eye; smoking; epilepsy; clinically significant systemic disease; recent alcohol consumption or inability to abstain during the study; and pregnancy or planned pregnancy during the study. Pregnancy and planned pregnancy were excluded as a protocol-defined precaution because the safety of the investigational formulations was not evaluated in pregnancy and pregnancy-related physiological changes could introduce additional variability. Additional protocol-defined exclusions were applied as specified in the registered trial.

2.4 Interventions

Xanthogreen Ultra (Self-emulsifiable)

Lutein ester oleoresin was obtained from dried flowers of Tagetes erecta L. using supercritical carbon dioxide extraction. The extract was standardized to ≥40% (w/w) lutein esters, quantified using validated high-performance liquid chromatography (HPLC). The standardized extract was incorporated into a lipid matrix containing predominantly monounsaturated fatty acids and food-grade excipients. The final self-emulsifiable formulation was standardized to 15% (w/w) lutein esters by HPLC and designated Xanthogreen® Ultra (LEU).

Xanthogreen TOS

Lutein ester extract derived from Tagetes erecta L. was prepared by supercritical carbon dioxide extraction and standardized to

≥40% (w/w) lutein esters by HPLC. The extract was processed with food-grade lipid excipients rich in monounsaturated fatty

acids to form a homogeneous lipid dispersion. The final product was standardized to 10% (w/w) lutein esters and designated Xanthogreen® TOS (LETOS).

Xanthogreen

Dried and milled flowers of Tagetes erecta L. were extracted using supercritical carbon dioxide technology to obtain lutein ester-rich oleoresin. The extract contained up to 40% (w/w) lutein esters by HPLC and was standardized to 20% (w/w) lutein esters for the final product, Xanthogreen® (LE).

Each daily capsule contained either 40 mg lutein ester (LE, Xanthogreen®; equivalent to 20 mg free lutein), 40 mg lutein ester in a true oil solution (LETOS, Xanthogreen® TOS; equivalent to 20 mg free lutein), or 20 mg lutein ester in a self-emulsifiable formulation (LEU, Xanthogreen® Ultra; equivalent to 10 mg free lutein). Placebo capsules contained 500 mg of a sunflower-oil and tocopherol blend. Active and placebo capsules were matched in appearance, weight, and labeling. Participants were instructed to take one capsule once daily after breakfast for 90 days. Compliance was assessed by capsule count and return of unused study product.

2.5 Primary, Secondary, and Exploratory Outcomes

The primary efficacy endpoint was change in MPOD from baseline. MPOD was measured by customized heterochromatic flicker photometry using the Macular Metrics II densitometer (Macular Metrics II, LLC, Rehoboth, MA, USA) at baseline and on Days 15 (±1), 30 (±1), 60 (±1), and 90 (±1). Measurements were obtained at 0.25°, 0.5°, and 1° eccentricities from the foveal center in each eye. Participants received standardized instructions and rested for approximately 15 minutes without

smartphone or other video-display use before testing.

Secondary efficacy outcomes were assessed during the same scheduled study visits as MPOD and included visual processing speed by critical flicker fusion, contrast sensitivity using the Pelli-Robson chart, intraocular pressure by applanation tonometry, and tear production using the Schirmer test. Visual processing speed was evaluated using critical flicker fusion. Flicker-to-fusion and fusion-to-flicker thresholds were assessed in repeated trials to reduce measurement variability [13].

Contrast sensitivity was assessed using the Pelli-Robson chart [14] during the same visits as MPOD. Participants rested for approximately 15 minutes without smartphone or other video-display use before visual testing. Intraocular pressure was measured by applanation tonometry [15]. Values were recorded in mmHg; the clinically usual reference range of 10–21 mmHg was used for descriptive safety interpretation [16]. Dry eye status was assessed using the Schirmer strip test [17]. Standardized

strips were placed in the lower conjunctival fornix of each eye for 5 minutes, after which the length of wetting was recorded in millimetres.

Serum lutein concentration was measured on Day 15 as an exploratory endpoint. Safety assessments included adverse-event monitoring throughout the study; vital signs at all visits; haematology, blood chemistry, and urinalysis at baseline and Day 90; and urine pregnancy testing at baseline and Day 90 in women of childbearing potential. Body weight and height were recorded during baseline physical examination, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Weight and BMI were collected as baseline descriptive characteristics and were not pre-specified efficacy outcomes.

2.6 Sample Size

The sample-size calculation was based on the primary MPOD comparison at the principal post-treatment time point rather than on the efficiency gain expected from repeated measurements. A prior study [1] reported a clinically meaningful between-group MPOD difference of 0.18 with an estimated pooled SD of approximately 0.18, corresponding to an effect size of about

1.0. At two-sided $\alpha = 0.05$ and 80% power, approximately 16–17 participants per group were required for a simple two-group comparison. Because three active formulations were to be compared with a common placebo, the target was increased conservatively to account for multiplicity and then inflated for an anticipated dropout rate of approximately 12%. The operational target was set at 28 participants per group and rounded upward to 32 per group (128 total) to provide additional precision. The repeated-measures analysis used all available post-baseline observations and was expected to improve precision relative to a single-time-point comparison

2.7 Randomization and Blinding

Participants were randomized in a 1:1:1:1 ratio using a computer-generated block-randomization schedule with variable block sizes of 2–5 created in R version 4.3.2. The allocation sequence was generated and retained by an independent statistician. Sequentially coded study-product packs were used at the participating sites so that investigators enrolling participants did not have access to the allocation sequence. The trial was double-blind. Participants, investigators, outcome assessors, and study staff remained unaware of treatment allocation. Active and placebo capsules were matched for appearance, weight, and labeling and were dispensed using coded study-product packs. The randomization code was held by an independent statistician and could be broken only for a medical emergency. No emergency unblinding occurred before database lock.

2.8 Statistical Methods

The prespecified efficacy population was a modified intention-to-treat (mITT) population, defined as randomized participants who received at least one dose of study product and had at least one post-baseline assessment of the primary endpoint. The per-protocol (PP) population included participants who completed the trial without major protocol deviations. All randomized participants who received at least one dose were included in the safety population. Continuous variables were summarized using mean, standard deviation, median, minimum, and maximum, and categorical variables by frequency and percentage. Longitudinal MPOD and other continuous outcomes were analyzed using mixed-effects models. Categorical outcomes were compared using the chi-square test, and serum lutein concentrations were compared using analysis of variance (ANOVA). Because the original statistical analysis plan did not prespecify a formal multiplicity-adjustment procedure for all repeated secondary and pairwise comparisons, secondary p-values should be interpreted as nominal; this is acknowledged as a limitation.

Three randomized participants were lost to follow-up before contributing post-baseline primary efficacy data. Accordingly, they were excluded from the mITT and PP efficacy populations but remained in the safety population. All statistical analyses were conducted using a two-sided significance level of 0.05, with $P < .05$ considered statistically significant. Statistical analyses were performed using SAS® software, version 9.4.

3. RESULTS AND DISCUSSION

3.1. Participant Flow

A total of 132 participants were screened between 18/12/2023 and 24/12/2023; four were ineligible and 128 were randomized equally to LE, LETOS, LEU, or placebo. Three participants (one each in LE, LETOS, and LEU) were lost to follow-up before a post-baseline primary efficacy assessment. Therefore, the mITT and PP efficacy populations each comprised 125 participants, while the safety population comprised all 128 randomized participants. Participant flow is shown in Fig 1.

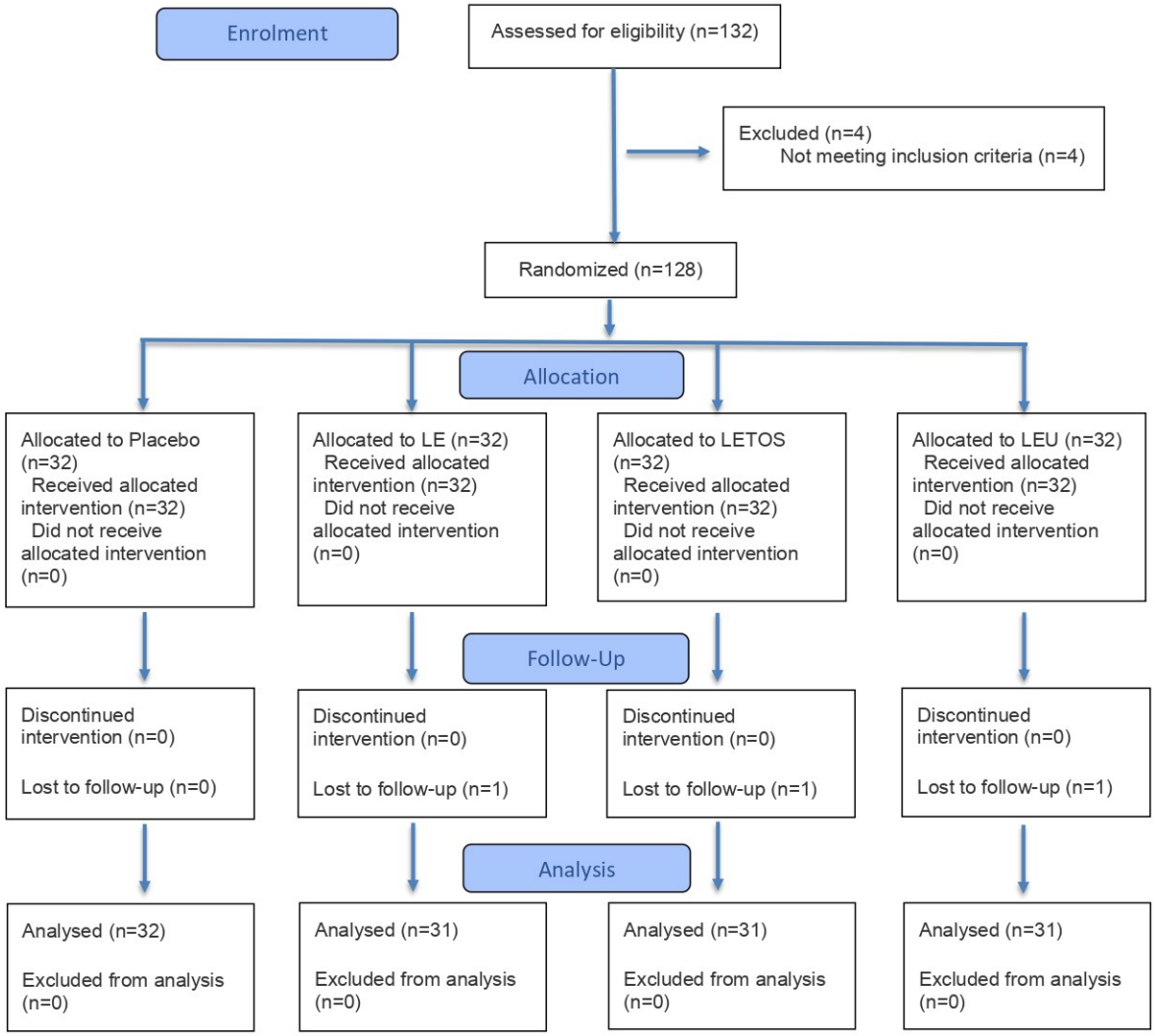


Fig. 1: CONSORT flow diagram of participants in the study. LE, lutein ester; LETOS, true oil solution of lutein ester; LEU, self-emulsifiable lutein ester.

3.2. Baseline Demographic Characteristics

Baseline age was similar across groups. Mean body weight and BMI differed statistically among groups at baseline (Table 1), whereas height and sex distribution did not. Weight and BMI were descriptive baseline characteristics and were not efficacy endpoints. Because only six of 128 participants were women, sex-stratified efficacy analyses were not considered reliable.

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Table 1. Baseline Demographic Characteristics (Mean (SD))

	Placebo	LE	LETOS	LEU	
Characteristics					**P value**
	(N = 32)	**(N = 32)**	**(N = 32)**	**(N = 32)**	
Age (years)	28.66 (7.83)	30.73 (8.12)	27.84 (6.06)	29.75 (7.09)	0.419
Weight (kg)	66.25 (9.94)	72.31 (10.94)	66.56 (7.19)	68.00 (7.64)	0.032
Height (cm)	170.84 (6.62)	170.14 (6.15)	169.69 (7.31)	168.81 (6.87)	0.677
BMI (kg/m2)	22.68 (3.08)	25.21 (3.85)	23.16 (2.50)	23.99 (3.68)	0.016
Sex					
Female	1 (3.12%)	2 (6.25%)	1 (3.12%)	2 (6.25%)	
Male	31 (96.88%)	30 (93.75%)	31 (96.88%)	30 (93.75%)	0.873

Each value represents Mean (SD); LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group. $p < 0.05$ is considered statistically significant.

3.3. Lutein Ester Products Improved MPOD

When the PP population was analyzed, no significant difference in MPOD was observed between the placebo and lutein ester groups at baseline. All lutein ester groups showed statistically significant ($p < 0.05$) improvements in MPOD at Days 30, 60, and 90 at the retinal positions 0.25R, 0.5R, and 1R from the center of the fovea in the right eye, and at 0.25L, 0.5L, and 1L from the center of the fovea in the left eye, compared with the corresponding retinal positions in the placebo group (Figs 2A and 2B and Table 2).

At baseline, the mean (SD) MPOD values at 0.25R, 0.5R, 1R, 0.25L, 0.5L, and 1L in the placebo group were 0.28 (0.03), 0.27 (0.02), 0.26 (0.02), 0.28 (0.02), 0.27 (0.02), and 0.26 (0.02), respectively. At Day 90, the corresponding MPOD values in the placebo group were 0.30 (0.02), 0.29 (0.02), 0.28 (0.02), 0.29 (0.02), 0.28 (0.02), and 0.27 (0.02), respectively (Figs 2A and 2B and Table 2).

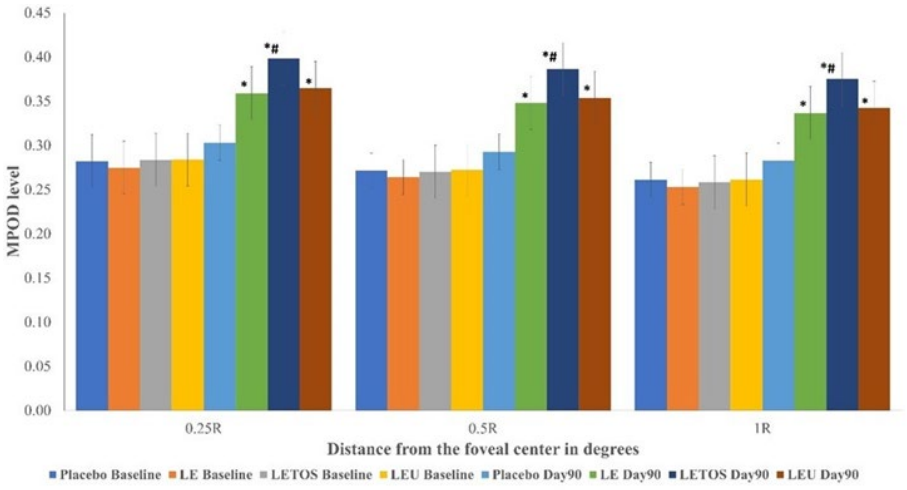


Fig 2A. Effect of Lutein Ester Formulations on MPOD in the Right Eye.

*p < 0.0001 compared to placebo group at respective retinal positions, #p < 0.0001 compared to the LE and LEU groups at respective retinal positions, 0.25R: 0.25-degree angle from the center of the fovea in the right eye, 0.5R: 0.5-degree angle from the center of the fovea in the right eye, 1R: 1-degree angle from the center of the fovea in the right eye, LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group, MPOD: Macular pigment optical density.

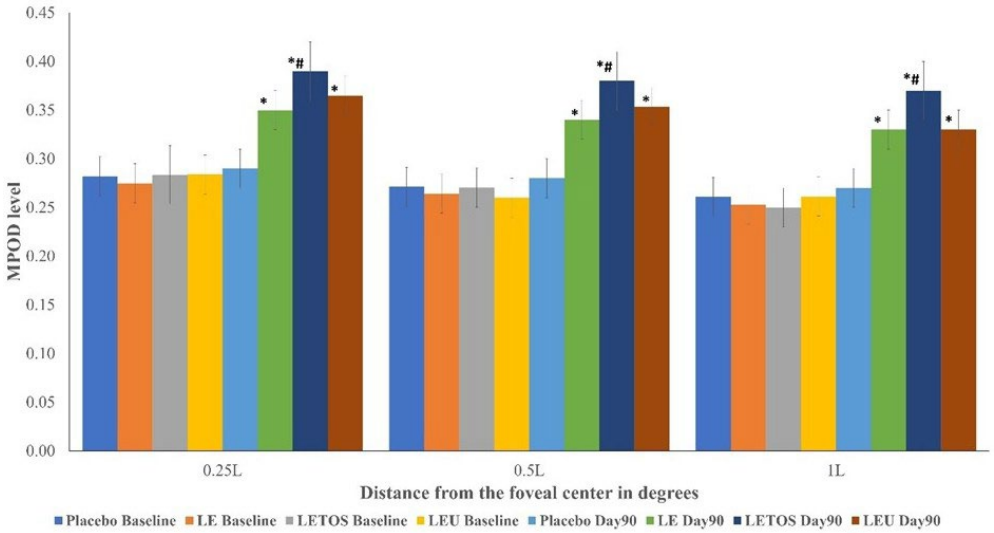


Fig 2B. Effect of Lutein Ester Formulations on Macular Pigment Optical Density in the Left Eye.

*p < 0.0001 compared to placebo group at respective retinal positions, #p < 0.0001 compared to the LE and LEU groups at respective retinal positions, 0.25L: 0.25-degree angle from the center of the fovea in the left eye, 0.5L: 0.5-degree angle from the center of the fovea in the left eye, 1L: 1-degree angle from the center of the fovea in the left eye, LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group, MPOD: Macular pigment optical density.

The maximum percentage improvement (8.74%) in MPOD within the placebo group from baseline was observed at Day 30 at 1R, while the minimum improvement (4.91%) was observed at Day 90 at 0.25L. In contrast, the lutein ester formulations showed a minimum percentage improvement (6.65%) in MPOD from baseline at Day 15 at 0.5L and a maximum improvement (45.13%) at Day 90 at 1R (Fig 3).

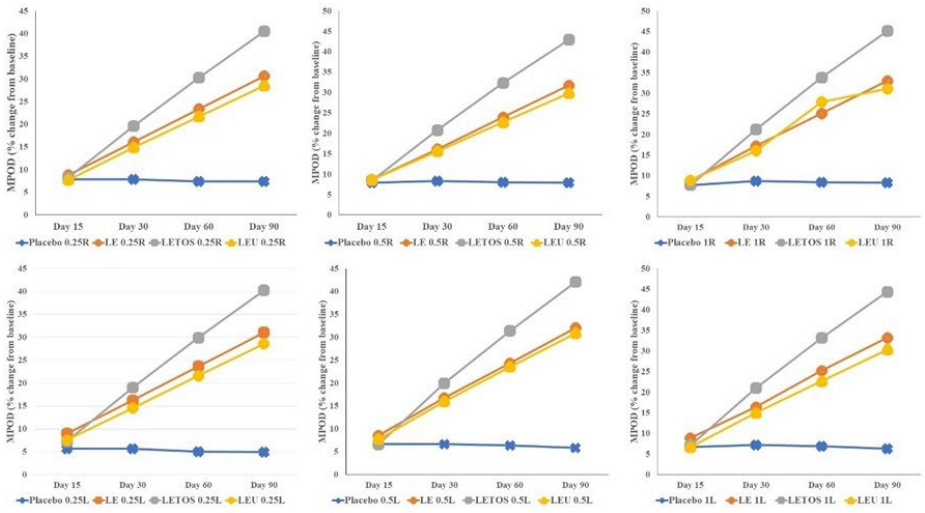


Fig 3. Percentage change in MPOD from baseline. (A) 0.25R: 0.25-degree angle from the center of the fovea in the right eye.

(B) 0.5R: 0.5-degree angle from the center of the fovea in the right eye. (C) 1R: 1-degree angle from the center of the fovea in the right eye. (D) 0.25L: 0.25-degree angle from the center of the fovea in the left eye. (E) 0.5L: 0.5-degree angle from the center of the fovea in the left eye. (F) 1L: 1-degree angle from the center of the fovea in the left eye. LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group, MPOD: Macular pigment optical density.

Among the lutein ester formulations, the LETOS group showed statistically significant ($p < 0.05$) improvements in MPOD at Days 30, 60, and 90 at the retinal positions 0.25R, 0.5R, and 1R of the right eye, and 0.25L, 0.5L, and 1L of the left eye, compared with the corresponding positions in the LE and LEU groups. The maximum percentage improvement from baseline in MPOD was observed at Day 90 at 1L (33.25%) in LE, at 1R (45.13%) in LETOS, and at 1R (31.11%) in LEU (Fig 3).

Table 2. Effect of interventions on Macular Pigment Optical Density (MPOD)

MPOD from the center of fovea in degrees							
Visits							
Groups	**0.25R**	**0.5R**	**1R**	**0.25L**	**0.5L**	**1L**	
Baseline	Placebo	0.28 (0.03)	0.27 (0.02)	0.26 (0.02)	0.28 (0.02)	0.27 (0.02)	0.26 (0.02)
	LE	0.27 (0.03)	0.26 (0.02)	0.25 (0.02)	0.27 (0.02)	0.26 (0.02	0.25 (0.02)
	LETOS	0.28 (0.03)	0.27 (0.03)	0.26 (0.03)	0.28 (0.03)	0.27 (0.02)	0.25 (0.02)
	LEU	0.28 (0.03)	0.27 (0.03)	0.26 (0.03)	0.28 (0.02)	0.26 (0.02)	0.26 (0.02)
Day 15	Placebo	0.30 (0.02)	0.29 (0.02)	0.28 (0.02)	0.30 (0.02)	0.29 (0.02)	0.27 (0.02)
	LE	0.30 (0.03)	0.29 (0.03)	0.28 (0.03)	0.29 (0.02)	0.28 (0.02)	0.27 (0.02)
	LETOS	0.31 (0.03)	0.29 (0.03)	0.28 (0.03)	0.30 (0.03)	0.28 (0.03)	0.27 (0.03)
	LEU	0.31 (0.03)	0.30 (0.03)	0.28 (0.03)	0.30 (0.02)	0.28 (0.02)	0.27 (0.02)
Day 30	Placebo	0.30 (0.02)	0.29 (0.02)	0.28 (0.02)	0.30 (0.02)	0.29 (0.02)	0.28 (0.02)
	LE	0.32 (0.03)*	0.31 (0.03)*	0.30 (0.03)*	0.31 (0.02)*	0.30 (0.02)*	0.29 (0.02)*
	LETOS	0.34 (0.03)*#	0.33 (0.03)*#	0.31 (0.03)*#	0.33 (0.03)*#	0.32 (0.03)*#	0.31 (0.03)*#
	LEU	0.33 (0.03)*	0.31 (0.03)*	0.30 (0.03)*	0.32 (0.02)*	0.31 (0.02)*	0.29 (0.02)*
Day 60	Placebo	0.30 (0.02)	0.29 (0.02)	0.28 (0.02)	0.29 (0.02)	0.29 (0.02)	0.28 (0.02)
	LE	0.34 (0.03)*	0.33 (0.03)*	0.32 (0.03)*	0.33 (0.02)*	0.32 (0.02)*	0.31 (0.02)*
	LETOS	0.37 (0.03)*#	0.36 (0.03)*#	0.35 (0.03)*#	0.36 (0.03)*#	0.35 (0.03)*#	0.34 (0.03)*#
	LEU	0.35 (0.03)*	0.33 (0.03)*	0.32 (0.03)*	0.34 (0.02)*	0.33 (0.02)*	0.31 (0.02)*
Day 90	Placebo	0.30 (0.02)	0.29 (0.02)	0.28 (0.02)	0.29 (0.02)	0.28 (0.02)	0.27 (0.02)
	LE	0.36 (0.03)*	0.35 (0.03)*	0.34 (0.03)*	0.35 (0.02)*	0.34 (0.02)*	0.33 (0.02)*
	LETOS	0.40 (0.03)*#	0.39 (0.03)*#	0.38 (0.03)*#	0.39 (0.03)*#	0.38 (0.03)*#	0.37 (0.03)*#
	LEU	0.36 (0.03)*	0.35 (0.03)*	0.34 (0.03)*	0.36 (0.02)*	0.35 (0.02)*	0.33 (0.02)*

Each value represents mean (SD) of 32 subjects in each group at baseline and mean (SD) of 32 subjects in the placebo group and mean (SD) of 31 subjects each in the lutein ester groups from visit 2 till the end of the study. *p < 0.0001 compared to placebo group at respective retinal positions, #p < 0.0001 compared to the LE and LEU groups at respective retinal positions, 0.25R: 0.25-degree angle from the center of the fovea in the right eye, 0.5R: 0.5-degree angle from the center of the fovea in the right eye, 1R: 1-degree angle from the center of the fovea in the right eye, 0.25L: 0.25-degree angle from the center of the fovea in the left eye, 0.5L: 0.5-degree angle from the center of the fovea in the left eye, 1L: 1-degree angle from the center of the fovea in the left eye, LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group.

3.4. Visual Processing Speed

In the PP analysis, at baseline, the mean (SD) visual processing speed values were comparable across all groups, ranging from 34.73 (0.53) to 34.98 (0.36), indicating no statistically significant differences. Over the course of the study, a gradual numerical improvement in visual processing speed was observed in all groups, including the placebo, from baseline to Day 90. On Day 60, the LE group demonstrated a statistically significant ($p < 0.05$) improvement in visual processing speed compared with the LETOS group, as indicated by a higher mean value [35.82 (1.32) vs 35.31 (1.05)]. No other between-group comparisons showed statistically significant differences at any time point. At Day 90, all active test item groups (LE, LETOS, and LEU) and the placebo group exhibited slight increases from baseline, with mean values ranging from 35.43 (0.33) to 35.56 (0.38), suggesting an overall trend toward improvement over time (Table 3).

Table 3. Effect on Visual Processing Speed

Groups	Baseline	Day 15	Day 30	Day 60	Day 90
Placebo	34.98 (0.36)	34.69 (0.37)	34.84 (0.48)	35.68 (1.27)	35.43 (0.33)
LE	34.73 (0.53)	34.68 (0.39)	34.89 (0.58)	35.82 (1.32)*	35.51 (0.36)
LETOS	34.87 (0.47)	34.68 (0.47)	34.62 (0.40)	35.31 (1.05)	35.56 (0.38)
LEU	34.95 (0.36)	34.76 (0.36)	34.82 (0.44)	35.69 (0.99)	35.48 (0.38)

LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group. *$p <$ 0.05 – LE versus LETOS.

3.5. Contrast Sensitivity (Pelli-Robson chart)

In the PP analysis, contrast sensitivity (CS) values at baseline were comparable across all groups in both eyes. From Day 30 onward, all lutein ester test items demonstrated significantly ($p < 0.05$) greater improvements in CS than placebo. A similar trend was noted in the left eye, where LE showed significant improvements at Days 60 and 90 ($p < 0.05$), and LETOS and LEU showed highly significant improvements from Day 30 through Day 90 ($p < 0.01$). At Day 90, the highest mean CS was recorded in the LETOS group 1.50 (0.22) in the right eye and 1.56 (0.24) in the left eye), indicating superior visual performance compared with placebo. No significant ($p > 0.05$) differences were found between the lutein ester groups (Table 4).

Table 4. Effect on Contrast Sensitivity

Groups	Baseline	Day 15	Day 30	Day 60	Day 90
Right eye					
Placebo	0.89 (0.19)	0.99 (0.14)	1.02 (0.15)	1.10 (0.23)	1.23 (0.23)
LE	0.86 (0.13)	1.05 (0.14)	1.13 (0.17)*	1.24 (0.22)**	1.37 (0.13)**

LETOS	0.90 (0.23)	1.10 (0.22)	1.21 (0.25)**	1.32 (0.31)**	1.50 (0.22)**
LEU	0.87 (0.19)	1.10 (0.26)	1.15 (0.27)**	1.21 (0.23)**	1.41 (0.16)**
Left eye					
Placebo	1.08 (0.28)	1.18 (0.20)	1.19 (0.16)	1.22 (0.21)	1.30 (0.19)
LE	1.02 (0.30)	1.20 (0.17)	1.27 (0.19)	1.38 (0.24)*	1.48 (0.12)*
LETOS	1.13 (0.30)	1.25 (0.23)	1.36 (0.25)**	1.43 (0.31)**	1.56 (0.24)**
LEU	1.07 (0.32)	1.27 (0.26)	1.31 (0.23)**	1.38 (0.24)**	1.49 (0.18)**

*$p < 0.05$ significant compared with placebo; **$p < 0.01$ significant compared with placebo; LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group.

3.6. Intraocular Pressure

In the PP analysis, mean (SD) intraocular pressure (IOP) values at baseline were comparable across all groups in both eyes, ranging from 14.45 (1.26) to 14.81 (1.11) mmHg. Throughout the study period, minor fluctuations in IOP were observed within each group at subsequent visits (Days 15, 30, 60, and 90); however, none of these changes reached statistical significance either within or between groups. In the right eye, mean IOP values remained stable, ranging from 12.75 (0.92) mmHg to 14.58 (0.85) mmHg across visits, with no consistent trend suggesting supplement-related effects. Similar findings were noted in the left eye, where IOP values ranged from 12.77 (0.99) mmHg to 14.81 (0.83) mmHg (Table 5). Overall, supplementation with the current lutein ester products (LE, LETOS, and LEU) did not produce any statistically significant change in intraocular pressure compared with placebo, indicating that all interventions were well tolerated with respect to ocular pressure. .

Table 5. Effect on Intraocular Pressure

Groups	Baseline	Day 15	Day 30	Day 60	Day 90
Right eye					
Placebo	14.53 (1.52)	12.75 (0.92)	13.25 (1.02)	13.31 (1.26)	14.22 (0.79)
LE	14.55 (1.09)	13.00 (1.24)	13.48 (1.26)	13.23 (0.96)	14.52 (0.63)
LETOS	14.45 (1.26)	13.26 (1.18)	13.68 (1.01)	13.42 (1.23)	14.58 (0.85)
LEU	14.52 (1.09)	12.94 (1.24)	13.39 (1.20)	13.10 (1.19)	14.45 (0.72)
Left eye					
Placebo	14.75 (1.11)	13.28 (1.30)	13.63 (1.04)	13.66 (1.29)	14.56 (0.84)
LE	14.58 (1.12)	13.13 (1.28)	13.68 (1.25)	14.16 (1.39)	14.77 (0.56)
LETOS	14.74 (1.39)	13.52 (1.46)	13.74 (1.21)	14.03 (1.14)	14.81 (0.83)
LEU	14.81 (1.11)	12.77 (0.99)	13.48 (1.03)	13.71 (1.19)	14.71 (0.64)

Each value represents Mean (SD); LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group.

3.7. Dry Eye (Schirmer's strip test)

Schirmer's strip test results demonstrated a progressive increase in tear production from the baseline over the 90-day intervention period in in both eyes across all study groups, including placebo, LE, LETOS, and LEU. Baseline Schirmer values were comparable across groups for both eyes. In the placebo group, mean (SD) Schirmer values of the right eye increased from

11.72 (1.61) mm at baseline to 14.78 (0.71) mm at Day 90. At Day 90, the mean (SD) Schirmer scores reached 15.06 (0.51) mm in the LE group, 15.19 (0.60) mm in the LETOS group, and 14.90 (0.70) mm in the LEU group, compared with 14.78 (0.71) mm in the placebo group. A similar pattern was observed in the left eye. The placebo group showed an increase from 12.09 (1.65) mm at baseline to 15.13 (0.61) mm at Day 90, whereas the LE, LETOS, and LEU groups increased to 15.29 mm (0.59),

15.26 (0.58) mm, and 15.06 (0.73) mm, respectively (Table 6). Overall, there were no statistically significant differences between the placebo and lutein ester product groups at any visit, indicating that the reduction in dry eye symptoms was comparable across all groups and may reflect a general improvement over time rather than a supplementation-specific effect.

Table 6. Effect on Dry Eye Symptoms

Groups	Baseline	Day 15	Day 30	Day 60	Day 90
Right eye					
Placebo	11.72 (1.61)	12.97 (1.58)	13.66 (1.33)	13.88 (1.13)	14.78 (0.71)
LE	11.65 (1.14)	12.74 (1.39)	13.32 (1.05)	13.81 (1.11)	15.06 (0.51)
LETOS	12.00 (1.73)	12.65 (1.60)	13.13 (1.23)	13.45 (1.31)	15.19 (0.60)
LEU	12.00 (1.48)	12.74 (1.32)	13.23 (1.15)	13.65 (1.05)	14.90 (0.70)
Left eye					
Placebo	12.09 (1.65)	13.41 (1.52)	13.91 (1.12)	14.34 (0.94)	15.13 (0.61)
LE	12.10 (1.49)	13.19 (1.35)	13.68 (1.08)	14.10 (1.14)	15.29 (0.59)
LETOS	12.23 (1.50)	12.94 (1.61)	13.48 (1.29)	13.71 (1.57)	15.26 (0.58)
LEU	12.55 (1.77)	13.23 (1.61)	13.65 (1.17)	13.90 (1.01)	15.06 (0.73)

Each value represents Mean (SD); LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group.

3.8. Acceptability of Lutein Ester Formulations

Both participant and physician assessments indicated higher acceptability for the lutein ester test items compared with placebo. At the end of the study, participant-rated acceptability was markedly higher in all active test item groups (LE, LETOS, and LEU) than in the placebo group. Among participants, "acceptable" or "perfectly acceptable" ratings were reported by 70.96% in the LE group, 48.39% in the LETOS group, and 74.19% in the LEU group, compared with only 18.75% in the placebo group. In contrast, "slightly unacceptable" and "unacceptable" responses were predominantly observed in the placebo group (65.63%), while such ratings were minimal or absent in the active supplementation groups. Physician evaluations similarly reflected greater acceptability of the active test items. The proportion of "acceptable" ratings increased from 21.88% in the placebo group to 45.16%, 61.29%, and 83.87% in the LE, LETOS, and LEU groups, respectively. "Unacceptable" ratings were reported by 78.12% of physicians for the placebo group but were nearly absent for the active test items (Table 7). Overall, both participants and physicians rated the lutein ester formulations suggesting superior tolerability, and overall user satisfaction with the active interventions.

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Table 7. Acceptability

Parameter	Placebo (N=32)	LE (N=31)	LETOS (N=31)	LEU (N=31)
Participant assessment				
Acceptable	6 (18.75%)	16 (51.61%)	13 (41.94%)	16 (51.61%)
Neutral	3 (9.38%)	3 (9.68%)	4 (12.90%)	0 (0.00%)
Perfectly acceptable	0 (0.00%)	6 (19.35%)	2 (6.45%)	7 (22.58%)
Slightly acceptable	2 (6.25%)	4 (12.90%)	8 (25.81%)	5 (16.13%)
Slightly unacceptable	15 (46.88%)	2 (6.45%)	4 (12.90%)	3 (9.68%)
Unacceptable	6 (18.75%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Physician assessment				
Acceptable	7 (21.88%)	14 (45.16%)	19 (61.29%)	26 (83.87%)
Neutral	0 (0.00%)	1 (3.23%)	2 (6.45%)	0 (0.00%)
Slightly acceptable	0 (0.00%)	15 (48.39%)	10 (32.26%)	5 (16.13%)
Unacceptable	25 (78.12%)	1 (3.23%)	0 (0.00%)	0 (0.00%)

Each value represents number (%) of subjects; LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group.

3.9 Serum Lutein concentrations

Serum lutein concentrations on Day 15 were compared among the four groups using ANOVA. Although mean values differed numerically, the between-group difference was not statistically significant ($p = 0.102$; Table 8). Because serum lutein was measured only on Day 15, this exploratory analysis does not characterize the full pharmacokinetic response over the 90-day intervention.

Table 8. Serum Lutein concentrations on Day 15

Category	Statistics	Placebo (N=32)	LEU (N=31)	LE (N=31)	LETOS (N=31)	P value
Lutein (ng/mL)	- N	32	31	31	31	0.102
	- Mean (SD)	150.41 (45.61)	137.45 (36.95)	158.91 (58.00)	172.37 (76.60)	
	- Median	141.71	131.89	155.92	158.48	
	- Minimum	79.45	81.06	51.01	86.16	
	- Maximum	268.54	238.3	278.12	458.46	

3.10. Safety of Lutein Ester Formulations

No adverse events were reported during the study. Vital signs remained within clinically acceptable ranges across groups. Hematological parameters showed no clinically meaningful treatment-related changes from baseline to Day 90 (Table 9).

Table 9. Hematology

Parameter	Visit	Placebo (N=32)	LE (N=32)	LETOS (N=32)	LEU (N=32)
Red blood count	Baseline	5.08 (0.51)	5.28 (0.47)	5.12 (0.42)	5.09 (0.34)
($\times 10^6$/L)	Day 90	5.13 (0.46)	5.26 (0.43)	5.15 (0.43)	5.14 (0.33)
Total Leukocyte	Baseline	6.82 (1.17)	6.91 (1.60)	7.33 (1.53)	7.26 (1.67)
count ($\times 10^3$/μL)	Day 90	6.59 (1.06)	6.48 (1.24)	6.66 (1.22)	6.83 (1.18)
Neutrophils (%)	Baseline	55.16 (7.44)	54.90 (10.02)	56.23 (9.13)	55.24 (9.60)
	Day 90	55.89 (9.14)	58.20 (8.82)	54.96 (9.06)	56.97 (8.19)
Eosinophils (%)	Baseline	3.33 (2.39)	3.68 (3.03)	3.24 (2.01)	3.23 (2.11)
	Day 90	4.93 (5.14)	4.81 (5.27)	5.91 (5.66)	4.70 (5.14)
Basophils (%)	Baseline	0.84 (0.49)	0.95 (0.37)	0.97 (0.41)	1.01 (0.48)
	Day 90	0.74 (0.61)	0.57 (0.39)	0.77 (0.52)	0.79 (0.66)
Monocytes (%)	Baseline	7.03 (2.35)	7.96 (1.65)	7.88 (1.72)	7.10 (2.07)
	Day 90	7.85 (1.75)	6.96 (1.71)	7.54 (1.74)	7.76 (1.85)
	Baseline	32.15 (8.54)	32.53 (8.85)	31.74 (8.38)	32.74 (9.18)
Lymphocytes (%)	Day 90	30.62 (6.33)	29.40 (5.99)	30.84 (6.33)	29.92 (5.70)
Platelets	Baseline	300.09 (60.95)	297.58 (69.95)	288.20 (64.79)	306.49 (56.87)
($\times 10^3$/μL)	Day 90	269.88 (77.47)	280.29 (56.14)	254.55 (79.66)	267.87 (56.93)
Hemoglobin	Baseline	14.65 (1.17)	14.43 (1.18)	14.60 (1.22)	14.29 (1.19)
(g/dL)	Day 90	14.65 (1.15)	14.49 (1.07)	14.36 (1.22)	14.46 (1.27)
Hematocrit	Baseline	47.17 (3.59)	47.62 (4.74)	47.38 (3.95)	46.74 (4.04)
(%)	Day 90	45.54 (3.80)	45.03 (3.77)	45.11 (3.88)	46.13 (3.42)

Each value represents Mean (SD); LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group.

Blood biochemical parameters remained within clinically acceptable ranges during the study, with no clinically meaningful treatment-related differences identified between placebo and the active groups from baseline to Day 90 (Table 10).

Table 10. Blood Biochemistry

Parameter	Visit	Placebo (N=32)	LE (N=32)	LETOS (N=32)	LEU (N=32)
AST	Baseline	26.16 (6.47)	28.03 (5.69)	25.44 (5.97)	26.91 (5.67)
(U/L)	Day 90	25.94 (4.25)	27.74 (5.32)	26.84 (4.37)	26.87 (4.72)
ALT	Baseline	30.06 (9.23)	30.06 (11.95)	28.06 (9.85)	29.69 (11.41)
(U/L)	Day 90	31.16 (7.33)	31.90 (10.48)	28.65 (8.99)	30.52 (7.40)
GTP	Baseline	31.66 (11.01)	32.97 (13.82)	34.44 (13.44)	32.91 (12.37)
	Day 90	32.09 (9.88)	33.03 (11.68)	33.35 (10.10)	32.90 (11.02)
ALP	Baseline	85.88 (20.39)	86.06 (22.79)	83.12 (19.83)	84.84 (25.84)
(U/L)	Day 90	89.59 (14.94)	88.97 (19.32)	90.23 (20.95)	88.58 (24.25)
Total bilirubin	Baseline	0.83 (0.21)	0.77 (0.24)	0.79 (0.23)	0.80 (0.24)
(mg/Dl)	Day 90	0.86 (0.20)	0.81 (0.19)	0.76 (0.21)	0.77 (0.19)
Total	Baseline	179.03 (34.51)	184.81 (33.24)	182.88 (35.70)	184.06 (40.76)
cholesterol	Day 90	182.66 (25.77)	186.03 (22.77)	183.65 (25.22)	181.97 (26.39)
(mg/dL)					
Triglycerides	Baseline	114.34 (31.15)	119.81 (25.89)	125.03 (30.11)	136.94 (28.92)
(mg/dL)	Day 90	117.16 (27.00)	119.19 (19.42)	125.45 (23.92)	135.29 (25.89)
HDL-C	Baseline	41.25 (5.15)	40.31 (3.71)	41.75 (6.34)	40.12 (3.14)
(mg/dL)	Day 90	42.62 (6.20)	41.68 (4.48)	41.87 (5.12)	42.06 (4.36)
LDL-C	Baseline	105.50 (16.10)	112.16 (19.21)	113.56 (15.67)	107.91 (15.91)
(mg/dL)	Day 90	105.19 (14.17)	110.39 (16.73)	109.58 (17.29)	106.74 (16.95)
BUN	Baseline	11.39 (2.47)	12.24 (3.00)	12.87 (2.92)	11.79 (2.79)
(mg/Dl)	Day 90	11.53 (1.96)	12.44 (2.77)	12.65 (2.59)	11.75 (2.14)
Serum	Baseline	0.89 (0.15)	0.96 (0.12)	0.95 (0.14)	0.93 (0.22)
creatinine (mg/dL)	Day 90	0.92 (0.16)	0.90 (0.14)	0.97 (0.13)	0.91 (0.17)
Glucose	Baseline	93.38 (20.93)	95.38 (23.77)	85.31 (15.30)	87.59 (13.11)
(mg/dL)	Day 90	92.45 (15.38)	95.94 (15.71)	88.97 (14.81)	86.90 (12.45)
Uric acid	Baseline	5.56 (1.12)	5.55 (0.90)	5.32 (1.02)	5.28 (1.15)
(mg/dL)	Day 90	5.55 (1.53)	6.01 (1.28)	5.46 (1.05)	5.76 (1.41)
Albumin	Baseline	4.70 (0.43)	4.80 (0.32)	4.83 (0.37)	4.84 (0.29)
(mg/dL)	Day 90	4.52 (0.23)	4.62 (0.32)	4.49 (0.62)	4.61 (0.24)

Each value represents Mean (SD); LE: Lutein ester group, LETOS: A true oil solution of lutein ester group, LEU: Lutein ester in emulsifiable form group.

Urinalysis findings remained clinically unremarkable across groups from baseline to Day 90.

4. DISCUSSION

This randomized, double-blind, placebo-controlled trial compared three lutein ester delivery formats over 90 days in healthy adults with relatively low baseline MPOD. All active groups showed greater MPOD improvement than placebo from Day 30 onward, and contrast sensitivity improved in the lutein ester groups. These findings are consistent with previous randomized trials and meta-analyses showing that lutein supplementation can increase macular pigment and improve selected aspects of visual function [18–22]. The present study extends that literature by directly comparing three SCFE-based lutein ester formulations under the same protocol.

LETOS showed the largest observed MPOD response among the active groups. A lipid-based true oil solution may plausibly facilitate carotenoid dispersion and micelle formation, and dietary lipids have been reported to enhance carotenoid absorption [8,10,23–25]. However, the formulation comparison should be interpreted cautiously because LE and LETOS provided lutein ester doses equivalent to 20 mg free lutein, whereas LEU provided an equivalent of 10 mg free lutein. The study was therefore not designed as a dose-equivalent head-to-head bioavailability trial, and the observed differences cannot be attributed solely to formulation technology.

Visual processing speed did not show a consistent treatment-specific benefit despite increases in MPOD. This outcome is influenced by several neural and cognitive factors and may require a longer intervention, larger sample size, or a more sensitive testing paradigm to detect small changes [13,26]. Schirmer test values increased across both active and placebo groups, suggesting that the observed dry-eye changes were not specific to lutein ester supplementation.

Serum lutein concentration was assessed only on Day 15 and did not differ significantly among groups. A single early measurement is insufficient to characterize systemic exposure or to link serum kinetics with retinal deposition. Serial pharmacokinetic sampling would be needed to test whether the formulations differ in absorption and whether those differences mediate subsequent MPOD responses.

No adverse events were reported, and no clinically meaningful treatment-related changes were identified in vital signs, hematology, blood chemistry, or urinalysis over 90 days. These observations are consistent with the established tolerability of lutein-containing supplements at commonly studied doses [13,27].

Strengths of the study include randomized allocation, double blinding, a placebo control, repeated MPOD measurements at multiple retinal eccentricities, and concurrent assessment of functional visual outcomes and laboratory safety. Use of repeated assessments allowed the temporal pattern of MPOD response to be described across the 90-day intervention.

Several limitations should be considered. First, the 90-day duration does not establish the longer-term plateau or persistence of macular carotenoid accumulation. Second, serum lutein was measured only on Day 15, preventing pharmacokinetic interpretation. Third, the study was powered primarily for MPOD and may have been underpowered for smaller differences in secondary outcomes such as visual processing speed. Fourth, the statistical analysis involved multiple retinal locations, time points, and pairwise comparisons; because a comprehensive multiplicity-adjustment procedure was not prespecified for all analyses, secondary p-values should be interpreted as exploratory. Fifth, only six participants were women, which limits generalizability to women and precludes meaningful sex-specific analysis. Finally, despite randomization, baseline weight and BMI differed across groups; these imbalances should be considered when interpreting between-group findings. Although the 90-day intervention period was adequate to demonstrate early increases in MPOD and associated functional changes, macular carotenoid kinetics indicate that progressive accumulation may continue beyond this timeframe. Longer supplementation periods (6–12 months), as reported in previous trials [28,29], would allow better characterization of steady-state retinal incorporation and temporal stability of visual function effects.

Our results support the use of lutein ester supplementation to increase MPOD and improve contrast sensitivity in healthy adults, with LETOS demonstrating particularly favorable performance. MPOD increase in LEU (at a dose equivalent to 10mg of free lutein) group also is quite significant (31.11% after 90 days) which is comparable that of free Lutein (10mg) and 5:1 ratio of lutein (10mg) and zeaxanthin (2mg) isomers [30,13].

Future studies should use dose-matched formulations, longer supplementation periods, and serial serum lutein measurements to directly relate systemic exposure to retinal deposition. Pharmacokinetic profiling would help determine whether the larger observed MPOD response with LETOS reflects formulation-dependent bioavailability. Larger and more sex-balanced cohorts

are also needed, including populations with low MPOD, high myopia, or early retinal disease, in whom the clinical relevance of improved MPOD and contrast sensitivity may be greater. Studies should additionally prespecify multiplicity control and clinically meaningful thresholds for functional outcomes.

5. CONCLUSION

Ninety days of supplementation with the three tested lutein ester formulations increased MPOD and improved contrast sensitivity compared with placebo in healthy adults with relatively low baseline MPOD. LETOS showed the largest observed MPOD improvement among the active formulations; however, this comparison should be interpreted cautiously because the lutein-equivalent dose differed for LEU. No clinically meaningful safety concerns were identified during the study. These findings support further dose-matched and longer-term studies to determine whether formulation-dependent differences in MPOD translate into sustained functional visual benefits.

DECLARATIONS

Ethics approval and consent to participate

The study protocol, informed consent form, and all associated documents were approved by the ACE Independent Ethics Committee and Vagus Institutional Ethics Committee prior to study initiation. Written informed consent was obtained from all participants prior to the initiation of any study-related procedures. Eligibility screening was conducted only after informed consent had been provided. The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guideline (ICH-GCP E6 R2), the Declaration of Helsinki, and applicable Indian Council of Medical Research ethical guidelines. The trial was prospectively registered with the Clinical Trials Registry–India on 30 November 2023 (CTRI/2023/11/060356).

Consent for publication

Not Applicable.

Availability of data and materials

The original contributions presented in this study are included in this article. Further inquiries can be directed to the corresponding author(s).

Competing interests

The authors declare that they have no competing interests related to this work. The sponsor participated in study design and manuscript preparation but did not influence the interpretation of the results or the decision to publish.

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