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# Safety and Efficacy study of Lutein (VitaLutein®) in healthy Japanese adults: A randomized, placebo-controlled, double-blind, parallel-group comparative study

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**ABSTRACT**

**Background:** Lutein is a natural pigment with antioxidant properties found in both the eye's lens and macula. Daily exposure to certain wavelengths of light -- particularly blue and infrared – can increase the eyes' vulnerability to oxidative damage caused by free radicals. However, lutein's antioxidant properties help protect cells from oxidative damage.

**Objective:** This study aimed to evaluate the reduction of oxidative stress in tears resulting from daily intake of VitaLutein®, within healthy Japanese adults. The safety of oral VitaLutein® intake was also assessed.

**Methods:** A randomized, placebo-controlled, double-blind, parallel-group study was conducted. Thirty-one healthy Japanese adults were randomized to either the placebo or VitaLutein® group. Participants were enrolled based on levels of 8-hydroxydeoxyguanosine (8-OHdG) in their tears. Fifteen adults were assigned to the VitaLutein® group and sixteen to the placebo group. After 8-weeks, all subjects were evaluated for oxidative stress, macular pigment optical density,

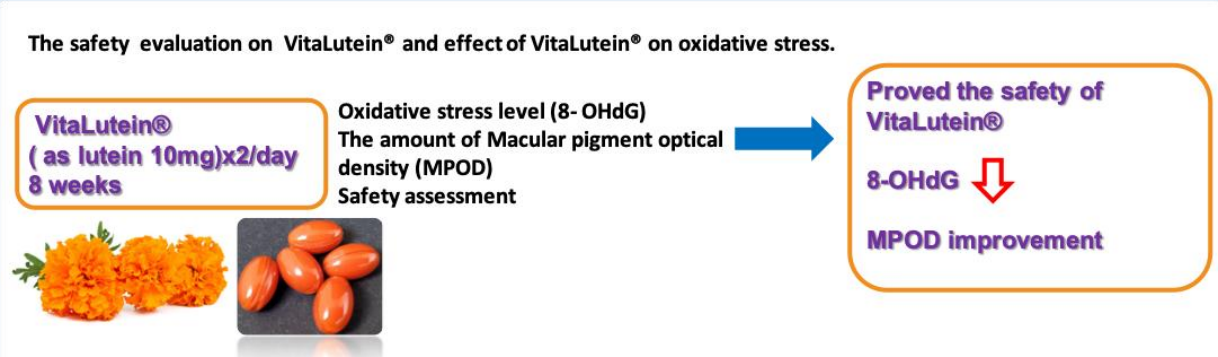
and dry eye symptoms. Safety assessments included urinalysis and blood tests.

**Results:** No adverse events were attributed to the test food during the study period. Levels of 8-OHdG were significantly reduced at week 8 compared to baseline in the VitaLutein® group. Additionally, participants with prolonged Visual Display Terminal (VDT) use maintained higher Macular Pigment Optical Density (MPOD) levels compared to the placebo group.

**Novelty:** This randomized controlled trial uniquely demonstrates the safety of VitaLutein® supplementation in healthy Japanese adults. This study provides preliminary evidence suggesting its potential to reduce tear oxidative stress (8-OHdG) and maintain macular pigment optical density (MPOD), particularly in individuals with prolonged extended VDT usage.

**Conclusions:** These results suggest that continuous ingestion of VitaLutein® supplements may reduce oxidative stress and maintain macular pigment. The product has also been proven safe in adult, human subjects.

**Key words:** VitaLutein®, Oxidative Stress, 8-hydroxy-2-deoxyguanosine(8-OHdG), Visual Display Terminal (VDT), macular pigment density (MPOD).(UMIN ID: UMIN000014590)




**Graphical abstract:** VitaLutein® supplements could be involved in the reduction of oxidative stress and maintenance of macular pigment.



## INTRODUCTION

Lutein is a xanthophyll, which is a type of carotenoid that contains many antioxidant properties that humans may obtain from their diet. Foods high in these properties include dark green and yellow vegetables. Therefore, xanthophyll is considered a bioactive compound in various foods [1]. Lutein acts as an antioxidant and protects plants from the damage of photo-induced free radicals [2] and improve eye health. These effects are due to its chemical structure, including nine conjugated double bonds in the polyene chain and high absorptivity in terms of blue light. Thus, it can act as an effective blue light filter for the retina [1,3]. The marigold flower (*Tagetes erecta*), a well-known natural source of lutein, contains approximately 3.7 to 5.7 times more lutein than many green leafy vegetables. In addition to its high lutein content, marigold can be utilized as a coloring agent, dietary supplement, beverage enhancer, and functional food ingredient [4–9]. The eyes are particularly susceptible to the damage caused by active oxygen

through everyday light exposure, notably blue and ultraviolet visuals [10]. Still, when there is a risk of oxidative damage to eye (photoreceptor) cells from excess light absorption, the antioxidant properties of lutein may prevent this occurrence [11]. Lutein also increases macular pigment density (MPOD), which is essential for a healthy macula and retina. This product is expected to be effective against age-related eye diseases such as macular degeneration and cataracts [7,12-13].

Functional foods (FFs) are defined as food products that provide health or therapeutic benefits beyond basic nutritional value. They support disease prevention and management through dietary interventions and are now widely adopted and marketed internationally [14]. A foundational step in functional food science is the identification of bioactive compounds—naturally occurring substances with proven health-promoting properties. These compounds, sourced from plants, include mushrooms and animal-derived materials, all of which provide a biochemical and therapeutic basis for functional foods [15].

Despite growing global interest, regulatory standards and the scientific criteria used to validate the efficacy of functional foods varies between countries, leading to public confusion. To address this, the Functional Food Center (FFC) has introduced a standardized and transparent framework for the development and evaluation of functional foods [16–18].

In Japan, the Foods with Function Claims system allows products to be labeled with functional claims based on supporting scientific evidence, provided under the responsibility of the food business operator. Importantly, such products do not require individual pre-approval by the Consumer Affairs Agency [19]. Within the Functional Food Center's classification system, these are considered Class C functional foods.

Traditionally, the safety of health foods was assumed based on historical consumption data. However, with increased awareness of potential health risks, there has been a shift toward formal safety assessments, often through clinical trials, to ensure consumer protection [20–22].

In this context, a randomized, placebo-controlled, double-blind, parallel-group clinical trial in healthy Japanese adults was conducted to evaluate the safety and efficacy of VitaLutein®. The study focused specifically on its potential to reduce oxidative stress in tear fluid.

## METHOD

**Study design:** This randomized, double-blind, placebo-controlled, parallel-group clinical trial aimed to assess the safety and effectiveness of VitaLutein® supplementation over 8-weeks in healthy Japanese adults, aged 30 to 49, who reported experiencing symptoms of dry eyes. An overview of the study design is presented in Figure 1.

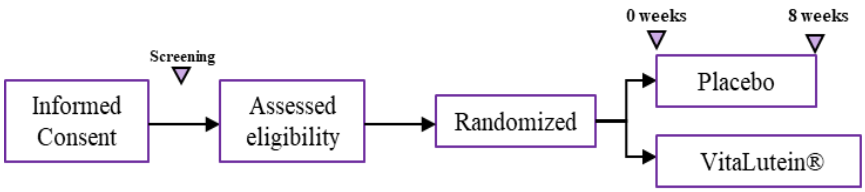



**Figure 1.** The outline of the study design.

**Subject and method:** This study was performed in by the Declaration of Helsinki (adopted 1964, amended 2008, added 2004) and was approved by the Ethics Committee (Approval number: 1407-1406-BJ02-01-TC) of Takara Medical Clinic, Japan, and registered for a clinical trial on the University Hospital Medical Information Network Clinical Trial Registry (UMIN000014590). Informed consent was obtained from all participants, and the

protection of the rights of the participants was considered.

***Participants:*** In this study, the participants were healthy adults who met the inclusion criteria, and did not meet any exclusion criteria.

Participants were eligible for inclusion if they were healthy Japanese males or females between the ages of 30 and 49, self-reported symptoms of dry eyes, and engaged in visual display terminal (VDT) activities. These activities included: using a computer or playing video games for more than 4 hours per day. Additional inclusion criteria required that participants did not routinely use blue light blocking glasses or screens, had a corrected visual acuity of 1.0 or higher in both eyes, and did not wear contact lenses.

**Exclusion criteria included:**

1. A history of severe medical conditions such as malignant tumors, heart failure, or myocardial infarction;
2. Current treatment for any of the following: atrial fibrillation, cardiac arrhythmias, liver or kidney disorders, cerebrovascular disease, rheumatologic conditions, diabetes, dyslipidemia, hypertension, or other chronic illnesses;
3. The presence of eye diseases such as entropion or trichiasis;
4. Untreated or improperly managed ametropia;
5. Significant astigmatism;
6. Color vision deficiency (achromatopsia);
7. Previous LASIK surgery;
8. Regular alcohol intake exceeding 100 grams per week or other causes of eye fatigue unrelated to neurological or regulatory dysfunctions;
9. Current use of medications or herbal supplements;
10. Known allergies to any components or related materials used in the study;
11. Participation in another clinical trial within the last three months;
12. Pregnancy, breastfeeding, or intention to become pregnant during the study period;
13. Any condition deemed by the study physician to make the individual unsuitable for participation.

All participants received a full explanation of the study protocol, provided by the principal investigator, along with written informed consent prior to enrollment. Medical monitoring, data collection, and health assessments were conducted by Nishi-Arai Ekimae Clinic Ophthalmology and Orthopedics and Takara Medical Clinic in Tokyo, Japan.

**Selection, Randomization, and Blinding**

Out of the 47 individuals who signed the consent form, 32 were deemed eligible for participation by the study physician, while one individual withdrew from the study. Enrollment was based on the following selection criteria:

1. Determination of eligibility by the principal investigator;
2. Elevated levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in tear fluid;
3. Receive a comprehensive explanation of the study's purpose and procedures, followed by signed informed consent.

The test foods were supplied by Bio Actives Japan Corporation (Tokyo, Japan) to the contract research organization Orthomedico Inc. Participants were randomly assigned to treatment groups that accounted for gender, age, and baseline data collected during the screening and pre-intervention (week 0) assessments to minimize potential confounders.

Randomization was completed by a designated allocation officer, who sealed the allocation form and the participant assignment list. The documents and sealed records of the test product were stored securely in a locked facility. The allocation table remained inaccessible until blinding was no longer necessary.

**Intervention**: Participants were instructed to take one

capsule twice daily—once before breakfast and once before dinner—for eight weeks. Depending on group assignment, they received either an active capsule (containing 10 mg of lutein under the brand name *VitaLutein®*) or a placebo capsule (containing only inactive excipients) to be taken with water.

**Outcome Assessment:** The primary outcome measures and safety evaluations were conducted at two time points:

- During the screening phase (before starting supplementation)
- After the eight-week intervention period

(1) Primary outcome: The Oxidative stress level, pigment amount of macula lutea, and dry eye evaluation were evaluated during pre-intake propanoyl lysine, and after 8 weeks of treatment.

1) The Oxidative stress level: Tears of both eyes were collected on the paper strips used for Schirmer's test and quantified for 8-OHdG and propanoyl lysine (PRL). 8-OHdG and PRL were measured at Healthcare Systems Co., Ltd. for chemical emission detection equipment (Aisin Seiki Co., Ltd.) with the antibody chip method [23].

1) Pigment amount of macula lutea: The amount of Macular pigment optical density (MPOD) was quantified using the macular pigment screener MPS2 (M.E. Technica). The photo absorption peak of lutein is 460nm, and the zeaxanthin peak is slightly longer than that. MPS2 is an instrument that uses 465 nm and 518 nm light to measure coloring densities in the 0.5 degree region from the central fovea to help diagnostics and assess the effectiveness of treatments for macular diseases and the measurement principle measures the transparency of light and calculates the optical density (MPOD) of the macular coloring [24].

2) Dry eye evaluation (Schirmer's test): Tear secretion was measured by hanging a long Schirmer's test strip (5 mm wide) on the lower eyelid for 5 minutes and measuring the length of the paper that is wet with tears.

(2) Safety assessment: Safety evaluations were assessed by physical examination (height, weight, temperature, Body Mass Index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and Heart rate (HR)), urinalysis (levels of protein, glucose, urobilinogen, bilirubin, ketone bodies, pH, and occult blood) and hematological tests (blood biochemistry test (white blood cell count(WBC), red blood cell count (RBC), hemoglobin(Hb), hematocrit value (Ht), platelet count (Plt), neutrophil count (Neut), neutrophil rate (Neut-R), lymphocyte ratio (Lymph), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP) , alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (T-Bil), direct bilirubin (D-Bil), indirect bilirubin (I-BIL), Cholinesterase (ChE), ZTT, total protein (TP), urea nitrogen (BUN), creatinine (Cre), creatine kinase (CK),Na, K, Cl, Ca, total cholesterol (T-cho), High-density lipoprotein (HDL), Low-density lipoprotein (LDL), triglyceride (TG).

**Statistical analysis:** Statistical analysis was conducted as two-sided tests with a 5% significance level. A significance level of less than 5% ($p < 0.05$) in the two-sided test is concluded to be a significant difference. 5% to less than 10% ($p < 0.10$) is a tendency present. The results of the experiments were tabulated as mean ± standard deviation, using Microsoft Excel 2007 and IBM SPSS ver. 18.0. The subgroup analysis was performed for participants who work relatively long hours per day on

VDT.

## RESULTS

**Study Flow and Participant Characteristics.** Figure 2 illustrates the progression of the clinical trial, outlining the screening, selection, and randomization process. A total of 32 qualified participants were enrolled and randomly allocated to either the placebo group or the VitaLutein® intervention group. One subject in VitaLutein® group did not participate in the study due to personal reasons. Table 1 provides a summary of baseline characteristics for both groups. No statistically significant differences were observed between the groups at the start of the study.

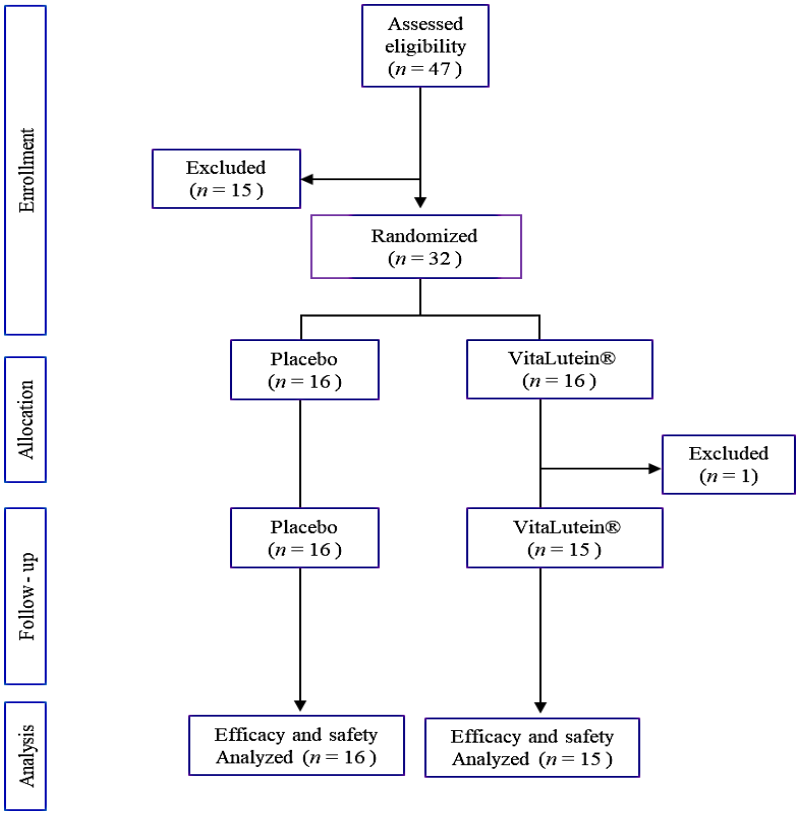



**Figure 2**. The flowchart of participation

**Table 1.** Participants' background information.

| | Placebo Group | VitaLutein® Group |
|---|---|---|
| **Age (years)** | 40.2±6.3 | 41.6±5.8 |
| **Sex (M/F)** | 4/12 | 4/11 |
| **Hight (cm)** | 161.1±6.7 | 163.8±7.2 |
| **Body Weight (kg)** | 57.8±16.4 | 55.8±11.7 |
| **BMI (kg/m2)** | 22.0±4.9 | 20.6±2.8 |

Mean±SD

**Oxidative stress level:** Table 2 illustrates the oxidative stress level result. There was no statistical difference between groups. In the VitaLutein® group, 8-OHdG improved significantly compared to before intake. In the VitaLutein® group, PRL was significantly higher than before intake.

**Table 2.** Oxidative stress level.

| | Unit | | 0 weeks | | | | 8 weeks | | | | Compared to 0 weeks (%) | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mean | SD | P value | | Mean | SD | P value | | | |
| **8-OHdG** | ng/mg・protein | VitaLutein® (*n*=15) | 6.12 | 4.09 | 0.881 | | 3.71 | 2.24 | 0.886 | | -39.4 | 0.012* |
| | | Placebo (*n*=16) | 5.90 | 4.09 | | | 3.52 | 4.27 | | | -40.4 | 0.165 |
| **PRL** | ng/mg・protein | VitaLutein® (*n*=15) | 2.29 | 1.61 | 0.528 | | 4.65 | 2.67 | 0.560 | | 102.5 | 0.002* |
| | | Placebo (*n*=16) | 2.71 | 1.98 | | | 3.92 | 4.43 | | | 44.7 | 0.365 |

**Pigment amount of macula lutea:** Table 3 illustrates the result of MPOD. There was no statistical difference between groups, and no significant changes were observed from before intake to 8 weeks after intake in either the VitaLutein® or placebo groups.

**Dry eye evaluation (Schirmer's test)**: No significant difference was observed in any test variables when compared between the VitaLutein® and placebo groups before ingestion. Schirmer (right) showed a significantly decreased VitaLutein® group compared to the placebo group after 8 weeks of ingestion. (p = 0.046) (Data not shown.) Schirmer (Left) and Schirmer (Mean) showed no significant difference after 8 weeks of intake between the VitaLutein® and placebo groups.

**Table 3.** The pigment amount of the macula lutea.

| | Unit | | 0 weeks | | | 8 weeks | | | Compared to 0 weeks (%) | P value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mean | SD | P value | Mean | SD | P value | | |
| **MPOD (Mean)** | - | VitaLutein® (*n*=15) | 0.58 | 0.11 | 0.659 | 0.58 | 0.14 | 0.529 | 0.3 | 0.916 |
| | | Placebo (*n*=16) | 0.55 | 0.16 | | 0.54 | 0.15 | | -2.5 | 0.487 |
| **MPOD (Right)** | - | VitaLutein® (*n*=15) | 0.57 | 0.12 | 0.883 | 0.60 | 0.15 | 0.176 | 5.3 | 0.231 |
| | | Placebo (*n*=16) | 0.58 | 0.16 | | 0.56 | 0.18 | | -3.7 | 0.428 |
| **MPOD (Left)** | - | VitaLutein® (*n*=15) | 0.58 | 0.13 | 0.349 | 0.56 | 0.15 | 0.841 | -4.6 | 0.384 |
| | | Placebo (*n*=16) | 0.53 | 0.17 | | 0.52 | 0.13 | | -1.3 | 0.740 |

**Subgroup analysis**: Half of the participants (8 in each group) who worked relatively long hours per day on VDT were selected as subgroups. The participants for analysis were 3 men and 5 women, age 41.9 ± 7.0 years in the VitaLutein® group, and 2 men and 6 women, age 38.5 ± 6.3 years in the placebo group.

Table 4 illustrates the results of subgroup analysis. 8-OHdG levels decreased significantly from before to 8 weeks after intake only in the VitaLutein® group. And MPOD (light) was significantly improved after 8 weeks of intake.

**Table 4.** Subgroup analysis.

| | Unit | | 0 weeks | | | 8 weeks | | | Compared to 0 weeks (%) | P value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mean | SD | P value | Mean | SD | P value | | |
| 8-OHdG | ng/mg · protein | VitaLutein® (*n*=8) | 5.82 | 3.23 | 0.690 | 2.64 | 1.52 | 0.377 | -54.6 | 0.035* |
| | | Placebo (*n*=8) | 6.74 | 5.47 | | 4.57 | 5.81 | | -32.1 | 0.519 |
| PRL | ng/mg · protein | VitaLutein® (*n*=8) | 2.04 | 1.17 | 0.357 | 3.66 | 3.01 | 0.519 | 78.8 | 0.191 |
| | | Placebo (*n*=8) | 3.03 | 2.70 | | 5.19 | 5.51 | | 70.9 | 0.391 |
| MPOD (Mean) | - | VitaLutein® (*n*=8) | 0.62 | 0.09 | 0.151 | 0.62 | 0.15 | 0.444 | 0.4 | 0.916 |
| | | Placebo (*n*=8) | 0.53 | 0.14 | | 0.49 | 0.14 | | -7.6 | 0.136 |
| MPOD (Right) | - | VitaLutein® (*n*=8) | 0.58 | 0.10 | 0.674 | 0.64 | 0.16 | 0.028* | 10.3 | 0.110 |
| | | Placebo (*n*=8) | 0.56 | 0.15 | | 0.49 | 0.18 | | -12.6 | 0.078 |
| MPOD (Left) | - | VitaLutein® (*n*=8) | 0.66 | 0.11 | 0.029* | 0.60 | 0.16 | 0.966 | -8.4 | 0.285 |
| | | Placebo (*n*=8) | 0.50 | 0.13 | | 0.49 | 0.11 | | -2.0 | 0.739 |

**Safety Evaluation:** The results of physical examinations, urinalysis, and hematological tests showed no problematic medical changes that may be associated with the test food intake. In addition, no study participants reported adverse events thought to be caused by the test food intake. Based on the above, there are no safety issues with the continuous intake of lutein-containing supplements for 8 weeks.

**Physical examination, hematological test, and urinalysis test:** Tables 5 and 6 show the results of the physical examination and hematological tests.

In physical examination, the VitaLutein® group showed significant differences in test variables such as body weight (p = 0.005), BMI (p = 0.005), body fat percentage (p = 0.021), and systolic blood pressure (p = 0.023). Additionally, compared with pre-ingestion, body weight rose by 1.2 % (55.8 → 56.5 kg), BMI rose by 1.3% (20.6 → 20.9 kg/m2), body fat percentage rose by 4.1% (23.0 → 23.9%; Data not shown) and systolic blood pressure rose by 6.8% (104.9 → 112.1 mmHg) respectively. The placebo group showed a significant difference in Diastolic blood pressure (p = 0.044). Further, diastolic blood pressure decreased 4.5% (68.3 → 65.3 mmHg) compared to the pre-ingestion group.

In the hematological test, the VitaLutein® group showed significant differences in Neut-R (p = 0.006), Lymph (p = 0.012), Neut (p = 0.049), ZTT (p = 0.017), and creatinine (p 0.020). Further, ZTT fell 6.9% (7.6 → 7.1 U) and Cre fell by 5.2% (0.70 → 0.66 mg/dl), respectively, compared to before ingestion.

In the urinalysis test, no problematic medical fluctuations associated with ingestion of the test food were observed in any study participants. (Data not shown)

Although a few parameters showed statistically significant changes before and after intake, all values remained within the normal reference range. The principal investigator concluded that these changes did not pose any safety concerns.

**Table 5.** Physical Examination.

| | Unit | | 0 weeks | | 8 weeks | | Compared to 0 weeks (%) | P value |
|---|---|---|---|---|---|---|---|---|
| | | | Mean | SD | Mean | SD | | |
| **Weight** | Kg | VitaLutein® (*n*=15) | 55.8 | 11.7 | 56.5 | 11.7 | 1.2 | 0.005** |
| | | Placebo (*n*=16) | 57.8 | 16.4 | 58.0 | 16.3 | 0.4 | 0.502 |
| **BMI** | $Kg/m^2$ | VitaLutein® (*n*=15) | 20.6 | 2.8 | 20.9 | 2.8 | 1.3 | 0.005** |
| | | Placebo (*n*=16) | 22.0 | 4.9 | 22.1 | 4.9 | 0.4 | 0.426 |
| **Systolic blood pressure (SBP)** | mmHg | VitaLutein® (*n*=15) | 104.9 | 12.2 | 112.1 | 9.2 | 6.8 | 0.023* |
| | | Placebo (*n*=16) | 112.9 | 11.6 | 110.3 | 18.2 | -2.4 | 0.264 |
| **Diastolic blood pressure (DBP)** | mmHg | VitaLutein® (*n*=15) | 62.2 | 7.3 | 65.3 | 7.1 | 5.0 | 0.123 |
| | | Placebo (*n*=16) | 68.3 | 9.1 | 65.3 | 10.9 | -4.5 | 0.044* |
| **Heart rate (HR)** | bpm | VitaLutein® (*n*=15) | 72.4 | 13.8 | 70.2 | 8.5 | -2.9 | 0.552 |
| | | Placebo (*n*=16) | 75.3 | 11.5 | 75.4 | 12.4 | 0.1 | 0.967 |

**Table 6** Hematological Examination.

| | Unit | | 0 weeks | | 8 weeks | | Compared to 0 weeks (%) | P value |
|---|---|---|---|---|---|---|---|---|
| | | | Mean | SD | Mean | SD | | |
| **WBC** | /μL | VitaLutein®(*n*=15) | 5480.0 | 1022.0 | 5700.0 | 1135.8 | 4.0 | 0.375 |
| | | Placebo | 5987.5 | 2122.5 | 5668.8 | 1407.0 | -5.3 | 0.433 |
| **RBC** | $10^4$/μL | VitaLutein®(*n*=15) | 435.9 | 33.9 | 441.3 | 42.8 | 1.3 | 0.274 |
| | | Placebo (*n*=16) | 445.9 | 33.2 | 448.3 | 38.6 | 0.5 | 0.611 |
| **Hb** | g/dL | VitaLutein®(*n*=15) | 13.0 | 1.2 | 13.3 | 1.4 | 2.8 | 0.093 |
| | | Placebo (*n*=16) | 13.5 | 1.5 | 13.5 | 1.6 | 0.2 | 0.832 |
| **Ht** | % | VitaLutein®(*n*=15) | 40.4 | 3.0 | 40.8 | 3.7 | 1.1 | 0.329 |
| | | Placebo (*n*=16) | 41.1 | 3.9 | 41.5 | 4.2 | 1.0 | 0.390 |
| **Plt** | $10^4$/μL | VitaLutein®(*n*=15) | 25.4 | 6.3 | 26.1 | 7.0 | 2.9 | 0.322 |
| | | Placebo(*n*=16) | 26.8 | 7.2 | 26.8 | 6.4 | -0.2 | 0.939 |
| **Neut** | /μL | VitaLutein®(*n*=15) | 3111.9 | 811.0 | 3530.4 | 1030.3 | 13.4 | 0.049* |
| | | Placebo (*n*=16) | 3611.9 | 1754.1 | 3267.0 | 1106.7 | -9.5 | 0.350 |
| **Neut-R** | /μL | VitaLutein®(*n*=15) | 56.4 | 8.3 | 61.3 | 7.8 | 8.7 | 0.006* |
| | | Placebo (*n*=16) | 58.2 | 9.0 | 56.7 | 10.0 | -2.5 | 0.535 |
| **Lymph** | % | VitaLutein®(*n*=15) | 33.2 | 6.0 | 29.6 | 6.2 | -10.9 | 0.012* |
| | | Placebo(*n*=16) | 33.9 | 8.0 | 35.1 | 7.6 | 3.5 | 0.564 |
| **AST** | U/L | VitaLutein®(*n*=15) | 18.2 | 5.1 | 18.5 | 7.2 | 1.8 | 0.714 |
| | | Placebo (*n*=16) | 21.2 | 4.7 | 20.7 | 5.5 | -2.4 | 0.620 |
| **ALT** | U/L | VitaLutein®(*n*=15) | 14.5 | 6.9 | 14.5 | 8.0 | 0.0 | 1.000 |
| | | Placebo (*n*=16) | 23.6 | 11.5 | 20.4 | 11.2 | -13.8 | 0.128 |
| **γGTP** | U/L | VitaLutein®(*n*=15) | 22.1 | 17.5 | 23.2 | 19.3 | 4.8 | 0.217 |
| | | Placebo (*n*=16) | 25.8 | 14.6 | 24.8 | 14.7 | -3.9 | 0.539 |
| **ALP** | U/L | VitaLutein®(*n*=15) | 166.7 | 45.0 | 155.8 | 41.0 | -6.6 | 0.185 |

| | Unit | | 0 weeks | | 8 weeks | | Compared to 0 weeks (%) | P value |
|---|---|---|---|---|---|---|---|---|
| | | | Mean | SD | Mean | SD | | |
| | | Placebo (*n*=16) | 191.9 | 47.9 | 191.8 | 55.3 | 0.0 | 0.990 |
| **LDH** | U/L | VitaLutein®(*n*=15) | 168.3 | 24.7 | 163.9 | 26.3 | -2.6 | 0.162 |
| | | Placebo (*n*=16) | 172.9 | 25.5 | 167.8 | 27.7 | -2.9 | 0.072 |
| **T-Bil** | mg/dL | VitaLutein®(*n*=15) | 0.9 | 0.4 | 0.9 | 0.3 | -0.8 | 0.909 |
| | | Placebo (*n*=16) | 0.8 | 0.3 | 0.7 | 0.2 | -5.0 | 0.383 |
| **D-Bil** | mg/dL | VitaLutein®(*n*=15) | 0.1 | 0.1 | 0.1 | 0.1 | 5.9 | 0.582 |
| | | Placebo (*n*=16) | 0.1 | 0.1 | 0.1 | 0.1 | -5.6 | 0.669 |
| **I-Bil** | mg/dL | VitaLutein®(*n*=15) | 0.8 | 0.4 | 0.7 | 0.3 | -1.8 | 0.803 |
| | | Placebo (*n*=16) | 0.6 | 0.2 | 0.6 | 0.2 | -4.9 | 0.401 |
| **ChE** | U/L | VitaLutein®(*n*=15) | 293.9 | 86.4 | 295.9 | 84.6 | 0.7 | 0.760 |
| | | Placebo (*n*=16) | 326.8 | 68.1 | 320.2 | 71.0 | -2.0 | 0.254 |
| **ZTT** | U | VitaLutein®(*n*=15) | 7.6 | 2.8 | 7.1 | 2.5 | -6.9 | 0.017* |
| | | Placebo (*n*=16) | 7.5 | 3.0 | 7.3 | 2.7 | -4.8 | 0.081 |
| **TP** | g/dL | VitaLutein®(*n*=15) | 7.2 | 0.3 | 7.2 | 0.3 | -0.5 | 0.722 |
| | | Placebo (*n*=16) | 7.4 | 0.4 | 7.3 | 0.5 | -1.4 | 0.245 |
| **BUN** | mg/dL | VitaLutein®(*n*=15) | 12.7 | 3.4 | 11.3 | 2.3 | -10.6 | 0.207 |
| | | Placebo (*n*=16) | 11.5 | 2.8 | 12.2 | 3.0 | 5.7 | 0.214 |
| **Cre** | mg/dL | VitaLutein®(*n*=15) | 0.70 | 0.17 | 0.66 | 0.17 | -5.2 | 0.020* |
| | | Placebo (*n*=16) | 0.68 | 0.13 | 0.65 | 0.14 | -3.9 | 0.056 |
| **CK** | U/L | VitaLutein®(*n*=15) | 103.9 | 92.7 | 77.2 | 23.8 | -25.7 | 0.259 |
| | | Placebo (*n*=16) | 81.1 | 32.2 | 89.5 | 58.8 | 10.4 | 0.382 |
| **Na** | mEq/L | VitaLutein®(*n*=15) | 140.8 | 2.0 | 139.7 | 1.7 | -0.8 | 0.076 |
| | | Placebo (*n*=16) | 139.8 | 1.3 | 139.8 | 1.7 | 0.0 | 1.000 |
| **K** | mEq/L | VitaLutein®(*n*=15) | 4.0 | 0.3 | 4.3 | 0.3 | 5.9 | 0.004* |
| | | Placebo (*n*=16) | 4.1 | 0.2 | 4.3 | 0.3 | 6.2 | 0.002* |
| **Cl** | mEq/L | VitaLutein®(*n*=15) | 103.0 | 1.9 | 102.5 | 1.5 | -0.5 | 0.411 |
| | | Placebo (*n*=16) | 102.1 | 2.1 | 102.3 | 1.8 | 0.2 | 0.594 |
| **Ca** | mg/dL | VitaLutein®(*n*=15) | 9.4 | 0.4 | 9.3 | 0.3 | -1.5 | 0.187 |
| | | Placebo (*n*=16) | 9.7 | 0.3 | 9.5 | 0.4 | -1.7 | 0.132 |
| **T-cho** | mg/dL | VitaLutein®(*n*=15) | 191.5 | 26.0 | 192.7 | 20.7 | 0.6 | 0.833 |
| | | Placebo (*n*=16) | 199.4 | 35.5 | 200.8 | 33.1 | 0.7 | 0.719 |
| **HDL-C** | mg/dL | VitaLutein®(*n*=15) | 67.2 | 13.0 | 70.7 | 14.2 | 5.2 | 0.084 |
| | | Placebo (*n*=16) | 67.6 | 18.1 | 71.1 | 17.1 | 5.2 | 0.093 |
| **LDL-C** | mg/dL | VitaLutein®(*n*=15) | 110.1 | 26.8 | 107.7 | 19.3 | -2.2 | 0.589 |
| | | Placebo (*n*=16) | 116.3 | 36.3 | 114.8 | 32.5 | -1.2 | 0.648 |
| **TG** | mg/dL | VitaLutein®(*n*=15) | 79.0 | 29.0 | 69.1 | 25.2 | -12.5 | 0.207 |
| | | Placebo (*n*=16) | 79.5 | 30.0 | 76.8 | 42.8 | -3.4 | 0.668 |

## DISCUSSION

This study evaluated the impact of a lutein-based dietary supplement on oxidative stress reduction, using 8-hydroxy-2'-deoxyguanosine (8-OHdG) and prolactin (PRL) levels in tears as biomarkers.

Numerous in vivo, in vitro, and clinical investigations [24–29] have proven lutein's antioxidant and anti-inflammatory properties in ocular tissues. These studies highlight its protective role in managing or preventing various eye conditions, including age-related macular

degeneration, diabetic retinopathy, retinopathy of prematurity, myopia, and cataracts. Lutein is classified as Generally Recognized as Safe (GRAS), with minimal risk of adverse effects even with prolonged use.

Among the commonly used biomarkers for oxidative stress in ocular surface tissues are 8-OHdG, 4-hydroxynonenal (HNE), and malondialdehyde (MDA). The DNA oxidative stress markers in the body, 8-OHdG and PRL are both oxidative stress markers originating from n-3 polyunsaturated fatty acids (PUFA) [30, 31]. Additionally, to examine the effectiveness of VitaLutein®, an additional analysis focusing on VDT working time was performed. The average VDT working time per day was calculated throughout the study period, and approximately half of the participants with relatively long working times were selected to constitute a subgroup. All analysis results showed 8-OHdG was significantly reduced from before ingestion until 8 weeks after, only in the VitaLutein® group. When stimulated by ultraviolet or blue light, ocular tissue was damaged, and oxidative stress agents such as 8-OHdG were produced [32]. Since the lutein-containing study food is a type of carotenoid that absorbs ultraviolet light and blue light [33], it inhibits ocular tissue damage caused by VDT work. Thus, the reduction in 8-OHdG shows that VitaLutein® supplement exerts a reducing effect on oxidative stress.

Previous studies have reported that lutein reduces 8-OHdG. Lung oxidative stress damage caused by PM2.5 has been reduced by lutein [34]. In addition, oxidative stress markers such as 8-OHDG in organs caused by thermal trauma improve with lutein supplementation [35]. This study first clarified the report that lutein intake reduces 8-OHdG in tears.

On the other hand, PRL in the VitaLutein® group was significantly increased. PRL is an oxidative stress marker associated with n-3 PUFA, and the relationship between n-3 PUFA-deficient mice and dry eyes has been reported [36]. However, since a significant increase was not observed in the group of participants with long VDT working hours, a relationship between the lutein-containing supplements and PRL secretion cannot be concluded. These results convey that lutein builds up in the ocular tissue through the continued intake of VitaLutein® supplement. The absorption of ultraviolet and blue light to prevent damage to the ocular tissue may inhibit the secretion of 8-OHdG.

Macular pigment is reduced by oxidative stress, resulting in age-related macular degeneration (AMD) [37]. No significant changes were observed in MPOD in either the VitaLutein® group or the placebo group from before ingestion to 8 weeks of ingestion. However, in the analysis of the sub-group constructed based on length of VDT working time, although no differences were observed from baseline until 8 weeks after, comparison of the VitaLutein® and placebo groups showed a significantly higher value in the MPOD of the right eye in the VitaLutein® group. Clinical studies in healthy participants and patients with AMD have suggested that MPOD increases with continuous ingestion of lutein [38, 39]. Although MPOD did not increase significantly with the ingestion of the VitaLutein® supplement over 8 weeks, it did inhibit decreases in MPOD due to VDT work, as the VitaLutein® group maintained higher levels than the placebo group. Further, it is unclear why the MPOD maintained a high value only in the right eye. However, dominant eye and differences in MPOD measurements of the left eye among the groups before ingestion may be considered. The lack of a significant placebo difference was likely due to the short intake duration. Previous studies have shown that lutein supplementation for at least 16 weeks leads to a greater increase in MPOD compared to placebo [40]. Additionally, continuous lutein intake over four months was associated with higher MPOD, improved contrast sensitivity, and better sleep quality versus placebo. These benefits were maintained even after discontinuing lutein supplementation [12].

The results of body measurements, physical examinations, urinalysis, blood tests, and vision tests

showed no problematic medical changes associated with ingestion of the test food (VitaLutein®).

Previous studies, particularly those involving obese individuals, have shown that lutein supplementation may aid in weight loss [41,42]. This is attributable to lutein's ability to regulate fat turnover and reduce oxidative stress [43]. This weight results in this study differ from those of previous studies.

The protocol instructed participants in the current study to avoid drastic changes in eating and drinking habits and maintain consistent dietary and lifestyle behaviors from one week before the initial examination through to the final examination.

A previous study on weight gain reported seasonal variations ranging from +0.42% to -0.26% [44]. Therefore, the body weight changes observed are considered insignificant and unrelated to lutein intake, as they fall within the range of known seasonal fluctuations.

Further, there were no reports from any of the study participants involving adverse events thought to be caused by ingestion of the test food (VitaLutein®). Therefore, it is evident that continuous ingestion of lutein-containing supplements over 8 weeks poses no safety risk.

**Limitations and directions for future research:** This study observed a significant reduction in 8-OHdG levels in the VitaLutein® group, when compared to the placebo group, which was not statistically significant. MPOD tended to improve only among participants in the VitaLutein® group who worked relatively long hours daily on VDTs. Potential factors influencing these results may include the duration of supplementation, sample size, and the absorption rate of lutein-containing supplements. Given that prior research indicates effectiveness with continuous intake over 6 to 12 months, the supplementation period must be reassessed, and the sample size must be redesigned based on the effect size of the observed outcomes. Further investigation regarding lutein absorption through the measurement of serum lutein concentrations after supplementation is necessary.

**Scientific Innovation and Practical Implications:** This study innovatively applies a randomized controlled design to evaluate the safety and potential ocular benefits of VitaLutein® in a specific population. The findings suggest a practical, safe dietary intervention for mitigating oxidative stress in the eye and supporting macular health, especially relevant for individuals with significant VDT screen time. While further research with more extended supplementation periods and larger sample sizes is warranted, this study offers initial evidence for the potential of lutein supplementation to support eye health in the digital age.

## CONCLUSION

This study suggests that continuous ingestion of VitaLutein® supplement over 8 weeks inhibits the secretion of 8-OHdG, while maintaining a high MPOD in the VitaLutein® group, compared with the placebo group in the sub-group composed of participants with long VDT working times. Thus, continuous ingestion of VitaLutein® supplement may reduce oxidative stress and maintain macular pigment. Therefore, the continuous ingestion of VitaLutein® is safe.

**List of Abbreviations**: VDT, Visual Display Terminal; 8-OHdG, 8-hydroxy-2-deoxyguanosine; MPOD, macular pigment density; FFs, Functional foods; BMI, body Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; FHC, food with Health Claims; FFC, Function Food Center; ACT, amorphous conversion technology; VAS, visual analogue scale; WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; Ht, hematocrit value; Plt, platelet count; Neut , neutrophil count; Neut-R, neutrophil ratio; Neut/Lymph, neutrophil/lymphocyte ratio; Baso, basophil ratio; Eosino, eosinophil ratio; Lymph, lymphocyte ratio; Mono, monocyte percentage; AST, ALT, γ-GTP, alkaline

phosphatase (ALP), LD (LDH), LAP;TP, total protein; T-Bil, total bilirubin; D-Bil, direct bilirubin; I-BIL, indirect bilirubin; CK, creatine kinase; Amy, serum amylase; BUN, urea nitrogen ; UA, uric acid; T-cho, total cholesterol ; TG, triglyceride; Glu, glucose; Fe, serum iron; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; HbA1c, and GA, glycol albumin.

**Competing interests:** Bio Actives Japan Corporation, the study's sponsor, entrusted Orthomedico Inc., Takara Clinic, and Nishi-Arai Ekimae Clinic Ophthalmology and Orthopedics with conducting the survey. Hyunjin Lee, Takayuki Itano and Faizal Mohamed are members of Bio Actives Japan Corporation. Naoko Suzuki is a member of Orthomedico Inc., Tsuyoshi Takara is a physician at Takara Clinic, and Takahiro Yamada is a physician at Nishi-Arai Ekimae Clinic Ophthalmology and Orthopedics.

**Author's contributions:** Hyunjin Lee: Conceptualization, Methodology, Funding acquisition, Project administration, Visualization, writing original draft preparation and Writing-review; Takayuki Itano: Conceptualization, Methodology, Funding acquisition, Visualization, and Writing-review; Faizal Mohamed: Methodology, Visualization, and Writing-review; Tsuyoshi Takara and Takahiro Yamada: Methodology, Data curation, writing original draft preparation and Writing - review; Naoko Suzuki: Methodology, Data curation and Formal analysis.

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## REFERENCES

1. Concepción RM, Avalos J, Bonet ML, Boronat A, Gomez GL, Mendez HD, et. al. A global perspective on carotenoids, Metabolism, biotechnology, and benefits for nutrition and health. *Prog. Lipid Res.* 2018; 70: 62-93. DOI: https://doi.org/10.1016/j.plipres.2018.04.004 1
2. Rodrigues AA, Shao A: The Science behind lutein. *Toxicol. Lett.* 2004; 150(1): 57-83. DOI: https://doi.org/10.1016/j.toxlet.2003.10.031 1
3. Bartlett H.E, Eperjesi F: Effect of lutein and antioxidant dietary supplementation on contrast sensitivity in age-related macular disease: A randomized controlled trial. *Eur. J. Clin. Nutr.* 2007; 61(9): 1121-1127. DOI: https://doi.org/10.1038/sj.ejcn.1602626 1
4. Kim SY, Hong SY, Choi HS, Kim JH, Jeong SH, Lee SY, et. al. Superfine Marigold Powder Improves the Quality of Sponge Cake: Lutein Fortification, Texture, and Sensory Properties. *Foods.* 2023 Jan 22; 12(3): 508. DOI: https://doi.org/10.3390/foods12030508 1
5. Becerra MO, Contreras LM, Lo NH, Diaz JM, Herrera GC: Lutein as a functional food ingredient: Stability and bioavailability. *Journal of Functional Foods* 2020; 66: 103771. DOI: https://doi.org/10.1016/j.jff.2019.103771 1
6. Low KL, Idris A, Yusof NM: Novel protocol optimized for microalgae lutein used as food additives. *Food Chem.* 2020 Mar 1; 307: 125631. DOI: https://doi.org/10.1016/j.foodchem.2019.125631 1
7. Goh KM, Tan ESS, Lim CSY, Tan PY, Biswas S, Lew LA, et al.: Effect of dietary supplementation with lutein, zeaxanthin, and elderberries on dry eye disease (DED) and immunity: a randomized controlled trial. *Nutrients* 2024; 16(24): 4366. DOI: https://doi.org/10.3390/nu16244366 1
8. Shi H, Nolan JM, Flynn R, Cabrero AP: Beyond food colouring: Lutein-food fortification to enhance health. *Food Bioscience* 2024; 59: 104085. DOI: https://doi.org/10.1016/j.fbio.2024.104085 1
9. Navaro DA, Raz O, Gabriel S, Shriqui VK, Gonen E, Boaz M: Functional Foods in fad diets: A review. *Functional Foods in Health and Disease* 2017; 7(9): 702-715. DOI: https://doi.org/10.31989/ffhd.v7i9.346 1
10. Research progress about the effect and prevention of blue light on eyes. *Int J Ophthalmol.* 2018 Dec 18; 11(12): 1999-2003. DOI: https://doi.org/10.18240/ijo.2018.12.20 1
11. Santosa S, Jone PJ: Oxidative stress in ocular disease: Does lutein play a protective role? *CMAJ.* 2005 Oct 11; 173(8): 861-862. DOI: https://doi.org/10.1503/cmaj.1031425 1
12. Vadiraj G, Bharadwa J, Thirumalesh MB, Ashwath HV, Anzar CA, Sundaram R, Prasad CP, Joseph MV, Bineesh Eranimose, Prasanna A. Reddy: Beneficial effects of a lutein-zeaxanthin complex on macular pigment optical density levels of healthy individuals with prolonged screen time. *Cureus* 2025; 17(2): e79481. DOI: https://doi.org/10.7759/cureus.79481 1
13. Buscemi S, Corleo D, Pace FD, Petroni ML, Satriano A, Marchesini G: The effect of lutein on eye and extra-eye health. *Nutrients* 2018 Sep 18; 10(9): 1321. DOI: https://doi.org/10.3390/nu10091321 1

14. Martirosyan D.M, Singh J: A new definition of functional food by FFC: what makes a new definition unique? *Functional Foods in Health and Disease* 2015; 5(6): 209-223. DOI: https://doi.org/10.31989/ffhd.v5i6.183 1
15. Martirosyan D.M, Kanya H, Nadalet C: Can functional foods reduce the risk of disease? Advancement of functional food definition and steps to create functional food products. *Functional Foods in Health and Disease* 2021; 11(5): 213-221. DOI: https://doi.org/10.31989/ffhd.v11i5.788 1
16. Martirosyan D: A comprehensive review on the role of food bioactive compounds in functional food science. *Functional Food Science* 2022; 3(2): 64-78. DOI: https://doi.org/10.31989/ffs.v2i3.906 1
17. Martirosyan D.M, Lampert T, Ekblad M: Classification and regulation of functional food proposed by the Functional Food Center. *Functional Food Science* 2022; 2(2): 25-46. DOI: https://doi.org/10.31989/ffs.v2i2.890 1
18. Martirosyan D.M, Ekblad M: Functional foods classification system: exemplifying through analysis of bioactive compounds. *Functional Foods Science* 2022; 2(4): 94-123. DOI: https://doi.org/10.31989/ffs.v2i4.919 1
19. Outline of Food Labelling Systems for Nutrition and Health Claims. Available at: https://www.caa.go.jp/en/policy/food_labeling/assets/food_labeling_cms206_241210_22.pdf 1. Retrieved on May 13, 2025.
20. Regarding health foods containing red yeast rice: Consumer Affairs Agency Japan. Available at: https://www.caa.go.jp/policies/health_foods/red_yeast_rice/ 1. Retrieved on May 13, 2025.
21. Hammond BR, Johnson BA, George ER: Oxidative photodegradation of ocular tissues: Beneficial effects of filtering and exogenous antioxidants. *Exp. Eye Res.* 2014; 129: 135-150. DOI: https://doi.org/10.1016/j.exer.2014.09.005 1
22. Sankhwar S.N, Verma N, Patel N, Kumar P, Goel A, Rungta M: A clinical investigation to determine the safety and efficacy of a novel, patented prunus domestica extract in benign prostatic hyperplasia. *Functional Foods in Health and Disease* 2025; 15(2): 129-143. DOI: https://doi.org/10.31989/ffhd.v15i2.1556 1
23. Shiojima Y, Takahashi M, Takahashi R, Moriyama H, Maruyama K, Bagchi D, et al. Safety of dietary undenatured type II collagen: a pilot open-label overdose clinical investigation. *Functional Foods in Health and Disease* 2022; 12(3): 103-115. DOI: https://doi.org/10.31989/ffhd.v12i3.897 2
24. Wu L.L, Chiou C.C, Chang P.Y, Wu J.T: Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. *Clin Chim Acta.* 2004 Jan; 339(1-2): 1-9. DOI: https://doi.org/10.1016/j.cccn.2003.09.010 2
25. Obana A: Non-invasive Measurement of Carotenoids in Human Eye and Skin. *The Journal of Japan Society for Laser Surgery and Medicine* 2021; 42(2): 64-70. DOI: https://doi.org/10.2530/jslsm.jslsm-42_0011 2
26. Kowluru R.A, Zhong Q, Santos J.M, Thandampallayam M, Putt D, Gierhart D.L: Beneficial effects of the nutritional supplements on the development of diabetic retinopathy. *Nutr Metab (Lond).* 2014 Jan 30; 11(1): 8. DOI: https://doi.org/10.1186/1743-7075-11-8 2
27. Tan J.S, Wang J.J, Flood V, Rochtchina E, Smith W, Mitchell P: Dietary antioxidants and the long-term incidence of age-related macular degeneration: The Blue Mountains Eye Study. *Ophthalmology* 2008; 115: 334-341. DOI: https://doi.org/10.1016/j.ophtha.2007.03.083 2
28. SanGiovanni J.P, Chew E.Y, Clemons T.E, Ferris F.L 3rd, Gensler G, Lindblad A.S, Milton R.C, Seddon J.M, Sperduto R.D: The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study: AREDS Report No. 22. *Arch. Ophthalmol.* 2007; 125: 334-341. DOI: https://doi.org/10.1001/archopht.125.9.1225 2
29. Li L.H, Lee J.C.Y, Leung H.H, Lam W.C, Fu Z, Lo A.C.Y: Lutein Supplementation for Eye Diseases. *Nutrients* 2020; 12: 1721. DOI: https://doi.org/10.3390/nu12061721 2
30. Ranard K.M, Jeon S, Mohn E.S, Griffiths J.C, Johnson E.J, Erdman J.W Jr: Dietary guidance for lutein: Consideration for intake recommendations is scientifically supported. *Eur. J. Nutr.* 2017; 56(3): 37-42. DOI: https://doi.org/10.1007/s00394-017-1580-2 2
31. Sakai K, Ochi T, Takeuchi M: An oxidative stress marker: 8-OHdG. *Analytical Bio-Science.* 2009; 32(4): 297-300. Available at: https://plaza.umin.ac.jp/j-jabs/32/32.297.pdf 2. Retrieved on May 13, 2025.
32. Hisaka S, Kato Y, Kitamoto N, Yoshida A, Kubushiro Y, Naito M, Osawa T: Chemical and immunochemical identification of propanoyllysine derived from oxidized n-3 polyunsaturated fatty acid. *Free Radic Biol Med.* 2009 Jun 1; 46(11): 1463-1471. DOI: https://doi.org/10.1016/j.freeradbiomed.2009.02.030 2
33. Kuse Y, Ogawa K, Tsuruma K, Shimazawa M, Hara H: Damage of photoreceptor-derived cells in culture induced by light emitting diode-derived blue light. *Sci Rep.* 2014; 4: 5223. DOI: https://doi.org/10.1038/srep05223 2
34. Bernstein P.S: New insights into the role of the macular carotenoids in age-related macular degeneration. Resonance Raman studies. *Pure Appl Chem* 2002; 74(8): 1419-1425.

DOI: https://doi.org/10.1351/pac200274081419 2

35. Chen X, Chen Y, Chen Y, Wang X, He M: Protective effect of lutein on oxidative stress damage caused by acute PM2.5 exposure in rats. *Ann Palliat Med.* 2020 Jul; 9(4): 2028-2036. DOI: https://doi.org/10.21037/apm-20-1138 2
36. AbuBakr H.O, Aljuayd S.H, Abou-Zeid S.M, Bahrawy A.E: Burn-induced multiple organ injury and protective effect of lutein in rats. *Inflammation.* 2018 Jun; 41(3): 760-772. DOI: https://doi.org/10.1007/s10753-018-0730-x 2
37. Harauma A, Saito J, Watanabe Y, Moriguchi T: Potential for daily supplementation of n-3 fatty acids to reverse symptoms of dry eye in mice. *Prostaglandins Leukot Essent Fatty Acids.* 2014 Jun; 90(6): 207-213. DOI: https://doi.org/10.1016/j.plefa.2014.02.005 2
38. Obana A: Effect of light on the eyes. *Nippon Laser Igakkaishi.* 2012; 32: 438-443. DOI: https://doi.org/10.2530/jslsm.32.438 2
39. Schalch W, Cohn W, Barker F.M, Kopche W, Mellerio J, Brid A.C, Robson A.G, Fitzke F.F, Van-Kuijk F.J: Xanthophyll accumulation in the human retina during supplementation with lutein or zeaxanthin - the LUXEA (LUtein Xanthophyll Eye Accumulation) study. *Arch Biochem Biophys.* 2007; 458(2): 128-135. DOI: https://doi.org/10.1016/j.abb.2006.09.032 2
40. Wang X, Jiang C, Zhang Y, Gong Y, Chen X, Zhang M: Role of lutein supplementation in the management of age-related macular degeneration: meta-analysis of randomized controlled studies. *Ophthalmic Res.* 2014; 52(4): 198-205. DOI: https://doi.org/10.1159/000363327 2
41. Machida N, Kosehira M, Kitaichi N: Clinical effects of dietary supplementation of lutein with high bio-accessibility on macular pigment optical density and contrast sensitivity: a randomized double-blind placebo-controlled parallel-group comparison trial. *Nutrients* 2020; 12(10): 2966. DOI: https://doi.org/10.3390/nu12102966 2
42. Sharafabad F.H, Esfanjani A.T, Ghoreishi Z, Sarreshtedari M: Lutein supplementation combined with a low-calorie diet in middle-aged obese individuals: effects on anthropometric indices, body composition and metabolic parameters. *British Journal of Nutrition* 2021; 126: 1028-1039. DOI: https://doi.org/10.1017/S0007114520004997 2
43. Canas J, Lochrie A, McGowan A.G, Schettino C, Hossain J, Balagopal P: Effect of a 2-week intense lifestyle intervention followed by 6-month carotenoid supplementation on fat depots, adiponectin and palmitoleate: a 6-month double-blind placebo-controlled pilot study in obese children (645.6). *The FASEB Journal* 2014; 28, Suppl. 1: 645.6. DOI: https://doi.org/10.1096/fasebj.28.1_supplement.645.6 3
44. Zhou J, Zhao D, Wang N, Zeng Z, Wang C, Hao L, Peng X: Effects of lutein supplementation on inflammatory biomarkers and metabolic risk factors in adults with central obesity: study protocol for a randomized controlled study. *Trials* 2020 Jan 6; 21: 32. DOI: https://doi.org/10.1186/s13063-019-3998-8 3
45. Helander E.E, Wansink B, Chieh A: Weight Gain over the Holidays in Three Countries. *N. Engl J Med.* 2016 Sep 22; 375(12): 1200-1202. DOI: https://doi.org/10.1056/NEJMc1602012 3