Original Article

# Efficacy of Oral Lycopene Supplementation for Photoprotection in Filipino Patients in a Tertiary Hospital in Makati: A Single-blind Randomized Controlled Trial

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## Abstract

**Background:** Ultraviolet radiation has been proven to result in unwarranted effects on the skin through reactive oxygen species (ROS) and direct DNA damage. Lycopene, a naturally occurring substance, acts as an antioxidant by neutralizing ROS.

**Objective:** The objective of the study was to determine the efficacy of oral lycopene supplementation for photoprotection in adult Filipino patients seen in a tertiary hospital in Makati City.

**Design:** The study design involves single-blind, parallel, randomized controlled trial.

**Methods:** Thirty-six Filipino patients aged 18 years old and above with Fitzpatrick Skin Phototype (FSP) III–V were divided into two groups using a computer-generated randomization. Group A received lycopene 500 mg/soft gel capsule two capsules per orem once daily for 12 weeks, while Group B received no intervention during the entire observation period. Minimal erythema dose (MED) of patients from both groups was assessed by a single treatment-blinded reader at baseline, week 6, and week 12.

**Results:** Group A showed a significant increase in MED across periods, with a 20.83% increase from baseline at week 6 and a 43.06% increase at week 12. Group B MED remained constant from baseline to week 6 and to week 12. These results show that there is a significant effect in the increase in MED as compared to the control group.

**Conclusion:** Oral lycopene is effective in increasing the MED of patients and may be used for photoprotection among patients with FSP III–V.

**Keywords:** Filipino, Fitzpatrick skin phototype III–V, lycopene, photoprotection

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## Introduction

The human skin is continuously exposed to different environmental agents that may either be beneficial or damaging. One of these agents is ultraviolet radiation (UVR), which is a nonionizing type of radiation emitted by the sun. Our body's natural defense versus UVR is mainly from the skin. UVR affects the skin by inducing erythema and pigmentation, with roles in photoaging and carcinogenesis. Its beneficial effects include Vitamin D production, mood stabilization, and as a treatment modality for various dermatologic diseases by inducing immunosuppression.[1,2]

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Since UVR is found almost everywhere, it is important to seek different ways of protecting the skin from its deleterious effects.

Readily available agents for photoprotection are mostly topical and they serve as physical barriers between the sun and the skin. Currently, we are seeing an increase in the use of systemic agents for photoprotection. These agents improve the response to oxidative damage, including that due to exposure to the sun.[3]

Studies have shown that carotenoids play a role in photoprotection by acting as physical quenchers to directly inactivate singlet molecular oxygen, an oxidative stress contributor.[4] Lycopene, beta-carotene, lutein, and astaxanthin are the particular types of carotenoids which not only act as antioxidants for protective effect but also through direct light-absorbing properties, regulation of ultraviolet light-induced gene expression, and suppression of inflammatory response.[5,6] The primary source of carotenoids in the human skin is through a diet rich in fruits, vegetables, and marine products.[4,7,8]

In several studies, lycopene was shown to have the highest antioxidant power,[9] as it is considered the most efficient singlet oxygen quencher,[10] greater than all carotenoids and twice greater than beta-carotene.[5]

Studies have been made correlating the photoprotective effects of oral supplementation of carotenoids, phytonutrients, and other vitamins in photoprotection among patients with lighter skin color (Fitzpatrick skin phototype [FSP] I–III).[9,11-13] However, data correlating the use of carotenoids, particularly lycopene, in photoprotection among patients with darker skin phototypes (FSP IV–VI) is yet to be established. Most Filipinos are categorized as FSP IV–V.[14] Darker skin phototypes have more protection from the effects of UVR due to the presence of melanin. However, even with the abundance of melanin, a search for additional sources of photoprotection, like naturally occurring substances such as lycopene is still needed.[1]

The goal of this randomized clinical trial is to objectively observe the effects of taking oral lycopene supplementation in photoprotection by measuring an increase in the minimal erythema dose (MED), which may signify photoprotective effects.

The general objective is to determine the efficacy of oral lycopene supplementation for photoprotection in adult Filipino patients seen in a tertiary hospital in Makati City. In this study, MED of patients with FSP III–V will be determined and compared at baseline, week 6, and week 12. Any adverse effects from oral lycopene supplementation throughout the 12-week study period will also be reported.

## Methods

### Selection and description of participants

This study was assessed through a single-blind, parallel, randomized controlled trial. It was conducted in a tertiary hospital in Makati City for 12 weeks from April 2021 to July 2021. The population of interest were adult Filipino patients aged 18 years old and above with an FSP III–V. Patients should have no intake of lycopene or any carotenoid supplementation for the past 3 months.

Excluded in the study were patients with the following history: (1) Known hypersensitivity or intolerance to lycopene or any of the supplement's ingredients, (2) Known history of malabsorption, hepatic disease, photosensitivity, and skin and other types of cancer, (3) Current use of vitamins or medicines with risk of hepatotoxicity and immunosuppression, (4) Current use of oral antioxidant supplements with known photoprotective effects, (5) Dermatologic abnormalities on the MED test area, (6) Occupation or hobbies entailing frequent sun exposure, (7) Pregnant or lactating women, and (8) Patients with special type of diet (e.g. vegan, vegetarian, pescatarian, etc.).

#### *Ethics and dissemination*

The protocol of this study adhered to the ethical considerations and ethical principles set out in relevant guidelines, including the Declaration of Helsinki, World Health Organization guidelines, the International Conference on Harmonization–Good Clinical Practice, and National Ethics Guidelines for Health Research.

#### *Research ethics approval and consent*

This study commenced only upon approval of the Institutional Review Board of the institution. No subject participated in this study without written documentation of informed consent duly signed and understood by the participants, and obtained by the primary investigator.

### Technical information

#### *Study medication*

Lycopene (containing 50 mg lycopene) 500 mg/soft gel capsule (Food and Drug Administration [FDA] Registration No: FR-4000002470845, valid until December 14, 2022)[15] contains bees wax, vegetable oil, gelatin, and glycerin. The nutrient profile of each soft gel includes 50 mg lycopene, 0.28 mg sodium, 0.05 g carbohydrate, 0.36 g fat, and 0.09 g protein, with a total energy of 15.39 kJ. Its recommended

daily dose, as indicated in the packaging bottle, is 2 soft gel capsules per orem, once a day.

It is an antioxidant supplement with no therapeutic claims and no established recommended daily allowance (RDA).[16] It is available in the market as a soft gel capsule and packaged in the bottle containing 100 soft gel capsules per bottle. Study medication was stored in a cool, dry place, away from direct sunlight, with a temperature not exceeding 30°C, without refrigeration or freezing.

### *Recruitment, allocation, and randomization*

Subjects were recruited in accordance with the eligibility criteria through nonprobability consecutive sampling. A written informed consent was signed by the subjects before the initiation of the study. Subjects were assigned with numbers, and using the Research Randomizer Software available at www.randomizer.org, they were assigned either in Group A who received 500 mg lycopene (50 mg lycopene) supplement as the treatment group, or in Group B who did not have intervention.

### *Blinding*

Assignment of treatment groups was known to an independent investigator, who did randomization, and the subject. The allocation and randomization were not disclosed to the primary investigator who did MED determination at baseline, week 6, and week 12 of treatment.

### *Intervention and follow-up*

Subjects were randomly assigned into one of two groups. Subjects in Group A received lycopene (50 mg lycopene) 500 mg/soft gel capsule two soft gel capsules per orem once daily for 12 weeks. Group B did not receive intervention during the entire observation period. Subjects in Group A were instructed to take two soft gel capsules per orem in the morning after breakfast. Pill-counting and assessment of medication compliance were assessed from week 6 until week 12 by the independent investigator.

Failure of the study participant to take at least 80% of the expected number of capsules within the 12-week supplementation period was considered a research drop-out.[17] Both study groups were required to fill out a diet diary daily for 12 weeks to monitor the type of food consumed by each participant [Appendix 1].

### *Outcome measures*

Baseline demographics, medical history, current oral and topical medication use, and FSP were obtained from each subject of both groups. FSP depends on the baseline skin pigmentation, sensitivity to sunburning, and ability to tan [Table 1].

Baseline examination included determination of MED before initiation of intervention. A narrow band UVB panel with dosages at mj/cm$^2$ was used. During UVR exposure, safety protocols were followed.

All subjects were assessed on initial visit (baseline) and on every follow-up (weeks 6 and 12) through MED determination and identification of adverse events, if any. Digital photography of the MED test area on both groups (either on the buttock, lower back or medial forearm) was done before and after the procedure as well as 24 h after procedure upon reading the MED.

MED was determined by exposing six (6) 2 × 2 cm areas of skin using a MED patch on the hidden area of the body such as the lower back, buttock, or medial forearm to gradually increasing amounts of UVR (200, 400, 600, 800, 1000, and 1200 mJ/cm$^2$). Only the areas tested were exposed. Each of the six (6) 2 × 2 cm area were then marked. The MED patch was removed only leaving the marks. Twenty-four hours after UVR exposure, reading was done by determining the lowest UVR dose that resulted in uniform erythema over the entire surface of one (1) 2 × 2 cm area. Topical sunblock was allowed to be used by the subject except on possible areas for MED determination.

## Statistics

### *Sample size computation*

The sample size was computed using OpenEpi version 3. Based on the study of Stahl, *et al*.,[18] the Δ-value (redness of the skin directly before and 24 h after UV irradiation) at week 4 was 5.4 ± 0.6 for control while 5.1 ± 0.8 for treatment group. Using these values and power of 95%, computation showed that the minimum required sample size is 18 per group, at 95% confidence level and accounting for 10% attrition rate.

## Statistical analysis

Descriptive statistics such as mean and standard deviation for continuous data and frequency and proportion for categorical data were used to summarize the demographic and clinical profile of the subjects. Differences in the characteristics were compared using Student's *t*-test for continuous variables and Chi-square test or Fischer's exact test for categorical variables. One-way repeated-measures analysis of variance was used in comparing outcomes measured at different time points. $P < 0.05$ were considered statistically significant. Stata ver 15 was used for data analysis.

## Results

A total of 18 subjects who received lycopene supplementation (Group A) and another 18 subjects

with no intervention (Group B) were included in the study. The baseline variables for both groups were comparable [Table 2]. A review of the diet diary of the subjects showed no deviation from their standard food preferences with no special type of diet done within the 12-week period.

A significant increase on MED was observed across periods for Group A [Table 3]. Specifically, results show that increase from baseline to week 6 was observed ($P = 0.0001$), where the change from baseline to week 6 is around 20. 83%. Similarly, from baseline to week 12, a significant increase on mean MED was observed ($P = 0.0001$) where 43. 06% average change was observed. Similarly, from week 6 to week 12, an average increase of 19.07% was observed ($P = 0.0001$).

Group B MED remained constant from baseline to week 6 and week 12 [Table 4]. Hence, when compared to Group A, intervention turned out to be significantly effective in increasing MED as compared to the control group, seen in both week 6 and week 12 [Table 5].

In Group A, 11.1% of subjects have experienced adverse effects, specifically, slight burning sensation over MED tested area, but this is not significantly different from Group B which has no reported adverse effects ($P = 0.15$).

## Discussion

UVR, an environmental agent affecting the skin, may be emitted by the sun or from artificial sources such as fluorescent and halogen lamps. Both UVA and UVB contribute to photoaging, immunosuppression, and carcinogenesis indirectly. UVA forms reactive oxygen species (ROS) while UVB causes direct DNA damage.[1,19]

FSP IV–V is common among Filipinos.[14] These skin phototypes have more melanin which offers better protection from the effects of UVR.[1] Melanin acts as a shield for epidermal DNA, a UV-absorbing agent, and a scavenger of ROS.[20] However, even with melanin, darker-skinned individuals need further photoprotection as there is still a possibility of erythema, pigmentation,

**Table 1: Fitzpatrick skin phototype[1]**

| Skin phototype | Burning and tanning reactions upon sun exposure | Color of unexposed skin |
|---|---|---|
| I | Always burns, never tans | Pale white |
| II | Always burns, then tans | White |
| III | Sometimes burns, can tan without prior burn | White |
| IV | Usually does not burn, tans easily and deeply | White to light brown |
| V | Rarely burns, tans easily | Brown, moderately pigmented |
| VI | Burns only with very high UVR doses, tans | Dark brown to black; darkly pigmented |

UVR: Ultraviolet radiation

**Table 2: Profile of patients**

| | Group A (*n*=18), *n* (%) | Group B (*n*=18), *n* (%) | *P* |
|---|---|---|---|
| Age (years), mean±SD | 28.9±3.3 | 29.1±5.4 | 0.8818 (NS) |
| Sex | | | |
| Male | 5 (27.8) | 2 (11.1) | 0.4018 (NS) |
| Female | 13 (72.2) | 16 (88.9) | |
| Civil status | | | |
| Single | 18 (100.0) | 14 (77.8) | 0.1039 (NS) |
| Married | 0 | 4 (22.2) | |
| Comorbidities | | | |
| With | 4 (22.2) | 5 (27.8) | 0.7215 (NS) |
| Bronchial asthma | | | |
| Allergic rhinitis | | | |
| Polycystic ovarian syndrome | | | |
| Hyperlipidemia | | | |
| Gastroesophageal reflux disease | | | |
| Without | 14 (77.8) | 13 (72.2) | |
| Allergies | | | |
| With | 4 (22.2) | 6 (33.3) | 0.7112 (NS) |
| Without | 14 (77.8) | 12 (66.7) | |
| Current medications | | | |
| With | 14 (77.8) | 10 (55.6) | 0.2890 (NS) |
| Without | 4 (22.2) | 8 (44.4) | |
| FSP | | | |
| III | 2 (11.1) | 4 (22.2) | 0.4496 (NS) |
| IV | 15 (83.3) | 12 (66.7) | |
| V | 1 (5.6) | 2 (11.1) | |

NS: Not significant, SD: Standard deviation, FSP: Fitzpatrick skin phototype

**Table 3: Mean minimal erythema dose on baseline, week 6, and week 12 for Group A**

| Group A | Mean±SD | *P* |
|---|---|---|
| Baseline | 666.7±118.8 | 0.0001* |
| Week 6 | 800.0±137.2 | |
| Week 12 | 944.4±165.3 | |
| **Pairwise comparison** | **Difference** | ***P*** |
| Baseline | | |
| Week 6 | −133.3 | 0.0001* |
| Week 12 | −277.7 | 0.0001* |
| Week 6 | | |
| Week 12 | −144.4 | 0.0001* |

*Significant. SD: Standard deviation

**Table 4: Mean minimal erythema dose on baseline, week 6, and week 12 for Group B**

| Group A | Mean±SD | *P* |
|---|---|---|
| Baseline | 766.67±141.42 | 1.000 (NS) |
| Week 6 | 766.67±141.42 | |
| Week 12 | 766.67±141.42 | |
| **Pairwise comparison** | **Difference** | ***P*** |
| Baseline | | |
| Week 6 | 0.0000 | 1.000 (NS) |
| Week 12 | 0.0000 | 1.000 (NS) |
| Week 6 | | |
| Week 12 | 0.0000 | 1.000 (NS) |

NS: Not significant, SD: Standard deviation

**Table 5: Comparison between Group A and B on the mean minimal erythema dose increase from baseline**

| | Mean±SD | | *P* |
|---|---|---|---|
| | Group A | Group B | |
| Amount of increase from | | | |
| Baseline to week 6 | 133.3±97.0 | 0.00±0.00 | 0.0001* |
| Baseline to week 12 | 277.7±139.6 | 0.00±0.00 | 0.0001* |

*Significant. SD: Standard deviation

skin aging, and cancer development from UVR exposure. This study included subjects with FSP III–V, considering the fact that most Filipinos belong to the darker spectrum but still some have fair skin.

To help minimize the unwarranted effects of UVR in the skin, photoprotection through topical and oral medications have been developed throughout the years.[21] This trial focused on oral supplementation of lycopene, a naturally occurring antioxidant, for photoprotection.

Several clinical trials similarly using oral lycopene or a combination of carotenoids for UVR protection were done in patients with FSP I-III and results were significantly positive, favoring these agents as photoprotectants.[9,11-13,18] One study done in 2003 compared β-carotene (24 milligrams (mg)/day) with a carotenoid supplement mixture containing β-carotene, lutein, and lycopene (8 mg/day for each). Results showed decreased intensity of erythema 24 h after solar light irradiation in both groups after 12 weeks of treatment.[22] A systematic review and meta-analysis by Dilokthornsakul *et al*. compared 4 studies with a total of 99 participants categorized as FSP I–II. They concluded that products with a lycopene content of 8–20 mg/day significantly reduced skin erythema formation and decreased biomolecular markers for photodamage, thus indicating that lycopene could be used for endogenous sun protection.[16]

In this current study of 36 subjects, with 18 subjects using 100 mg/day of lycopene for 12 weeks, results were congruent to previous clinical trials done. Among patients who received lycopene supplementation, an increase in MED was observed by 43.06% from baseline. MED is the lowest dose of UVR that produces erythema in an individual.[1] Higher MED signifies a higher tolerance and protection from UVR. This increase in MED within the 12-week period indicates better photoprotection. The difference of this trial from previous studies is the population tested which involves patients with FSP III-V.

Adverse effects of oral lycopene were not reported in studies determining the efficacy of lycopene for photoprotection.[16] Lycopene is not known to be toxic to humans and daily supplementation as high as 120 mg/day did not show any adverse effects.[23] Adverse effects reported in this study were observed during the MED testing process at baseline. The adverse effects were not related to lycopene intake.

Limitations of the study include phototesting with UVB only due to the unavailability of a device within the facility that emits both UVA and UVB. Furthermore, measurement of lycopene levels was not done due to the absence of the test in the study setting.

The authors of this study recommend further controlled large-scale studies with a longer follow-up to be conducted for better assessment of intervention response. A placebo with similar physical features of the intervention is also recommended to allow further blinding. At the time of the study, no FDA-approved placebo similar to the intervention was available. If accessible, photo testing involving both UVA and UVB should be considered. UVA and UVB contribute to UV-induced skin damage and using a device which covers both can be beneficial. Other outcome measures such as lycopene blood levels are also recommended to provide a more definite correlation between the photoprotective effects and oral lycopene intake.

## Conclusion

This randomized controlled trial demonstrated the significant benefits of oral lycopene on photoprotection among patients

with FSP III–V. It exhibited that lycopene supplementation positively increases MED over time. With this evidence, patients with darker skin phototypes may be advised to take oral lycopene supplements or increase their intake of lycopene-containing foods to promote further protection from the unwarranted effects of ultraviolet radiation. Oral lycopene may serve as an adjunct, but the findings of this study do not replace the basic principles of photoprotection, which include behavioral modifications minimizing sun exposure, proper clothing, and the use of topical sunscreens.

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Nil.

## Conflicts of interest
There are no conflicts of interest.

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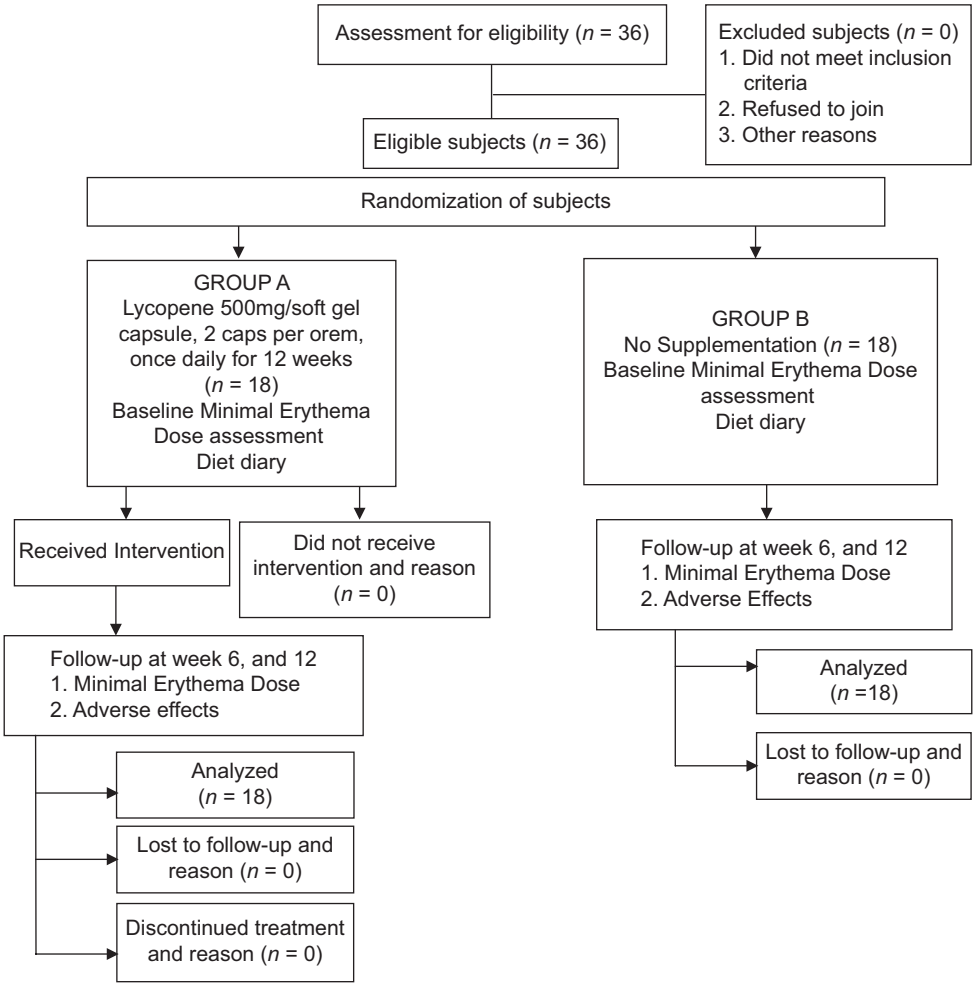
## Appendix

## Appendix 1




**Methodology**